AstraZeneca

PROTOCOL SYNOPSIS

A Phase III, Multicentre, Randomised, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of Intravenous Ceftaroline Fosamil Versus Intravenous Ceftriaxone in the Treatment of Adult Hospitalised Patients With Community-Acquired Bacterial Pneumonia in Asia

Study centre(s) and number of patients planned

This study will be conducted in approximately 692 randomised patients recruited, within the Asian districts including, but may not be limited to, China, India, Korea, Taiwan and the Philippines. A total of about 50 to 56 centres will participate with patient recruitment ranging from 32 to 240 patients per district.

Study period		**Phase of development**
Estimated date of first patient enrolled	3Q2011	III
Estimated date of last patient completed	1Q2013	III

Objectives

Primary objective

The primary objective of this study is to determine the non-inferiority in clinical cure rate of ceftaroline treatment compared with that of ceftriaxone treatment at the Test-of-Cure (TOC) visit in Clinically Evaluable (CE) Population of adult hospitalised patients with community-acquired bacterial pneumonia (CABP).

Secondary objectives

The secondary objectives are to evaluate:

- Clinical response at the End-of-Therapy (EOT)
- Clinical response at the TOC in the Modified Intent-to-Treat (MITT), microbiological Modified Intent-to-Treat (mMITT), and Microbiologically Evaluable (ME) Populations
- Microbiological response at the TOC visit
- Overall (clinical and radiographic) response at the TOC visit
- Clinical and microbiological response by pathogen at the TOC visit
- Clinical relapse at the Late Follow-up (LFU) visit
- Microbiological re-infection/recurrence at the LFU visit
- Safety

Exploratory objectives

The exploratory objectives are to evaluate:

- Ceftaroline PK in a sub-group of patients
- Ceftaroline exposure and the antimicrobial response relationship
- To quantify the length of stay in hospital, and rates of ICU admission by clinical outcome
- To characterise and explore resolution of patient reported symptoms of CABP

Study design

This is a Phase III, multi-centre, randomised, double-blind, comparative efficacy and safety study of intravenous (IV) ceftaroline fosamil 600 mg q12h versus IV ceftriaxone 2 g q24h (defined as study drug therapy) administered for 5 to 7 days, in approximately 692 hospitalised adult patients with CABP. The study consists of a baseline visit, a 5–7 day treatment period, an EOT, TOC and a LFU visit. The baseline assessments, to determine patient eligibility, must occur within 24-hours of study Day 1 (defined as the first administration of study drug). Block randomisation using either an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS), stratified by district, will be used to assign patients (1:1) to the ceftaroline or ceftriaxone group. The IVRS/IWRS will monitor disease severity and ensure that at least 25% of patients randomised are

Pneumonia Outcomes Research Teams (PORT) risk class IV. To maintain blinding the study drug will be prepared and adjusted by unblinded pharmacy or study site staff.

An optional pharmacokinetic (PK) sub-study will be conducted in approximately 200 patients.

Target patient population

The target patient population is comprised of male and female adult hospitalised patients, in the Asian region, with CABP as defined by radiographic and microbiologic inclusion criteria and whose severity of disease is a PORT Risk Class Determination III or IV (see Appendix D).

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 alkalising agent to control pH of the constituted solution to pH 4.8 to 6.2. Patients randomised to ceftaroline will receive 600 mg IV q12h (±2h), infused over 60 (±20) minutes. Each 60-minute infusion will be divided into 2 sequential 30 (±10) minute bags or bottles containing 50% of the total dose. The individual bags/bottles will be administered in immediate succession. For ceftaroline dose adjustments see Section 5.5.3.1

Comparator, dosage and mode of administration

Ceftriaxone for Injection is supplied as 1 g/vial (2 vials for a 2 grams dose) and a 2 grams dose will be infused over 30 (±10) minutes q24h (±2h). IV saline placebo will also be infused to maintain blinding. It is not necessary to make dose adjustments of ceftriaxone for patients with mild (50 mL/min <CLCR ≤80 mL/min) or moderate (30 mL/min <CLCR ≤50 mL/min) renal insufficiency.

Study Drug Dosing Overview in Patients with Normal Renal Function

Treatment Group	First Daily Dose		Second Daily Dose	
	Infusion 1 30 (± 10) min	Infusion 2 30 (± 10) min	Infusion 1 30 (± 10) min	Infusion 2 30 (± 10) min
Ceftaroline fosamil	Ceftaroline 300 mg	Ceftaroline 300 mg	Ceftaroline 300 mg	Ceftaroline 300 mg
Ceftriaxone	Ceftriaxone 2 g	Placebo	Placebo	Placebo

Duration of treatment

Baseline assessments for study eligibility will occur within 24 hours prior to administration of the first dose of study drug therapy. The duration of treatment with study drug is 5 to 7 days. An EOT visit will occur on the last day the study treatment regimen is administered. The

TOC visit will occur 8 to 15 days after the last dose of study drug is administered, and an LFU visit will occur 21 to 35 days after the last dose of study drug is administered (see Table 1). Patient participation will require between 26 and 42 days.

Discontinuation of investigational product, Guidance to investigators on when to end study drug therapy and information regarding the complete withdrawal from the study (withdrawal of informed consent) are described in Sections 5.8, 5.8.1, and 5.9 respectively).

Outcome variable(s):

Primary Endpoint

The primary efficacy endpoint will be the per-patient clinical cure rate at the TOC visit in the CE population.

Secondary Endpoints:

Efficacy:

- Per-patient clinical cure rate at the TOC visit in the MITT, mMITT and ME Populations
- Per-patient clinical cure rate at the EOT visit in the CE and MITT Populations
- Per-patient microbiological favourable outcome rate at the TOC visit in the mMITT and ME Populations
- Per-patient overall success rate at the TOC visit in the CE and MITT populations
- Per-pathogen clinical cure rate and microbiological favourable outcome at the TOC visit in the ME and mMITT populations
- Per-patient clinical relapse rate at the LFU visit in the CE and MITT populations who were clinically cured at the TOC visit
- Per-patient microbiological re-infection or recurrence rate at the LFU visit in patients in the ME Population who had a favourable microbiological outcome at the TOC visit

Safety in MITT Population:

- Adverse events (AEs)
- Electrocardiogram (ECG)
- Laboratory assessments
- Physical examinations

- Vital signs

Exploratory endpoint

- PK parameters derived from population PK analysis, and potential PK/PD relationships (will be reported separately)
- Length of hospital stay as measured at LFU visit
- Admission to an Intensive Care Unit as measure at LFU visit
- CAP-SYM 18 scores at baseline, day 2, 4, EOT, TOC and LFU visit

Statistical methods

The sample size for this study has been based on the primary outcome variable of clinical cure rate at the TOC visit in the CE Population. Assuming a point estimate for the clinical cure rate of 85% in the ceftriaxone treatment group, and 85% in the ceftaroline group in the CE Population, a non-inferiority margin of 10%, a power of 90%, and a 77.5% evaluability rate, a total sample size of 692 patients is required (346 patients in each treatment group).

The primary objective of this study is to determine the non-inferiority in the clinical cure rate for ceftaroline compared to that for ceftriaxone at the TOC visit in the CE Population in adult patients with CABP. A two-sided 95% confidence interval (CI) for the observed difference in the cure rate (ceftaroline group minus ceftriaxone group) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI. This method corresponds to the expanded Farrington-Manning test (Farrington CP and Manning G 1990) for stratified designs with Cochran-Mantel-Haenzel weights. Non-inferiority of ceftaroline will be concluded if the lower limit of the 95% CI is -10% or higher.

If the clinical cure rates for ceftaroline are higher than that seen in ceftriaxone group and non-inferiority has been established in CE Population, a test of superiority will be conducted in the CE and MITT populations. Superiority of ceftaroline will be concluded if the two-sided p-value is less than 0.05 in both the CE and MITT populations.

An additional assessment of the treatment group-by-district interaction on the primary efficacy outcome measure will be performed descriptively. The primary efficacy measure will be summarized by treatment group and district.

For each secondary efficacy outcome measure, a two-sided 95% CI will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

The safety analysis will be performed using the MITT Population. Safety parameters include adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiogram (ECG) parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses. No inference will be made for safety analysis. Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment ceftaroline but actually received ceftriaxone) will be accounted for in the actual treatment group received.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
ABG	Arterial blood gas
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
C	Celsius
CABP	Community-acquired bacterial pneumonia
CAP-SYM 18	Community Acquired Pneumonia-Symptom Questionnaire18
CBC	Complete blood count
CE	Clinically evaluable
CI	Confidence interval
CLCR	Creatinine clearance
CLSI	Clinical Laboratory Standards Institute
Cmax	Maximum drug plasma concentration
Cmin	Minimum drug plasma concentration
CSA	Clinical study agreement
cSSSI	Complicated skin and skin structure infection
CT	Computed tomography
CV	Coefficient of variation
CXR	Chest radiograph
dL	Decilitre
DMC	Data Management Centre
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End-of-Therapy
ESRD	End stage renal disease
FDA	Food and Drug Administration
g	Gram

Abbreviation or special term	Explanation
GCP	Good clinical practice
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	Kilogram
Kit ID	Kit identification
L	Litre
LFU	Late Follow-up
MDRSP	Multi-drug resistant Streptococcus pneumoniae
ME	Microbiologically Evaluable
MedDRA®	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MIC90	Minimum inhibitory concentration required to inhibit the growth of 90% of organisms
µMol	Micromole
MITT	Modified Intent-to-Treat
MITTE	Modified Intent-to-Treat Efficacy
mMITT	Microbiological Modified Intent-to-Treat
mg	Milligram
min	Minutes
mL	Milliliter
mm	Millimeter

Abbreviation or special term	Explanation
MRSA	Methicillin-resistant Staphylococcus aureus
OAE	Other significant adverse event
PBP	Penicillin binding protein
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PORT	Pneumonia Outcomes Research Team
PRP	Penicillinase-resistant penicillin
PRSP	Penicillin-resistant Streptococcus pneumoniae
PT	Prothrombin time
PTT	Partial thromboplastin time
PVL	Panton-Valentine leucocidin
q12h	Every 12 hours
q24h	Every 24 hours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SI	Système International d'Unités
t1/2	Terminal elimination half-life
TEAE	Treatment emergent adverse event
TOC	Test-of-Cure
UA	Urinalysis
UAT	Urinary Antigen Test
WBDC	Web Based Data Capture
WBC	White blood cell (count)

1. INTRODUCTION

1.1 Background

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 in the Asian population. Despite advances in medical care and antimicrobial therapy, CABP remains an important cause of mortality and hospitalisation.

1.1.1 Summary of Microbiological and Pharmacology Studies

The spectrum of activity of ceftaroline includes bacterial pathogens important in respiratory disease as well as those important in skin and skin structure infections. Ceftaroline is a broad-spectrum agent active against gram-positive organisms including resistant isolates such as multidrug-resistant *S. pneumonia* (MDRSP) and methicillin-resistant *Staphylococcus aureus* (MRSA). The activity of ceftaroline against gram-negative species includes respiratory pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*. Ceftaroline is active against gram-negative organisms producing common TEM and SHV β-lactamases, although it is poorly active against strains that produce extended spectrum β-lactamase (ESBL) enzymes or those that hyperproduce AmpC β-lactamase. Consequently, ceftaroline is active against many species of Enterobacteriaceae, including *Escherichia coli*, but is poorly active against isolates that are ceftazidime-resistant owing to production of these β-lactamases. Ceftaroline is inactive against most isolates of *Pseudomonas aeruginosa* and other nonfermentative gram-negative species.

Ceftaroline, like other β-lactam antibiotics, inhibits bacterial cell growth by interfering with cell wall biosynthesis. This occurs through binding of the β-lactam to the transpeptidase active site of penicillin binding proteins (PBPs), which carry out the final steps in cell wall biosynthesis. Ceftaroline has been shown to bind with high affinity to PBPs in *S. pneumoniae* including PBP2x, alterations of which are common in penicillin-resistant *Streptococcus pneumoniae* (PRSP) isolates. Ceftaroline has also been shown to bind with high affinity to PBPs from methicillin-susceptible *Staphylococcus aureus* (MSSA), and unlike other available β-lactams, it also binds efficiently to PBP2a, the additional PBP present in MRSA.

Ceftaroline was effective in animal models of infection that included mouse thigh and lung infections with gram-negative and -positive species, endocarditis models of infection in rat and rabbit with *S. aureus*, and pneumonia studies in rabbit with PRSP. Ceftaroline exhibited short to modest postantibiotic effects *in vitro* and *in vivo*, similar to other antibiotics of the cephalosporin class. In combination with other antimicrobial agents in vitro, ceftaroline showed no antagonistic effects, with most tested combinations producing either no effect or additivity. Some cases of synergy have been observed, in particular, for the combination of ceftaroline with aminoglycosides against resistant gram-negative strains. Ceftaroline had no unusual requirements for in vitro testing during minimum inhibitory concentration (MIC) determinations, and variations in growth conditions during susceptibility testing were generally well tolerated with little resulting effect on MIC values.

The investigator's brochure (IB) provides additional information about non-clinical studies performed using ceftaroline.

1.1.2 Clinical Experience

Ceftaroline has been evaluated in healthy adult, elderly and adolescent patients, and in patients with mild to severe renal impairment, as well as in patients with end-stage renal disease (ESRD) requiring hemodialysis. The clinical development program consisted of 17 studies (3153 patients): 11 Phase I Clinical Pharmacology studies (305 patients), 2 Phase II complicated Skin and Skin Structure Infection (cSSSI) studies (242 patients), and 4 Phase III studies (2606 patients); 2 in cSSSI (1378 patients) and 2 in CABP (1228 patients). The safety and efficacy of ceftaroline has been demonstrated in patients with cSSSI and in patients with moderate-to-severe CABP.

Two phase 3 studies have been conducted in CABP (Studies P903-08 and P903-09). These studies were multinational, Phase III studies with nearly identical designs. Patients with new or progressive pulmonary infiltrate(s) on chest radiography, with clinical signs and symptoms consistent with CABP, with the need for hospitalisation and IV therapy were enrolled in the studies. Patients were given study medication IV, the route proposed for marketing; a switch to oral therapy was not allowed.

Ceftriaxone was the active control agent in both phase 3 CABP studies. It is widely accepted as a standard-of-care therapy for CABP. The dose of ceftriaxone used in the phase 3 CABP studies was 1 gm IV q24h. The only difference between the two pivotal Phase III CABP studies was the use of adjunctive macrolide therapy. The brief course of clarithromycin (2 doses of 500 mg q12h starting on Study Day 1) was administered in Study P903-08 to provide initial coverage against atypical organisms (eg, if baseline *Legionella pneumophila* urinary antigen testing was delayed) and allowed for the involvement of additional countries.

Ceftaroline fosamil at a dose of 600 mg administered as a 60-minute IV infusion q12h for 5 to 7 days was demonstrated to be effective for the treatment of CABP caused by susceptible isolates, including the following gram positive and gram negative microorganisms: *S. pneumoniae* (including cases with concurrent bacteremia), *S. aureus*, *H. influenzae*, *H. parainfluenzae*, and *K. pneumoniae*. Dosage adjustment for moderate renal impairment is recommended.

Finally, for the treatment of CABP, ceftaroline fosamil was shown to be non-inferior to ceftriaxone (with or without clarithromycin) in the clinical cure rate at TOC in the two coprimary populations (MITT and CE). Non-inferiority was also demonstrated in the clinical response at EOT in the two coprimary populations and in the per-patient microbiological response at TOC in the mMITT and ME Populations.

In summary, in each of these adequate and well-controlled studies, non-inferiority was demonstrated for all prospectively defined analyses across all analysis populations.

1.2 Rationale for conducting this study

The rationale for conducting this study is to assess efficacy and safety in the Asian adult hospitalised patient population. The study will evaluate the use of ceftaroline in adult hospitalised CABP patients in the Asian region.

1.3 Research Hypothesis

This study is designed to test the hypothesis that the clinical cure rate of ceftaroline is non- inferior to that of ceftriaxone at the TOC visit in the CE Population of adult hospitalised patients with CABP.

1.4 Benefit/risk and ethical assessment

There is an unmet medical need for a safe, well-tolerated, effective broad-spectrum antibiotic with balanced anti-gram positive and anti-gram negative spectrum and activity against resistant pathogens (MRSA) in the Asian region. Safety and tolerability of ceftaroline have been assessed in 2 previous Phase III trials.

Two large, pivotal, Phase III studies were fully consistent in demonstrating that ceftaroline is non-inferior to ceftriaxone in patients with CABP as evidenced by the lower limit of the 95% CI around the treatment difference in cure rates (ceftaroline minus ceftriaxone) being greater than the pre-specified non-inferiority boundary of -10% in the co-primary CE and MITTE Populations of each study.

The therapeutic benefits of ceftriaxone for the treatment of bacterial infections are documented in the ceftriaxone package insert and published literature.

1.4.1 Known risks

The pooled Phase 3 cSSSI and CABP studies consisted of 1305 adult subjects treated with the proposed recommended dose of ceftaroline fosamil and 1301 adult subjects treated with an active comparator (ie, vancomycin plus aztreonam for cSSSI and ceftriaxone for CABP). In these studies, 1227 (94%) subjects received ceftaroline fosamil for 5 to 14 days.

In the pooled Phase 3 studies for cSSSI and CABP, the incidences of treatment-emergent adverse events (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% of subjects in the pooled Phase 3 studies. The most common TEAEs ≥ 2% in the ceftaroline group were diarrhoea (4.6%), headache (4.4 %), nausea (4.2 %), insomnia (2.8%), constipation (2.1 %) and vomiting (2.1%). In addition, a collection of multiple adverse event terms representing a potential allergic reaction occurred at a frequency of 5.4% for ceftaroline. The most common TEAEs ≥ 2% in the comparator group were pruritus (4.5%), nausea (3.8%), diarrhoea (3.2%), headache (3.1%), insomnia (2.4%) and hypokalemia (2.3%). The incidences of individual TEAEs were similar in the two treatment groups.

The therapeutic risks of IV ceftriaxone are well established (ceftriaxone package insert). The following AEs (related or of uncertain aetiology), were observed in clinical studies: eosinophilia (6%); thrombocytosis (5.1%); elevations of GOT (3.1%) or GPT (3.3%); diarrhoea (2.7%); leukopenia (2.1%); rash (1.7%); elevations of blood urea nitrogen (1.2%); and pain, induration and tenderness at the infusion site (1%). Less frequently reported AEs (<1%) were anaemia, hemolytic anaemia, neutropenia, lymphopenia, thrombocytopenia, prolongation of the prothrombin time (PT), pruritus, fever or chills, phlebitis, nausea or vomiting, dysgeusia, elevations of alkaline phosphatase and bilirubin, elevations of creatinine and the presence of casts in the urine, headache or dizziness, moniliasis or vaginitis, and diaphoresis and flushing.

1.4.2 Potential Risks

Risks associated with Study Drug

Cephalosporins are among the most commonly used classes of antimicrobials. Typical class effects include hypersensitivity and allergic reactions, diarrhoea, skin rash, leukopenia, thrombocytopenia, eosinophilia, positive Coombs' test, and elevation of hepatic enzymes. These effects are generally transient and spontaneously reversible after administration of the cephalosporin has been stopped. Severe reactions to cephalosporins (eg, seizures, nephrotoxicity, hemolytic anaemia, severe cutaneous reactions, anaphylaxis, death) are infrequent.

Pseudomembranous colitis has been reported with nearly all antimicrobial agents, and may range in severity from mild to severe. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antimicrobial agents. As with other antibacterials, prolonged use of cephalosporins may result in overgrowth of non-susceptible organisms.

In studies conducted with ceftaroline, typical cephalosporin-class effects were seen with a low frequency and severity; typically these events did not warrant treatment other than conservative measures.

Risks associated with study procedures

Features of the study design that might introduce risk to the patients independent of the investigational product include venipunctures, thoracentesis and arterial blood sampling.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine the non-inferiority in clinical cure rate of ceftaroline treatment compared with that of ceftriaxone treatment at the Test-of-Cure (TOC) visit in Clinically Evaluable (CE) Populations of adult hospitalised patients with community-acquired bacterial pneumonia.

2.2 Secondary objectives

The secondary objectives are to evaluate:

- Clinical response at the End-of-Therapy (EOT)
- Clinical response at the TOC in the MITT, mMITT and ME Populations
- Microbiological response at the TOC visit
- Overall (clinical and radiographic) response at the TOC visit
- Clinical and microbiological response by pathogen at the TOC visit
- Clinical relapse at the Late Follow-up (LFU) visit
- Microbiological re-infection/recurrence at the LFU visit
- Safety

2.3 Exploratory objectives

The exploratory objectives are to evaluate:

- Ceftaroline PK in a sub-group of patients
- Ceftaroline exposure and the antimicrobial response relationship
- To quantify the length of stay in hospital, and rates of ICU admission by clinical outcome
- To characterise and explore resolution of patient reported symptoms of CABP

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 III, multi-centre, randomised, double-blind, comparative efficacy and safety study of intravenous (IV) ceftaroline fosamil 600 mg q12h versus IV ceftriaxone 2 g q 24 h (defined as study drug therapy) administered for 5 to 7 days in approximately 692 hospitalised, adult patients with CABP. It is being conducted in approximately 50 to 56 centres, each centre recruiting about 7 to 15 patients. Approximately, 5 districts within the Asian region will be participating as follows: China: ≅ 240 patients, India: ≅ 230 patients, Korea: ≅ 105 to 110 patients, Taiwan:≅ 80 patients, and the Philippines: ≅ 32 patients.

The severity of each patient's disease will be calculated according to the Pneumonia Outcomes Research Team (PORT) (Fine MJ et al 1997) (see Appendix D). Only those patients with a PORT Risk Class Determination of III or IV are eligible.

The study consists of the baseline visit, 5 to 7 day treatment period, followed by the EOT, TOC and LFU visits. Patients providing informed consent will be enrolled in the study then, upon meeting all study eligibility criteria, randomised to receive either IV ceftaroline or IV ceftriaxone. Baseline assessments for study eligibility will occur within 24-hours prior to administration of the first dose of the study treatment regimen (defined as study drug therapy) and continues for a minimum treatment duration of 5 days up to a maximum of 7 days. An EOT visit will occur on the last day the study treatment regimen is administered, followed by the TOC visit (8 to 15 days), and a LFU visit (21 to 35 days), after the last dose of study drug is administered (see Table 1). Patient participation will require between 26 and 42 days. Study Day 1 is defined as the day that the study drug is first administered; subsequent study days are defined by the number of consecutive calendar days thereafter. Block randomisation using an IVRS/IWRS, stratified by district, will be used to assign patients (1:1) to the ceftaroline or ceftriaxone group. The IVRS/IWRS will monitor disease severity and ensure that at least 25% of patients randomised are PORT IV. To maintain blinding the study drug will be prepared and adjusted by unblinded pharmacy or unblinded study site staff. Ceftaroline fosamil may be adjusted at any time, including the initial dose, if the patient's creatinine clearance (CL_{cr}) level indicates moderate renal impairment as estimated by the Cockcroft-Gault formula. This dose may be readjusted when renal function improves (see Section 5.5.3). It is not necessary to make dose adjustments of ceftriaxone for patients with mild (50 mL/min <CLCR ≤80 mL/min) or moderate (30 mL/min <CLCR ≤50 mL/min) renal insufficiency.

An optional population pharmacokinetics (PK) sub-study will be conducted in approximately 200 patients.

Figure 1 Study design

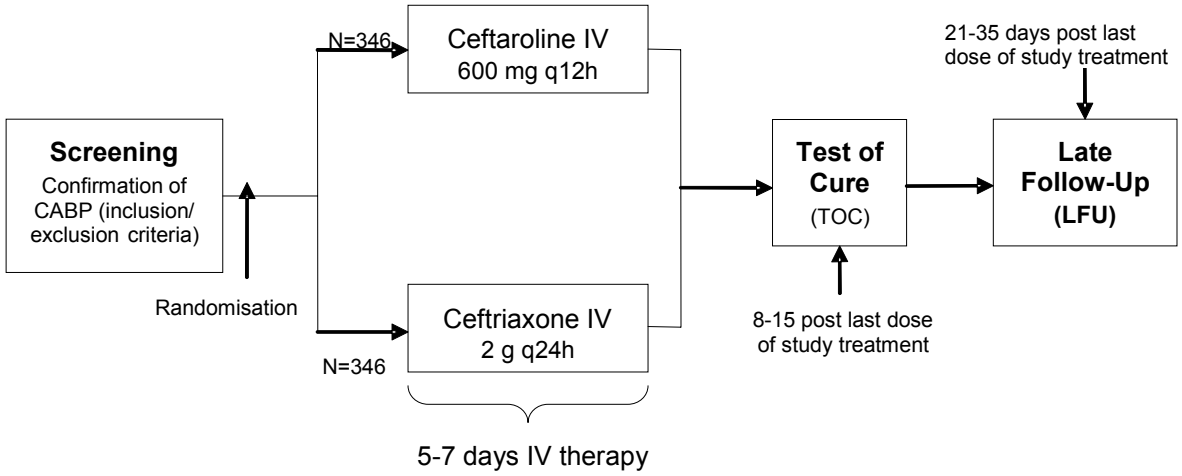


Table 1 Schedule of assessments

Assessment / Procedure	Base-line[a]	Day 1[a]	Day 2	Day 3	Day 4	Days 5-6	EOT[b]	TOC[c]	LFU[d]
Informed Consent[e]	X								
CAP-SYM 18 PRO[f]	X		X		X		X	X	X
Inclusion / Exclusion Criteria Assessed[g]	X								
Medical / Surgical / Smoking history	X								
Prior / concomitant medication[h]	X	X	X	X	X		X	X	X
Physical examination[j]	X			X			X	X	
CABP signs / symptoms[k]	X	X	X	X	X		X	X	X
PORT Score[l] / Diagnosis	X								
Vital signs[m]	X	X	X	X	X	X	X	X	
Pulse oximetry[n]	X	X	X	X	X	X	X	X[n]	
12-lead ECG[o]	X			X			X	X	
CXR or CT scan[p]	X							X	X
Laboratory tests[q]	X			X			X[r]	X	
Additional laboratory tests (blood)[s]	X[s]						X[s]	X[s]	X[s]
CL_{CR} estimated[t]	X			X			X		
Pregnancy test[u]	X						X		
L. pneumophila & pneumococcal UAT[v]	X								
Sputum specimen[w]	X	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]
Pleural fluid specimen[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]
Blood for culture[y]	X	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]
Record adverse events[z]	X	X	X	X	X	X	X	X	
Record SAEs	X	X	X	X	X	X	X	X	X
Administer study drug		X[a]	X	X	X	X	X[aa]		
Resource Use									X
PK sample[bb]				X					

[a] Baseline: completed within 24-hours prior to infusion of the first dose (Day 1) of study drug

[b] EOT must be performed on the last day the study drug therapy is administered (if the last dose occurs at night, except ECG recording, these can be performed in the a.m. of the following day). If discontinuing early or withdrawing, the patient should have all EOT assessments performed on the day of discontinuation or withdrawal

[c] TOC: 8 to15 days after administration of the last dose of study drug

[d] LFU performed 21to 35 days after administration of the last dose of study drug

[e] Written informed consent must be obtained prior to any study procedures or assessments

[f] CAP-Symptom 18 questionnaire should be completed prior to any other study related procedures (see Appendix I)

[g] Verify patient meets all eligibility criteria prior to randomisation

[h] Record prior medications taken within 4 weeks prior to baseline

[j] Complete physical exam performed at baseline, including height and weight measurements; brief physical exam performed on Day 3 (±1 day), EOT and LFU. For definitions of each type of physical exam, see Section 6.4.6 and Appendix H

[k] CABP signs and symptoms include, but may not be limited to: cough, pleuritic chest pain, dyspnoea and sputum production and character.

- All signs and symptoms from the episode prior to this current CABP diagnosis must also be recorded at baseline.
- Categorize the symptom intensity by using the AE variables (see Section 6.4.3) of Absent, Mild, Moderate or Severe.
- For the purposes of this study, also record patient's ability to maintain oral intake and mental status. Categorize their mental status as normal or altered (reference definition of mental status in Appendix D).

[l] Determine patient's disease severity using PORT Score determination and confirm patient meets PORT Risk Class Determination III or IV (see Appendix D)

[m] Record resting vital signs, daily, including heart rate, blood pressure (after in a supine position for 5 min), respiratory rate and temperature (oral, rectal, or tympanic), while the patient remains on study treatment, at EOT and TOC. Measure the temperature in the a.m. and p.m. and record the patient's highest daily temperature.

[n] Record oxygen saturation at baseline, daily while patient remains on the study drug therapy, at the EOT visit, and if medically indicated at the TOC visit

[o] Obtain 12-lead ECGs:

- Baseline: three 12-lead ECGs separated by at least 1 minute, within a 15 minute period
- Day 3 (±1 day), EOT and TOC: one 12-lead ECG recording within 60 minutes of the end of Infusion 2

[p] Chest X-ray / CT scan (see App. E) NOTE: these are not obtained at TOC or LFU for previous treatment failures

[q] Laboratory tests include: haematology, clinical chemistry, PT/INR, PTT, RDW, MCV, reticulocyte count, haptoglobin, urinalysis and urine microscopy at times indicated in Table 1, (see Appendix G and Laboratory Manual).

[r] EOT Laboratory tests not performed if previous tests were within prior 24 hours

[s] Additional Laboratory tests (blood): Reference: Appendix G and Laboratory Manual

- Baseline: c-reactive protein
- Baseline and LFU: serology for atypicals
- Baseline, EOT and TOC: direct Coombs
- Arterial blood gas (ABG) to measure pH, P_aO_2 & P_aCO_2, (according to investigator's judgment eg, hypoxic)

[t] CLcr will be calculated at times indicated in Table 1 and as medically indicated

[u] Urine pregnancy test for women of child-bearing potential and those who are <2 years postmenopausal EOT laboratory tests not performed if previous laboratory tests were within prior 24 hours

[v] Results of *L. pneumophila* urinary antigen test (UAT) must be available before randomisation. Patients with a positive result are excluded from participation

[w] Obtain sputum specimen, culture, perform Gram's stain and susceptibility testing (see Laboratory Manual):

- At baseline
- Repeat if medically indicated,

- At EOT (if deemed a treatment failure),
- At TOC (if deemed a treatment failure and was not previously categorized a failure),
- At LFU if medically indicated (eg, patient experiencing a relapse)

[x] Obtain pleural fluid specimen only if medically indicated on any study day, repeat samples are not required

[y] Obtain blood sample to culture and perform susceptibility testing (see Laboratory Manual):

- At baseline,
- If medically indicated (e.g., persistent or new signs and/or symptoms)
- Repeat until negative and at EOT and TOC if the previous blood culture was positive
- At EOT (if negative at previous visit but medically indicated and/or deemed a treatment failure at EOT)
- At TOC (if not a failure at EOT but medically indicated and/or deemed a treatment failure at TOC)
- At LFU if medically indicated (e.g., patient is experiencing a relapse)

[z] Additional information is required for AEs of haemolytic anaemia, acute renal failure and seizure/confusion and DILI(drug-induced liver injury), irrespective of seriousness

[aa] Study drug infusion may occur on the same calendar day as the EOT, but must be completed before EOT assessments begin

[bb] For those patients that have consented to participate in the optional PK portion of the study, obtain their written consent. Collect plasma samples from the dose which is the most convenient for collecting plasma samples on Day 3 of treatment (see Table 2). Start and stop times of Infusions 1 and 2 for the PK sampling daily dose on Day 3 must be recorded. The plasma sample handling and processing instructions will be provided in a separate, detailed Laboratory Manual

Table 2 PK sample schedule

Study Day / Dose	PK Sampling Time
Day 3 / Dose convenient for plasma samples collection[c]	Plasma samples for drug analysis will be obtained at the following times on **Day 3** following the administration of the dose convenient for plasma samples collection from patients participating in the optional PK substudy[a]: • Within 15 minutes prior to the start of Infusion 1[b] (trough) • Within 5 minutes following the end of Infusion 2 (peak) • Between 1 and 3 hours after the end of Infusion 2 • Between 4 and 8 hours after the end of Infusion 2

[a] It is expected that 200 patients will participate in the optional PK sub-study which should produce PK samples from approximately 100 patients randomised to each treatment group. Additional information on sample collection, processing and shipment can be found in a separate Laboratory Manual.

[b] See Section 5.5.2 and Table 4 for infusion information

[c] Plasma samples collection for PK can be collected from the administration of dose convenient for the collection on Day 3 of treatment.

3.2 Rationale for study design, doses and control groups

The purpose of this study is to demonstrate non-inferiority in the clinical cure rate of ceftaroline treatment compared to that of ceftriaxone treatment in adult Asian patients hospitalised with CABP.

The therapeutic dose of ceftaroline (600 mg q12h) that will be administered was based on epidemiological data, susceptibility profiles of ceftaroline, PK/PD modelling and simulation (see IB for a detailed discussion of PK modelling results). It is also supported by previously

conducted global studies in CABP patients in which ceftaroline was shown to be safe and effective (studies P903-08, P903-09).

Ceftriaxone has been selected as the comparator agent in this study. Ceftriaxone is a third-generation cephalosporin that has activity against the most common typical pathogens, including *S. pneumoniae* and is a globally accepted therapeutic agent for the treatment of CABP. Ceftriaxone was chosen as the active comparator agent, as both ceftriaxone and ceftaroline are in the same cephalosporin class. In addition, ceftriaxone was used as the comparator in the previously conducted global phase CABP studies of ceftaroline.

The dosage regimen for ceftriaxone, 2 g q24h, is consistent with the recently revised label recommendations by FDA for the use of ceftriaxone in adults. Various studies have demonstrated that the PK exposure of cephalosporins is similar in the Caucasian and Asian populations. A prospective clinical study in CAP in China (Liu YN et al 2006) indicates that the MIC90 of ceftriaxone against *S. pneumoniae* is at 0.25 mg/L level. Major pathogens of CABP in China are also shown to be similar with that in western countries. Based on this information, the dosing of ceftriaxone is considered suitable for covering pathogens in Asian including Chinese CABP patients.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening. The reason for screen failure should be recorded on the patient screening log.

Each patient 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 patients should fulfil the following criteria:

1. Males and females 18 or more years of age

2. CABP meeting the following criteria:

- Radiographically-confirmed pneumonia (new or progressive pulmonary infiltrate(s) on CXR or CT scan consistent with bacterial pneumonia)

  AND

- Acute illness (≤7 days duration) with at least three of the following clinical signs or symptoms consistent with a lower respiratory tract infection:

  – New or increased cough

- Purulent sputum or change in sputum character
- Auscultatory findings consistent with pneumonia (eg, rales, egophony, findings of consolidation)
- Dyspnoea, tachypnea, or hypoxemia (O_2 saturation <90% on room air or pO_2 <60 mmHg)
- Fever greater than 38ºC oral (>38.5ºC rectally or tympanically) or hypothermia (<35ºC)
- White blood cell count greater than 10,000 cells/mm^3 or less than 4,500 cells/mm^3
- Greater than 15% immature neutrophils (bands) irrespective of WBC count

AND

- PORT Risk class III or IV (PORT score >70 and ⩽130) (see Appendix D).

3. The patient must require initial hospitalisation, or treatment in an emergency room or urgent care setting, by the standard of care and be hospitalised while receiving study drug

4. The patient's infection would require initial treatment with IV antimicrobials

5. Female patients of child-bearing potential, and those who are fewer than 2 years post-menopausal, must agree to, and comply with, using highly effective methods of birth control (ie, condom plus spermicide, combined oral contraceptive, implant, injectable, indwelling intrauterine device, sexual abstinence, or a vasectomized partner) while participating in this study

6. Patient must provide written informed consent prior to any study-specific procedures, and a willingness and ability to comply with all study procedures.

4.2 Exclusion criteria

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

1. PORT score ≤70 (PORT Risk Class I and II), PORT score >130 (PORT Risk Class V), or requiring admission to an intensive care unit

2. CABP suitable for outpatient therapy with an oral antimicrobial agent

3. Confirmed or suspected respiratory tract infections attributable to sources other than community-acquired bacterial pathogens (eg, ventilator-associated pneumonia,

hospital-acquired pneumonia, visible/gross aspiration pneumonia, suspected viral, fungal, or mycobacterial infection of the lung)

4. Non-infectious causes of pulmonary infiltrates (eg, pulmonary embolism, chemical pneumonitis from aspiration, hypersensitivity pneumonia, congestive heart failure)

5. Pleural empyema (not including non-purulent parapneumonic effusions)

6. Microbiologically-documented infection with a pathogen known to be resistant to ceftriaxone, or epidemiological or clinical context suggesting high likelihood of a ceftriaxone-resistant "typical" bacterial pathogen (eg, *Pseudomonas aeruginosa*, MRSA). Epidemiological clues to potential MRSA infection include residence in a nursing home or assisted living facility, existence of an ongoing local MRSA infection outbreak, known skin colonization with MRSA, recent skin or skin structure infection due to MRSA, intravenous drug use, and concomitant influenza. Patients with risk factors for MRSA infection who have predominance of gram-positive cocci in clusters on sputum Gram's stain should also be excluded.

7. Infection with an atypical organism (*M. pneumoniae*, *C. pneumoniae*, *Legionella spp*.) is confirmed, or suspected based upon the epidemiological context, or infection with *L. pneumophila* is confirmed by the urinary antigen test at baseline

8. Previous treatment with an antimicrobial for treatment of CABP within 96 hours leading up to randomisation

EXCEPTION: patients may be eligible despite prior antimicrobial therapy if they meet the following conditions:

EITHER:

- A single dose of an oral or intravenous short-acting antibiotic for CABP (see Appendix F for a list of allowed and disallowed antibiotics)

OR BOTH OF THE FOLLOWING:

- Unequivocal clinical evidence of treatment failure (eg, worsening signs and symptoms) following at least 48 hours of prior systemic antimicrobial therapy
- Isolation of an organism resistant to the prior, systemic, antimicrobial therapy

9. Failure of ceftriaxone (or other third-generation cephalosporin) as therapy for this episode of CABP or prior isolation of an organism associated with this episode of CABP and resistant in vitro to ceftriaxone

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

11. Past or current history of epilepsy or seizure disorder

EXCEPTION: well-documented febrile seizure of childhood

12. Requirement for concomitant antimicrobial or systemic antifungal therapy for any reason

    EXCEPTIONS: topical antifungal or antimicrobial therapy, a single oral dose of any antifungal for treatment of vaginal candidiasis

13. Neoplastic lung disease, cystic fibrosis, progressively fatal disease, chronic neurological disorder preventing clearance of pulmonary secretions, or life expectancy of less than or equal to 3 months

14. Probenecid administration within 3 days prior to initiation of the study treatment regimen or requirement for concomitant therapy with probenecid

15. Infections or conditions requiring concomitant systemic corticosteroids

    EXCEPTION: the corticosteroid dose equivalent is less than 40 mg prednisone per day

16. Severely impaired renal function ($CL_{CR} \leqslant 30$ mL/min) estimated by the Cockcroft-Gault formula

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

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

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

17. Evidence of significant hepatic, haematological, or immunologic disease determined by the following:

    – Known acute viral hepatitis

    – Aspartate aminotransferase (AST; also known as glutamic oxaloacetic transaminase) or alanine aminotransferase (ALT; also known as glutamic pyruvic transaminase) level greater than 5-fold the upper limit of normal or total bilirubin greater than 2-fold the upper limit of normal.

- Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
- Current or anticipated neutropenia defined as less than 500 neutrophils/mm^3
- Thrombocytopenia with platelet count less than 60,000 cells/mm^3
- Known infection with human immunodeficiency virus and either a CD4 count less than or equal to 200 cells/mm^3 at the last measurement or current diagnosis of another Acquired Immune Deficiency Syndrome-defining illness

18. Evidence of immediately life-threatening disease, including, but not limited to, current or impending respiratory failure, acute heart failure, shock, acute coronary syndrome, unstable arrhythmias, hypertensive emergency, acute hepatic failure, active gastrointestinal bleeding, profound metabolic abnormalities (eg, diabetic ketoacidosis), or acute cerebrovascular events

19. Residence in a nursing home or assisted living facility that provides 24-hour medical supervision (not including extended living facilities for ambulatory elderly persons) or hospitalisation within 14 days prior to onset of symptoms (ie, healthcare-associated pneumonia)

20. Women who are pregnant (confirmed by a urine pregnancy test) or nursing

21. Participation in any study involving administration of an investigational agent or device within 30 days prior to randomisation into this study or previously participated in the current study

22. Previous participation in a study of ceftaroline

23. Unable or unwilling to adhere to the study-specified procedures and restrictions

24. Any condition that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data

25. Involvement in the planning and/or conduct of the study (applies to AstraZeneca, Forest and Cerexa staff, their representatives and/or staff at the study site).

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no specific dietary or activity restrictions other than those typical for a patient with CABP.

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Patient enrolment, randomisation and initiation of investigational product

The investigator will:

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

2. Assign potential patient a unique enrolment number, beginning with 'E" followed by 7 numerical digits identifying the centre number (always 4 positions with leading zeros) and enrolment number (always 3 positions with leading zeros consecutively assigned)

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

4. Inform unblinded pharmacy and/or unblinded study staff who obtains unique randomisation code (patient number) and unique Kit identification (Kit ID) numbers and ensures administration of blinded study drug occurs within 24-hours of baseline assessments (see Pharmacy Manual). If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

5.2.1 Procedures for randomisation

A stratified, blocked, computer-generated randomisation schedule is prepared by the AstraZeneca Biostatistics Department using GRand (a Global Randomisation system developed and validated by AstraZeneca), then loaded into IVRS/IWRS which will be used to assign patients in a 1:1 ratio to either the ceftaroline fosamil or ceftriaxone treatment group. The IVRS/IWRS will monitor disease severity and ensure that at least 25% of patients randomised are PORT IV. After patient eligibility is verified at the baseline visit, and using IVRS/IWRS, the study site's unblinded Pharmacist and/or unblinded study staff will obtain the randomisation code and unique Kit ID numbers for that patient's supply of medication.

5.3 Procedures for handling patients incorrectly enrolled, randomised or administered investigational product

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

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

The AstraZeneca Study Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped, (see Section 5.8).

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The Sponsor, Clinical Research Organization, Investigators, study staff participating in patient care or clinical evaluations, and patients will be blinded to study drug assignment until all patients have completed the study and the database is locked. Unblinded pharmacy staff or unblinded study staff (not participating in patient care) will be responsible for maintaining accountability and preparing the blinded study drug, ensuring all infusion bags or bottles are appropriately labelled and masked according to the Pharmacy Manual. The 600-mg dose of ceftaroline fosamil (for modified dose, see Section 5.5.3) infused over 60- minutes is split in this study into two 300-mg infusions over 30 minutes each q12h (±2h). The 2 grams dose of IV ceftriaxone is infused over 30 minutes followed by IV saline placebo infused over 30 minutes q24h (±q2h). Twelve hours after the infusions of the IV ceftriaxone and IV saline placebo (ie, between IV ceftriaxone/IV placebo infusions) patients in the ceftriaxone group will receive two consecutive IV saline placebo infusions, each infused over 30 minutes q24h (±2h). The ceftriaxone and placebo infusions will correspond with the q12h (±2h) ceftaroline infusions thus maintaining the blind.

The Sponsor or Clinical Research Organization will assign an unblinded monitor to confirm drug accountability.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken by the investigator or blinded study staff except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. If the blind is broken, the date, the time, and the reason must be documented /recorded via IVRS/IWRS and in any associated AE report. The investigator is responsible for ensuring this documentation is maintained and reports the action to AstraZeneca, without revealing the treatment given to the patient to the blinded AstraZeneca staff.

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

5.5 Treatments

5.5.1 Identity of investigational product(s)

5.5.1.1 Ceftaroline fosamil for injection

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 alkalising 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.

For IV administration, Ceftaroline fosamil for injection is constituted with 20.0 mL of sterile water for injection; the entire contents of the resulting solution are transferred to an infusion bag/bottle containing sterile sodium chloride 0.9% for dilution of the infusion. Please refer to the Pharmacy Manual for detailed information on study drug preparation.

5.5.1.2 Ceftriaxone for injection

Ceftriaxone for Injection is supplied as 1 g/vial (2 vials for a 2 grams dose) using commercially available material. Consult the local product information regarding administration, warnings, precautions and AEs reported with the use of ceftriaxone. Refer to the Pharmacy Manual for information regarding formulation and preparation of ceftriaxone.

Table 3 Investigational product

Investigational product	Dosage form and strength	Manufacturer
Ceftaroline fosamil	Powder for Intravenous Solution, 600 mg	
Ceftriaxone	Powder for Intravenous Solution, 1 g/vial	

5.5.2 Doses and treatment regimens

Patients are required to be hospitalised during treatment with study drug.

5.5.2.1 Ceftaroline fosamil

Patients randomised to ceftaroline fosamil will receive 600 mg IV q 12h (±2h), infused over 60 (±20) minutes for 5 to 7 days. To maintain study blinding, each 60-minute infusion will be divided into 2 sequential 30 (±10) min infusions containing 50% of the total dose. The individual infusion bags/bottles will be administered in immediate succession (see Table 4).

5.5.2.2 Ceftriaxone

Patients randomised to receive IV ceftriaxone will receive a dose of 2 g infused over 30 (±10) min immediately followed by IV saline placebo infused over 30 (±10) minutes, q24h (±2h) for

5 to 7 days. Twelve hours after each dose of ceftriaxone and saline placebo (ie, between ceftriaxone doses), patients in this group will receive two consecutive saline placebo infusions, each infused over 30 (±10) minutes q24h (±2 h). The ceftriaxone and saline placebo infusions will correspond to the q12h (±2h) infusions of ceftaroline, thereby maintaining the blind (see Table 4).

Table 4 Study Drug Dosing Overview in Patients with Normal Renal Function

Treatment Group	First Daily Dose		Second Daily Dose	
	Infusion 1 30 (± 10) min	Infusion 2 30 (± 10) min	Infusion 1 30 (± 10) min	Infusion 2 30 (± 10) min
Ceftaroline fosamil	Ceftaroline 300 mg	Ceftaroline 300 mg	Ceftaroline 300 mg	Ceftaroline 300 mg
Ceftriaxone	Ceftriaxone 2 g	Placebo	Placebo	Placebo

5.5.3 Dose Adjustment

5.5.3.1 Ceftaroline fosamil

At any time, (including Day 1), the dose of ceftaroline fosamil may be adjusted by unblinded pharmacy staff or unblinded study staff to 2 consecutive infusions of ceftaroline fosamil (200 mg) each infused over 30 min (±10 min) q12h (±2h) for patients with moderate renal impairment (30 mL/min $<CL_{CR} \leq 50$ mL/min), as estimated by the Cockcroft-Gault formula. At any time, the dose of ceftaroline fosamil may be readjusted to 2 consecutive infusions of ceftaroline fosamil (300 mg) each infused over 30 min (±10 min) q12h (±2h) when renal function improves (CL_{CR} >50 mL/min).

If, at any time a patient's estimated CL_{CR} is less than or equal to 30 mL/min during treatment contact the AstraZeneca study physician.

5.5.3.2 Ceftriaxone

It is not necessary to adjust the dose of ceftriaxone for patients with mild (50 mL/min $<CL_{CR} \leq 80$ mL/min) or moderate (30 mL/min $<CL_{CR} \leq 50$ mL/min) renal insufficiency.

If at any time a patient's estimated CL_{CR} is less than or equal to 30 mL/min during treatment, contact the AstraZeneca study physician.

5.5.4 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. Patient kit label text will be translated into local language.

The vial labels will be labelled with a minimum of the following information:

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

Please refer to the Pharmacy Manual for the information contained on the label attached to the infusion bag/bottle.

5.5.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions as indicated below. For additional information please refer to the Pharmacy Manual.

5.5.5.1 Ceftaroline fosamil

Vials of ceftaroline fosamil for injection dry mixture should be stored refrigerated at 2°C to 8°C until ready for use. Constituted and diluted ceftaroline fosamil IV infusion bags / bottles should be administered promptly. For additional storage information, please refer to the Pharmacy Manual.

5.5.5.2 Ceftriaxone

Ceftriaxone should be stored in accordance with local product information.

5.6 Concomitant and post-study treatment(s)

All antimicrobial and non-antimicrobial therapy administered within 4 weeks prior to baseline will be documented in the electronic case report form (eCRF). Patients who received systemic antimicrobial therapy (see Appendix F) for the treatment of the current CABP within 96 hours prior to study randomisation will be excluded from the study unless they meet the specific criteria delineated in Section 4.

Concomitant systemic antimicrobial agents are not permitted and their use, for any reason other than the patient being considered a treatment failure, must be discussed with the AstraZeneca study physician before administration.

The use of probenecid is not allowed within 3 days prior to dosing with study drug therapy or during the period of time encompassing administration of study drug therapy.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5.7 Treatment compliance

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

The blinded investigator or blinded medically qualified delegate will administer the blinded study drug and record the date, time, specific infusion number and volume infused, or check a box if the infusion was missed. This information will be verified by the blinded monitor at monitoring visits. This will assure treatment compliance.

All used (partially or completely infused) and unused infusions bags/bottles must be returned to the pharmacy. It is the responsibility of the blinded monitor to ensure these are returned, and the unblinded monitor to perform accountability.

5.7.1 Accountability

Study drug will be dispensed to, and administered by, the blinded investigator or blinded medically qualified delegate (as documented per local requirements in the CSA), by the unblinded site pharmacist or unblinded study staff. Records of study drug usage should include the identification of the person to whom the study drug was administered, the quantity and date of administration, and a record of unused or partially used study drug. The unblinded pharmacist or unblinded study staff is responsible for maintaining accurate study drug accountability records throughout the study. Each administration of study drug will be documented in the eCRF.

Additionally, it is the blinded investigator's responsibility to ensure that a process for handling blinded and unblinded study treatments is established. This includes but is not limited to:

- Deliveries of such products are correctly received by a responsible person (eg, pharmacist)
- Deliveries are recorded
- Study drug is handled and stored safely and properly
- Study drug provided for this study are used only as directed in the study protocol
- Appropriate unblinded study personnel and the unblinded study monitor account for all drugs received at the site, dispensed for the patient, and returned to the

pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved

- At the end of the study, after accountability has been performed and documented, site personnel account will arrange for appropriate destruction or return of all partially used or unused drugs to a designated facility or AstraZeneca for destruction. It must be possible to reconcile delivery records with records of study drug use and destroyed/returned stock. The unblinded pharmacist should sign certificates of delivery and return.

The drug accountability will be verified by AstraZeneca' s unblinded study monitor or designee during on-site monitoring visits. Infusion bags will be disposed of according to hospital regulations. Empty vials should be retained. Contents of the study drug containers must not be combined.

Refer to the Pharmacy Manual for additional information.

5.8 Discontinuation of investigational product

Patients may discontinue study drug at any time. Those patients who discontinue prematurely from the study treatment regimen should always be asked about the reason(s) and the presence of any AE(s). The EOT assessments should be performed on the last day the study treatment regimen is administered and all other visits occurring after the EOT should be performed, (see Table 1). AE(s) should also be followed, as appropriate (see Section 6.4.3 and 6.4.4).

The following reasons for premature discontinuation of study drug may include, but are not limited to:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Severe non-compliance to study protocol
- Safety
  - Occurrence of an AE that, in the opinion of the Investigator, warrants the patient' s permanent discontinuation from study drug therapy
  - Suspected or confirmed pregnancy (see Section 13.3) or nursing during the study drug administration period. Female patients whose pregnancy test is positive at the EOT visit must be followed through the immediate postnatal period or until termination of the pregnancy
  - Development of a clinically significant laboratory abnormality that requires discontinuation from study drug therapy.
- Insufficient therapeutic effect (see Section 5.8.1).

If a patient is withdrawn from the study, see Section 5.9.

5.8.1 Guidance to Investigators on When to End Study Drug Therapy

Patients who are improving clinically will receive at least 5 days but not more than 7 days of study drug therapy. Study drug therapy should continue until all signs and symptoms of the baseline infection have resolved or improved to such an extent that no further antimicrobial therapy is necessary. Prior to ending study drug therapy, the patients must:

- Be afebrile (temperature ≤ 38°C oral or ≤ 38.5°C rectally or tympanically) for at least 24 continuous hours, with temperature recorded twice daily

- Have had resolution of all signs and symptoms of CABP, or substantial improvement in signs and symptoms of CABP, such that the Investigator considers antibiotic therapy to be no longer required. Substantial improvement includes a return to pre-CABP baseline levels for patients with decreased pulmonary function (eg, patients with chronic obstructive pulmonary disease).

An insufficient therapeutic effect may be determined prior to the planned EOT visit. This determination will require an assessment of clinical status including the synthesis of symptoms and signs data (both local and systemic) and available laboratory data. Patients who are deemed to have an insufficient therapeutic effect should be considered treatment failures and discontinued from study drug therapy. For the purposes of this study, the following categories and guidelines are provided:

- Clinical Worsening: Patients who show systemic or local signs of clinical worsening may be prematurely discontinued from study drug therapy at any time. If the Investigator deems the benefit-to-risk ratio of continuing study drug therapy acceptable, administration of study drug for at least 48 hours is encouraged prior to discontinuation

- Lack of Clinical Progress: For patients who are stable, yet do not show signs of improvement, the Investigator is encouraged to continue study drug therapy for a minimum of 72 hours before such patients are considered clinical failures and prematurely discontinued from study drug

- Resistant Pathogen(s): In the event that an organism resistant to one or more of the potential study drugs is isolated, the Investigator will determine whether the patient remains on study drug therapy. The Investigator may decide to continue study drug therapy if, in his opinion, there is clear and continuing clinical improvement while on therapy, since the patient may be receiving a treatment to which the organism is susceptible. But, if it is the Investigator's opinion that the patient is not benefiting from the study drug, he may decide to prematurely discontinue study drug therapy and to initiate an alternative and appropriate therapy

5.9 Withdrawal from study

Patients may be withdrawn from the study (ie, investigational product and assessments) at the request of the Principal Investigator or Sponsor. Patients are also, at any time, free to withdraw from study (withdrawal of informed consent) without prejudice to further treatment. Patients should be encouraged to have all EOT assessments performed at the time of withdrawal. Such patients will always be asked about their reason(s) and the presence of AE(s). If possible, they will be seen and assessed by an investigator, and followed up for AE(s) (see Section 6.4.3 and 6.4.4).

Reasons for withdrawal from the study may include, but are not limited to:

- Withdrawal of informed consent
- Significant patient non-compliance, defined as refusal or inability to adhere to the clinical study protocol (CSP) requirements
- Investigator determines that it is in the best interest of the patient to withdrawal from the study due to reasons other than AE

Withdrawn patients will not be replaced.

6. COLLECTION OF STUDY VARIABLES

The investigator will ensure that data are recorded in a timely fashion on the eCRF as specified in the study protocol and in accordance with the instructions provided.

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 on the eCRFs 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. The investigator will sign the completed electronic Case Report Forms. A copy of the completed eCRFs will be archived at the study site.

6.2 Data collection and enrolment

Patients meeting selection criteria as specified in Section 4 are eligible to participate in the study. Each patient will undergo baseline procedures as outlined in Table 1 and Appendix H within 24 hours prior to administration of the first dose (Day 1) of study drug. Those patients meeting eligibility criteria will continue Day 1 - EOT, TOC and LFU visits, as appropriate. Procedures for these visits are identified in Table 1 and Appendix H.

6.3 Efficacy

6.3.1 Microbiological Assessments of CABP

6.3.1.1 Sputum Samples for Culture

Obtain adequate sputum samples for culture, Gram's staining, and susceptibility testing at baseline, during the study drug period (Study Day 1 up to Day 7) if medically indicated; at the EOT and TOC visits, if the patient is deemed a clinical failure or if medically indicated; and at the LFU visit if medically indicated and the patient is relapsing. Sputum samples are not obtained at the TOC or LFU visits if the patient was previously deemed a failure. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist), if medically indicated. Attempts to collect an adequate sputum sample may be repeated if appropriate. Perform culture and susceptibility testing at the local laboratory and send all isolates that are not contaminants (see list below) to the central laboratory for confirmation of organism identity and susceptibility.

The following organisms are considered sputum contaminants, rather than primary pathogens of CABP, and should not be sent to the central laboratory for confirmation of organism identity and susceptibility:

- Fungi (yeast and molds, eg, *Candida spp*. and *Aspergillus spp*.), unless there is evidence of a secondary fungal infection
- *Enterococcus spp*. or Group D *streptococci*
- *Viridans streptococci*
- *Coagulase-negative staphylococci*
- *Micrococcus spp*.
- *Neisseria spp.* other than *N. meningitidis* and *N. gonorrhoeae*
- *Corynebacterium spp*. and other coryneforms
- *Lactobacillus spp.*
- *Vibrio spp*.
- *Capnocytophaga spp*.
- *Cardiobacterium spp*.
- *Flavobacterium spp.*

Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests (to determine the MIC) and Clinical Laboratory Standards Institute (CLSI)

disk diffusion tests. Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of sputum cultures.

6.3.1.2 Pleural Fluid Samples for Culture

Obtain pleural fluid samples for culture, Gram's staining, and susceptibility testing as medically indicated during the study (from baseline to the EOT visit). When pleural fluid cultures are required, collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Perform culture and susceptibility testing at the local laboratory and send **all** isolates to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and Clinical and Laboratory Standards Institute CLSI disk diffusion tests. Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of pleural fluid cultures.

6.3.1.3 Blood Samples for Culture

Obtain blood for culture at baseline and as medically indicated from Study Day 1 to the TOC visit. Repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora). Obtain blood for culture at the LFU visit only if medically indicated and the patient is experiencing clinical relapse. Blood for culture is not obtained at the TOC or LFU visits if the patient was previously deemed a failure.

When blood cultures are required, obtain one aerobic bottle and one anaerobic bottle from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests.

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of blood cultures.

6.3.1.4 Blood Samples for Serology Testing

Obtain blood samples for serology testing for atypical pathogens at baseline and at the LFU visit.

6.3.1.5 Urine Samples for Antigen Testing

Obtain urine samples for *L. pneumophila* serogroup 1 and *S. pneumoniae* antigen detection at baseline. Results for the Legionella antigen test (a rapid in vitro immunochromatographic assay) must be available before enrolment (see Laboratory Manual). Patients with a positive Legionella antigen test at baseline should not be enrolled in the study.

6.3.2 Clinical Response Definitions

6.3.2.1 Clinical Response at the EOT and TOC Assessments

Clinical outcome assessments (see Table 5) will be made by the Principal Investigator at the EOT and TOC visits. Clinical response will be classified as cure, failure, or indeterminate based on clinical outcome. A favourable clinical response is "clinical cure". A clinical failure occurring at an earlier time point will be carried forward to the TOC visit.

Table 5 Clinical Response Assessments at the EOT and TOC Visits

Outcome	Definition
Clinical Cure	Total resolution of all signs and symptoms of pneumonia (ie, CABP), or improvement[a] to such an extent that further antimicrobial therapy is not necessary
Clinical Failure[b]	Any of the following: * Persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that requires alternative antimicrobial therapy * Treatment-limiting AE leading to discontinuation of the study treatment regimen, when patient required alternative antimicrobial therapy to treat the pneumonia * Death wherein pneumonia (ie, CABP) is considered causative
Indeterminate	Study data are not available for evaluation of efficacy, for any reason including treatment change prior to completing at least 48 hours of the study treatment regimen; death wherein pneumonia is clearly non-contributory, lost to follow-up, or extenuating circumstances preclude classification as a cure or failure

[a] Clinical improvement includes the absence of fever (temperature ≤38°C oral or ≤38.5°C rectally or tympanically) for at least 24 continuous hours, with temperature recorded twice daily, in addition to a substantial improvement in signs and symptoms of CABP. Substantial improvement includes a return to pre-CABP baseline levels for patients with decreased pulmonary function (eg, patients with chronic obstructive pulmonary disease).

[b] Clinical failures at EOT are carried forward to TOC.

6.3.2.2 Assessment of Clinical Relapse at the LFU Visit

Patients who were considered clinically cured at the TOC assessment will be reassessed at the LFU visit for evidence of continuing favourable response (no relapse). Patients with relapse of signs and symptoms of pneumonia (eg, new or increased cough, increased sputum production, purulent sputum or change in sputum character, dyspnoea, tachypnea, hypoxemia, auscultatory findings consistent with pneumonia, pleuritic chest pain) that require additional

antimicrobial therapy will be considered to have relapsed. Patients for whom data are unavailable at LFU will be assigned an "Indeterminate" response.

6.3.3 Radiographic Response Definitions

Radiographic outcome assessments (see Table 6) will be made at TOC and LFU visits, as outlined in the Schedule of Assessments (see Table 1). The TOC and LFU radiographic evaluations should be performed using the same modality (CXR or chest CT scan) as the baseline evaluation. Interpretation of radiographic studies and preparation of the radiographic report should be performed by an appropriately qualified (ie, certified or licensed according to applicable regional requirements) radiologist according to procedures outlined in Appendix E. Investigators will use the radiographic report as the basis for assigning the outcome as a radiographic success, failure, or indeterminate.

Table 6 Radiographic Outcome Categories

Outcome	Definition
Radiographic Success	CXR or chest CT scan is resolved, improved, or stable compared to the baseline CXR or CT scan.
Radiographic Failure	CXR or chest CT scan has unequivocally worsened compared to the baseline CXR or CT scan.
Indeterminate	CXR or CT scan not performed, missing, or cannot be adequately interpreted to determine an outcome.

6.3.4 Microbiological Response Definitions

6.3.4.1 Per-Pathogen Microbiological Response

A microbiological outcome at the TOC visit will be determined in the mMITT and ME populations for each pathogen isolated at baseline (see

Table 7). Microbiological outcome categories are eradication, presumed eradication, persistence, presumed persistence, and indeterminate, as defined in the table below. Favourable microbiological outcomes are eradication or presumed eradication. Unfavourable microbiological outcomes are persistence or presumed persistence.

Table 7 Microbiological Outcome Categories

Outcome[a]	Definition	
Favourable	Eradication	An adequate source specimen[b] demonstrates absence of the original baseline pathogen.
	Presumed eradication	An adequate source specimen[b] was not available to culture and the patient was assessed as a clinical cure.
Unfavourable	Persistence	Source specimen demonstrates continued presence of the original baseline pathogen.
	Presumed persistence	An adequate source specimen[b] was not available to culture and the patient was assessed as a clinical failure.
Indeterminate	Indeterminate	An adequate source specimen[b] was not available to culture and the patient's clinical response was assessed as indeterminate.

[a] The microbiological outcomes at TOC are only applicable to patients who are not clinical failures at EOT. Patients who are failures at EOT will have the corresponding microbiological outcome determined from EOT cultures and carried forward to TOC. If no EOT culture is available for patients who are clinical failures at EOT, then the microbiological outcome at TOC will be presumed persistence. Otherwise, the microbiological outcome at TOC will be determined from cultures obtained at the TOC visit window. If no culture is available in the TOC window then the microbiological outcome at TOC will be presumed from the clinical response (see Table 5) at TOC.

[b] An adequate source specimen is defined as any sample that may yield the growth of a CABP pathogen eg, blood, respiratory specimens, or pleural fluid.

Note: For the special case of pneumococcal infection identified via a urinary antigen test only, the microbiological outcome will always be presumed from the clinical outcome (see Table 5), unless a post-baseline respiratory culture is positive for *Streptococcus pneumoniae,* in which case the microbiological outcome will be persistence. For patients with co-infection with an atypical, the outcome for atypical pathogens will be presumed from the clinical response (see Table 5).

6.3.4.2 Per-Patient Microbiological Response

Per-patient microbiological response at the TOC visit will be determined in the mMITT and ME Populations based on individual outcomes for each baseline pathogen. In order for a patient to have a favourable microbiological response, the outcome for each baseline pathogen must be favourable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavourable (persistence or presumed persistence), the patient will be considered to have an unfavourable microbiological response.

6.3.4.3 Microbiological Categories for Pathogens Identified After Baseline Assessment

Microbiological categories for pathogens identified after the baseline assessment are super-infection, new infection, colonization, and re-infection or recurrence, as defined in Table 8.

Table 8 Categorization of Bacterial Pathogens Identified After Baseline Assessment

Super-infection	Isolation of a new pathogen(s) (other than the original baseline pathogen(s)) during the period up to and including EOT from cultures of the original CABP, or a new CABP at the same site, regardless of susceptibility to study drugs, in a patient who has signs and symptoms of infection requiring alternative antimicrobial therapy.
New Infection	Isolation of a new pathogen (other than the original baseline pathogen) determined at TOC or LFU regardless of susceptibility to study drugs, in a patient who has signs and symptoms of infection requiring alternative antimicrobial therapy
Colonization	Isolation of an organism from the original CABP site that is not associated with signs and symptoms of active infection and does not require antimicrobial therapy. Colonization will be determined only at EOT and TOC when an assessment of clinical response is performed.
Microbiologic re-infection or recurrence	Isolation of a baseline pathogen from the original CABP site, at the LFU visit, in patients who had favourable clinical and microbiological responses at TOC. To be defined as a recurrent infection, pathogens must be associated with emergence or worsening of clinical signs and symptoms, with or without laboratory evidence of active infection, and require antimicrobial therapy.

6.3.5 Overall Clinical and Radiographic Response Definition

Overall response (clinical and radiographic response, see Table 5 and Table 6) will be determined at the TOC visit. It will be classified as 'success' or 'failure' with an overall favourable response, 'success', defined as clinical cure and either radiographic success or radiographic indeterminate.

6.4 Safety

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

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition from the signing of the informed consent, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, 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. AEs may also include complications that occur as a result of protocol mandated procedures and distinguished as such.

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, 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 patient 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.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period up to and including the TOC visit. SAEs will be collected from time of signature of informed consent throughout the treatment period up to and including the LFU visit.

Follow-up of unresolved adverse events

Any AE(s) that is unresolved at the LFU visit is 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 patient 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)
- Date and time when the AE started and stopped
- Intensity (rating scale for in-patients)
  - Mild (awareness of sign or symptom, but easily tolerated)
  - Moderate (disturbing but still tolerable)
  - Severe (intolerable)
- 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 patient's withdrawal from study (yes or no)
- Outcome.

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

- 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

- Causality assessment in relation to Additional Study Drug
- 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 6.4.2. 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.

Additional information will be requested and collected when an AE of seizure, haemolytic anaemia, acute renal failure and DILI(drug-induced liver injury) is reported, irrespective of seriousness. For Cases of Potential Hy's Law (increase in both AST or ALT ⩾3xULN and total bilirubin ⩾2xULN), additional information will be requested and collected.

Intolerability of the Study Treatment

All AEs that, in the opinion of the Investigator, may represent intolerance of the study treatment and/or their administration must be marked as such on the AE eCRF. In general, these events will be temporally related to the study treatment. Examples of possible systemic reactions representing intolerability of the study treatment are fever, flushing, or nausea temporally related to the study treatment. Examples of local infusion site reactions are erythema, pain, induration swelling, or phlebitis at the infusion site. These systemic and local reactions must be recorded in the AE eCRF. For local reactions the investigator will distinguish those AEs which are related to mechanical infusion malfunction and/or administration technique from those which are related to the administration of the study treatment itself and recorded as such on the eCRF.

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, including comparator, 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.

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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of

signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests 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 (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the Investigational Product (IP) is being studied. It may be an increase in the severity of the disease under study (DUS) and/or increases in the symptoms of the disease. Any event or extended hospitalisation that is unequivocally due to disease progression must not be reported as an SAE unless it is believed that the study drug actively contributed to the progression of the disease (ie, not by way of insufficient therapeutic effect). Insufficient therapeutic effect will be captured as an efficacy outcome. Instances of, or discontinuation due to insufficient therapeutic effect (ie, lack of efficacy) should not be collected as AEs.

6.4.4 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 inform appropriate AstraZeneca representatives (see Table 11) within one day ie, immediately but **no later than the end of the next business da**y of when he or she becomes aware of it.

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

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives (see Table 11) of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

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 (see Table 11).

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

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in Table 1.

See Appendix G for the laboratory variables that will be measured and Section 7.1 for blood volume.

6.4.6 Physical examination

Physical examinations will be performed according to the schedule specified in Table 1 and Appendix H.

A complete physical examination will be performed at baseline and include an assessment of the following:

- General appearance, including skin and measuring your height and weight
- Resting vital signs, including heart rate, blood pressure (after in a supine position for 5 min), respiratory rate, and temperature (oral, rectal or tympanic)
- Head and neck (including ears, eyes, nose and throat)
- Lymph nodes
- Thyroid
- Musculoskeletal / extremities, including spine
- Cardiovascular system
- Lungs

- Abdomen,
- Neurological systems.

A brief physical examination will be performed on Day 3 (±1 day), EOT and LFU and include the following:

- General appearance, including skin
- Resting vital signs, including heart rate, blood pressure (after in a supine position for 5 min), respiratory rate, and temperature (oral, rectal or tympanic)
- Cardiovascular system
- Lungs
- Abdomen

6.4.7 ECG

Standard 12-lead ECGs will be recorded and assessed according to the schedule in Table 1. ECGs should be standard 12-lead ECG with a lead II rhythm strip, covering at least 5 complexes in the supine position after the patient has rested in this position for 5 minutes.

6.4.8 Vital signs

6.4.8.1 Respiratory rate, pulse and blood pressure

Resting vital signs, including heart rate and blood pressure (measured after in a supine position for 5 min) and respiratory rate, will be assessed using non-invasive equipment after the patient has been at rest for 5 minutes in a supine position according to the schedule specified in Table 1.

6.4.8.2 Body temperature

Body temperature (oral, rectal or tympanic) will be measured in degrees Celsius according to the schedule specified in Table 1. The highest temperature in the morning and again in the afternoon will be recorded while the patient is receiving study drug.

6.5 Resource Use

Patients date of discharge and ICU admission status will be collected at the LFU visit. Length of stay will be calculated as date of discharge minus date of informed consent + 1.

6.6 Patient Reported Symptoms

Patient reported symptoms will be collected utilising the CAP-SYM 18 questionnaire (see Appendix I), which has been shown to be a practical, scientifically sound and

psychometrically validated patient based outcome measure of CAP-related symptoms (Lamping D et al 2002).

The questionnaire should be administered at visits described in Table 1.

Paper versions of the CAP-SYM 18 questionnaires will be administered via an interview format by an appropriate health care professional. The CAP-SYM 18 should be administered before any investigations or discussions about their disease with the clinic staff. The patient should be reminded that there are no right or wrong answers and the interviewer should read the questions exactly as written on the questionnaire. Under no circumstances should help be given in interpreting the questions or in selecting responses. Study staff should record the reason for non-compliance of patients who could not or refused to complete questionnaires.

Translations of questionnaires will be provided in relevant languages. Where a questionnaire version is not available in a patient's first language, they will not be expected to complete the questionnaire and this reason for non-completion should be recorded.

6.7 Optional Pharmacokinetics sub-study

6.7.1 Collection of samples

Approximately 200 patients will participate in the optional PK sub-study. Blood samples (5 mL) for determination of ceftaroline, ceftaroline fosamil, ceftaroline M-1 and possibly ceftriaxone concentrations in plasma will be taken at the times presented in the Schedule of assessments (see Table 1) and the PK sample schedule (see Table 2).

Blood samples will be collected into chilled sodium heparin tubes, and then centrifuged immediately in a refrigerated centrifuge to separate the plasma. Plasma will be transferred into prepared and chilled test tubes and immediately frozen at -70°C or below.

Detailed instructions on how to collect, label, store, and ship plasma PK samples will be described in a separate Laboratory Manual. It is very important that the time and date of each PK sample collection as well as the start and stop times of Infusions 1 and 2 for the PK sampling daily dose on Day 3 are recorded in the eCRF.

For blood volumes see Section 7.1.

6.7.1.1 Determination of drug concentration

Samples for determination of ceftaroline, ceftaroline fosamil, ceftaroline M-1 and possibly ceftriaxone in human plasma will be analysed by a Contract Research Organization (CRO) 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 may be conducted on the biological samples to further investigate reproducibility of incurred samples. Any results from such analyses will be included in the bioanalytical study contribution report.

Selected plasma samples from this study may be retained for possible future analysis of metabolites. The outcome of any analysis will be reported in a separate study and the results will not affect the outcome or be referred to as part of this study.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 9 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical Chemistry[a]	4.5	8[b]	36
	Haematology[c]	2.0	8[b]	16
Direct Coomb's test		2	3	6
C-Reactive Protein		2	2[b]	4
PT/INR, PTT		1.8	4	7.2
Arterial Blood Gas (ABG)[d]		2-4	[d]	[d]
Serology		2	4[b]	8
Blood for Culture[e]		5/sample	4	20
Total				97.2[f]
Pharmacokinetic samples (optional)		5	4	20
Total with optional PK				117.2[f]

[a] Includes haptoglobin
[b] Duplicate samples for local and central laboratory
[c] Includes reticulocyte, RDW, MCV
[d] ABG is taken only as medically indicated
[e] Additional sample will be obtained if previous blood culture was positive or as medically indicated
[f] Additional sample may be required as medically indicated

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses.

7.2.1 Pharmacokinetic samples

Plasma samples will be analysed and stored within the established stability period of the validated method(s).

7.3 Labelling and shipment of biohazard 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 patient 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 at each centre keeps full traceability of collected biological and PK samples from the patients 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 optional PK samples

If a patient withdraws consent to the use of optional PK 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 PK samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator will ensure:

- Ensures patients' withdrawal of informed consent to the use of optional PK samples is notified immediately to AstraZeneca
- Ensures that optional PK samples from that patient, 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 optional PK samples are

disposed/destroyed, the action documented and the signed document returned to the study site

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

AstraZeneca ensures the biobank or central laboratory(ies) holding the optional PK samples is/are informed about the withdrawn consent immediately and samples that have not yet been analysed 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 Patient 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 patients. 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 patient into the study.

The Ethics Committee should approve all advertising used to recruit patients 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 patient 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.

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

8.4 Informed consent

The Principal Investigator(s) at each centre will:

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

The PK component of this study is optional. An optional PK informed consent form (ICF) must be signed and dated by each patient to allow participation. The above criteria also pertains to the PK ICF.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating 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 by the national regulatory authority, 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 patient 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 patients 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 patient 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 Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

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

9.3 Monitoring of the study

To maintain blinding of the study drug, during the study, both blinded and unblinded AstraZeneca representatives will have regular contacts with the study site.

The blinded AstraZeneca representative will:

- Provide information and support to the investigator(s)
- Confirm that facilities and staff remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the clinical chart and the eCRFs, including the data entry of and responses to queries issued, and that biological samples are handled in accordance with the Laboratory Manual
- Perform source data verification (SDV), (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's optional pharmacokinetic samples is reported and these samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The unblinded AstraZeneca representative will verify study drug accountability from receipt of study drug through declaration of clean file and data base lock (see Section 5.7.1).

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

9.3.1 Source data

It is a prerequisite of this study that the study monitor has direct access to source data for data verification.

9.4 Study agreements

The Investigator at each/the centre 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 patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

9.4.1 Archiving of study documents

An electronic copy of the eCRF will be provided to the investigational site after the study database has been locked and will be archived at the investigational site as 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 patient undergoing the study'.

The study is expected to start in 3Q2011 and to end by 1Q2013.

The study may be terminated at individual centres 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 ASTRAZENECA DATA MANAGEMENT CENTRE (DMC)

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry.

Data management will be performed by DMC. The data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed /queried and updated as needed. Data queries will be raised for inconsistent, impossible or missing data and must be resolved in a timely manner. Clean file occurs when all data have been declared clean and signed by the investigator. The data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Dictionary coding

Adverse Events and medical/surgical history will be classified according to the terminology of the most current version of Medical Dictionary for Regulatory Activities MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at DMC.

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). Data Management will ensure that the data collection tool (eg, eDiary, IVRS/IWRS etc) will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced from the clinical database 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 efficacy variable(s)

See Section 6.3

11.2 Calculation or derivation of safety variable(s)

See Section 6.4

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 Discontinued due to Adverse Events (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.

11.3 Calculation or derivation of pharmacokinetic variables

Individual pharmacokinetic parameters for Asian CABP patients will be derived via a population modelling approach. The ceftaroline concentration, patient demographic, disease

status data, etc, in Asian PK sub-study will be combined with the data used to develop the population PK model in CABP patients in previous clinical programs to form a new data set. The previously developed population PK model will be re-evaluated with the new data set by re-estimating the model parameters, backward elimination of the previously elected covariates and forward selection of the potential significant covariates for the updated data set.

Individual compartmental PK parameters for patients with ceftaroline plasma concentration available will be calculated by the empirical Bayesian estimate, and individual non- compartmental PK parameters, C_{max}, C_{min}, $AUC_{(0\text{-}12hr)}$ and $t_{½}$ will be derived from the predicted ceftaroline concentration time courses. All the derived PK parameters will be descriptively summarized. A separate population PK modelling analysis plan will be prepared and the PK results will be reported separately.

Ceftriaxone plasma concentrations may be analysed by a similar population PK modelling and the results may be reported separately.

11.4 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

A PK/PD target analysis in Asian CABP patients may be conducted by appropriate methods based on the exposure derived from the population PK model and clinical or microbiological response. The PK/PD relationship between clinical or microbiological response and magnitude or success/failure to achieve the PK/PD target, individual demographic factors, disease status, etc, may be analysed by a multivariable logistic regression analysis. A simulation of probability of target attainment may also be conducted. A separate data analysis plan may be prepared, and the results may be reported separately if a PK/PD target analysis can be performed.

11.5 Calculation or derivation of health economic variable

See Section 6.5.

11.6 Calculation of CAP-Symptom 18 variables

See Section 6.6

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

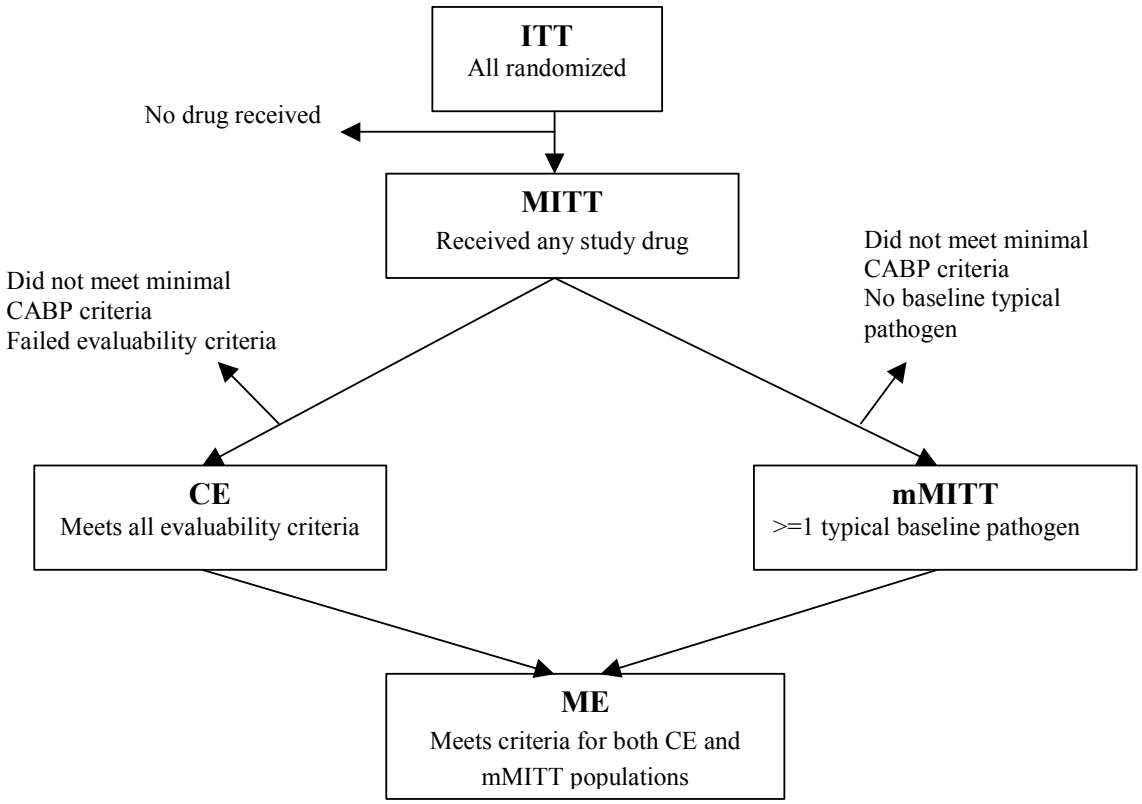
12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The following figure shows the relationship among efficacy analysis sets graphically.

Figure 2 Efficacy analysis sets

The detailed definition of each efficacy analysis set is described as below.



12.1.1.1 Intent-to-Treat (ITT) Population

The ITT Population will consist of all randomised patients. A patient is considered randomised when the Pharmacist or Pharmacist's designee receives the IVRS/IWRS-generated patient number.

12.1.1.2 Modified Intent-to-Treat (MITT) Population

The MITT Population will consist of all randomised patients who receive any amount of study drug.

12.1.1.3 Microbiological Modified Intent-to-Treat (mMITT) Population

The mMITT Population will be a subset of the MITT Population and will include patients for whom at least one "typical" bacterial pathogen has been isolated from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid) and urinary antigen testing and who meet the minimal disease criteria for CABP. Patients with *M. pneumoniae* or *C. pneumoniae* or *L. pneumophila* as the sole causative pathogen of infection will be excluded from the mMITT Population.

12.1.1.4 Clinically Evaluable (CE) Population

The CE Population will be a subset of the MITT Population and will include patients who meet the minimal disease criteria for CABP and all evaluability criteria, including patients

who received at least the pre-specified minimal amount of the intended-dose and duration of study drug therapy, for whom sufficient information regarding the infection is available to determine the patient's outcome, and for whom there are no confounding factors that interfere with the assessment of that outcome; patients with an atypical pathogen as a sole causative pathogen of the infection will be excluded from the CE Population.

In addition to meeting the above criteria, patients must meet the following specific conditions:

- At least 48 hours of study drug therapy received in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE
- At least 72 hours of study drug therapy received in order to be considered an evaluable clinical cure
- At least 80% of the intended doses of study drug therapy received. Compliance is determined as the total number of received doses divided by the total number of intended doses based on the first and last date and time of study drug administration
- Clinical response assessment at TOC (8 - 15 days after EOT), or a clinical failure at EOT or at any time up to 15 days after EOT is allowed. For patients who died a 28 day window up to and including 28 days after EOT is allowed
- A patient with an indeterminate response at TOC is not included in the CE population unless the reason for the indeterminate response is "Death where CABP is non causative"
- Did not receive more than one dose of an alternative (non-study) systemic antimicrobial that was potentially effective for the treatment of CABP, for a reason other than treatment failure.

12.1.1.5 Microbiologically Evaluable (ME) Population

The ME Population includes patients who meet criteria for both the CE (Section 12.1.1.4) and mMITT (Section 12.1.1.3) Populations.

At the TOC visit, the Principal Investigator will collect a microbiology specimen from blood, sputum, and pleural fluid samples only if medically indicated. Hence, many or most patients will not have a TOC microbiology specimen available for analysis. If a suitable specimen cannot be collected, the per-pathogen microbiological outcome will be "presumed eradicated" or "presumed persistent" based on the clinical response.

12.1.2 Safety analysis set

The MITT population will be used to summarise safety data, ie, patients who received at least one dose of randomised investigational product, (ceftaroline fosamil, ceftriaxone) and for whom any post-dose data are available. Throughout the safety results sections, erroneously

treated patients (eg, those randomised to treatment ceftaroline fosamil but actually received ceftriaxone) will be accounted for in the actual treatment group received.

12.2 Methods of statistical analyses

Inferential statistical analyses as specified will be conducted and all comparisons will be between the ceftaroline and ceftriaxone groups. Two-sided 95% confidence intervals will be constructed for assessment of non-inferiority and a two-sided alpha level of 0.05 will be used for significance; no adjustment will be made for multiple comparisons. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided. Listings of individual patients' data will also be produced. A comprehensive SAP will be prepared and finalized prior to unblinding and analysis of the data.

12.2.1 Analysis of study population and patient characteristics

Enrolment, protocol deviations, and discontinuations from the study will be summarized by treatment group. Protocol deviations are defined as any variation from the protocol including enrolment of a patient who did not meet all inclusion and exclusion criteria, and failure to perform the assessments and procedures within the required time frame. Important deviations will be summarised by treatment group.

Demographics (age, race, gender), medical and surgical history, PORT Risk Class, baseline assessment of the clinical symptoms and signs of CABP, microbiological assessment of blood, sputum, and pleural fluid specimens, and administration of study treatment will also be summarized.

12.2.2 Efficacy analyses

12.2.2.1 Primary efficacy endpoints

The primary objective of this study is to determine the non-inferiority in the clinical cure rate for ceftaroline compared to that for ceftriaxone at the TOC visit in the CE Population in adult patients with CABP. A two-sided 95% confidence interval (CI) for the observed difference in the cure rate (ceftaroline group minus ceftriaxone group) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI. This method corresponds to the expanded Farrington-Manning test (Farrington CP and Manning G 1990) for stratified designs with Cochran-Mantel-Haenzel weights. Non-inferiority of ceftaroline will be concluded if the lower limit of the 95% CI is -10% or higher.

If the clinical cure rates for ceftaroline are higher than that seen in ceftriaxone group and non-inferiority has been established in CE Population, a test of superiority will be conducted in the CE and MITT populations. Superiority of ceftaroline will be concluded if the two-sided p-value is less than 0.05.

An additional assessment of the treatment group-by-district interaction on the primary efficacy outcome measure will be performed descriptively. The primary efficacy measure will be summarised by treatment group and district.

12.2.2.2 Secondary efficacy endpoints

For each secondary efficacy outcome measure listed in Table 10, a two-sided 95% CI for the difference between cure, success and favourable outcome rates (ceftaroline minus ceftriaxone) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985) Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Patient Clinical Cure Rate at the TOC Visit in the MITT, mMITT and ME Populations

The per-patient clinical cure rate at the TOC visit in the MITT and mMITT Populations will be determined as:

$$\frac{\text{Number of patients with outcome=clinical cure}}{\text{(Number of patients with clinical cure + Number of patients with clinical failure + Number of patients with indeterminate)}}$$

By definition, patients in the ME Population must have sufficient information for the determination of clinical outcome. Thus, the per-patient clinical cure rate in the ME Population is defined as:

$$\frac{\text{Number of patients with clinical cure}}{\text{(Number of patients with clinical cure + Number of patients with clinical failure)}}$$

The number and percentage of patients classified as clinical cure, clinical failure, or indeterminate (by definition, indeterminates are excluded from the ME population) will be tabulated for both treatment groups.

A two-sided 95% CI for the difference in clinical cure rates (ceftaroline minus ceftriaxone) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Patient Clinical Cure Rate at the EOT Visit in the MITT and CE Populations

The per-patient clinical cure rate at the EOT visit in the MITT and CE Populations will be determined to support the findings at the TOC visit. The number and percentage of patients classified as clinical cure, clinical failure, or indeterminate (by definition, indeterminates are excluded from the CE Population) will be tabulated for both treatment groups.

A two-sided 95% CI for the difference in clinical cure rates (ceftaroline minus ceftriaxone) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Patient Microbiological Favourable Outcome Rate at the TOC Visit in the ME and mMITT Populations

Per-Patient Microbiological Response in the ME Population

This efficacy analysis will be conducted in the ME Population, which by definition excludes patients with indeterminate responses (see Section 12.1.1.5). Per-patient responses at the TOC visit will be based on per-pathogen outcomes for each pathogen isolated at baseline (see Section 6.3.4.2). Microbiological outcome categories are eradication, presumed eradication, persistence and presumed persistence, as defined in

Table 7.

Favourable microbiological outcomes are eradication or presumed eradication. Unfavourable microbiological outcomes are persistence or presumed persistence. To have an overall favourable microbiological response, the outcome for each baseline pathogen must be favourable. The proportion of patients with an overall favourable microbiological response will be defined as:

$$\frac{\text{Number of patients with eradication + Number of patients with presumed eradication}}{\text{(Number of patients with eradication + Number of patients with presumed eradication + Number of patients with persistence + Number of patients with presumed persistence)}}$$

The number and percentage of patients in each treatment group recorded as having a favourable (eradication or presumed eradication) and unfavourable (persistence or presumed persistence) microbiological response will be tabulated.

A two-sided 95% CI for the difference in overall favourable microbiological response (ceftaroline minus ceftriaxone) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Patient Microbiological Response in the mMITT Population

This analysis will be used to support the favourable outcome of microbiological response (eradication or presumed eradication) in the ME Population. The microbiological response for the mMITT Population will be reported at the TOC visit. Per-patient responses will be based on per-pathogen outcomes for each pathogen isolated at baseline (see Section 6.3.4.2). Microbiological outcome categories are eradication, presumed eradication, persistence and presumed persistence, as defined in

Table 7.

Favourable microbiological outcomes are eradication or presumed eradication. Unfavourable microbiological outcomes are persistence or presumed persistence. To have an overall favourable microbiological response, the outcome for each baseline pathogen must be favourable. If the only outcome available is indeterminate (or both EOT and TOC assessments

are missing), the final outcome for the patient will be considered indeterminate. Superinfections will not be considered in the microbiological response. The proportion of patients with an overall favourable microbiological response will be defined as:

$$\frac{\text{Number of patients with eradication + Number of patients with presumed eradication}}{\text{(Number of patients with eradication + Number of patients with presumed eradication + Number of patients with persistence + Number of patients with presumed persistence + Number of patients with Indeterminate)}}$$

The number and percentage of patients with favourable responses (eradication or presumed eradication), unfavourable (persistence or presumed persistence) or indeterminate will be tabulated for both treatment groups.

A two-sided 95% CI for the difference in overall favourable microbiological response (ceftaroline minus ceftriaxone) will be computed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Patient Overall Success Rate at the TOC Visit in the CE and MITT Populations

The overall response will be assessed programmatically by combining the clinical response with the radiographic response. To be an overall success the patient must be deemed a clinical cure and either a radiographic success or radiographic indeterminate.

The per-patient overall success rate at the TOC visit in the CE and MITT Populations will be determined. The number and percentage of patients classified as overall success or overall failure will be tabulated for both treatment groups.

Two-sided 95% CI for the difference in overall response rates (ceftaroline minus ceftriaxone) will be constructed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Pathogen Clinical Cure Rate and Microbiological Success Rate at the TOC Visit in the mMITT and ME Populations

Clinical response by baseline pathogen will be determined as the proportion of patients with a clinical cure for each pathogen isolated at baseline. The number and percentage of mMITT and ME Populations in each treatment group recorded as a clinical cure, clinical failure, and indeterminate (see Section6.3.2) will be tabulated per baseline pathogen. Two-sided 95% CIs for the difference in clinical cure rate per baseline pathogen will be derived where deemed appropriate.

Microbiological response by baseline pathogen will be determined as the proportion of patients with a favourable microbiological response (eradication or presumed eradication) for each pathogen isolated at baseline. The number and percentage of mMITT and ME Populations in each treatment group recorded as having a microbiologically favourable (eradication or

presumed eradication), unfavourable (persistence or presumed persistence), or indeterminate outcome (see Section 6.3.4.1) will be tabulated per baseline pathogen. Two-sided 95% CIs for the difference in microbiological response rate per baseline pathogen will be derived where deemed appropriate.

Per-Patient Clinical Relapse Rate at the LFU Visit

This analysis will be performed in the subset of patients in the CE Population who were a clinical cure at the TOC visit. The number and percentage of patients in each treatment group that have relapsed at the LFU visit will be tabulated.

Two-sided 95% CI for the difference in relapse rates (ceftaroline minus ceftriaxone) will be constructed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Per-Patient Microbiological Re-infection/Recurrence Rate at the LFU Visit

This analysis will be performed in the subset of patients in the ME Population who had a favourable microbiological outcome at the TOC visit. The number and percentage of patients in each treatment group that have a re-infection or recurrence at the LFU visit will be tabulated.

Two-sided 95% CI for the difference in re-infection/recurrence rates (ceftaroline minus ceftriaxone) will be constructed using the method proposed for stratified designs by Miettinen and Nurminen (Miettinen O et al 1985). Cochran-Mantel-Haenzel weights will be used for the stratum weights (defined by district) in the calculation of the CI.

Table 10 Secondary Efficacy Endpoints

Population	Subset(s)	Assessment	Per-patient Evaluation	Outcomes
MITT, mMITT and ME		TOC	Clinical response	Cure Failure Indeterminate (MITT and mMITT)
MITT and CE		EOT	Clinical response	Cure Failure Indeterminate (MITT only)
mMITT and ME		TOC	Microbiological response	Favourable: eradication or presumed eradication Unfavourable: persistence, presumed persistence, or indeterminate (mMITT only)

Population	Subset(s)	Assessment	Per-patient Evaluation	Outcomes
MITT and CE		TOC	Overall response	Success: clinical cure and either a radiographic success or radiographic indeterminate Failure: either clinical failure or clinical indeterminate, or radiographic failure
mMITT and ME	Per pathogen	TOC	Clinical response	Cure Failure Indeterminate (mMITT only)
mMITT and ME	Per pathogen	TOC	Microbiological response	Favourable: eradication or presumed eradication Unfavourable: persistence, presumed persistence, or indeterminate (mMITT only)
CE	Clinically cured at TOC	LFU	Clinical response	Continued response Relapse
ME	Micro-biologically favourable outcome at TOC	LFU	Microbiological re-infection / recurrence	No re-infection or recurrence Re-infection or recurrence

12.2.3 Pharmacokinetic data

In the PK sub-group, plasma concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 will be summarized using the descriptive statistics (number of patients, geometric mean, coefficient of variation (CV), arithmetic mean, standard deviation (SD), median, minimum and maximum).

The derived PK parameters (C_{max}, C_{min}, $AUC_{(0\text{-}12hr)}$ and $t_{½}$) will be summarized for each treatment group using the descriptive statistics (number of patients, geometric mean, coefficient of variation (CV), and reported in a separate population PK report.

12.2.4 Safety analyses

The safety analysis will be performed using the MITT Population. Safety parameters include adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiogram (ECG) parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses. No inference will be made for safety analysis. Throughout the safety results sections, erroneously treated

patients (eg, those randomised to treatment ceftaroline but actually received ceftriaxone) will be accounted for in the actual treatment group received.

12.2.4.1 Exposure of treatment

The treatment period in this study is defined for 5 to 7 days. The numbers and percentages of patients in each treatment group that took investigational product for 5, 6 and 7 days, respectively, will be tabulated.

12.2.4.2 Adverse events

All AEs will be classified by system organ class and by preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®) and those that occurred at baseline and after administration of the investigational products will be summarised in separate lists. AEs occurred after administration of the investigational products will be classified by system organ class and by preferred term using MedDRA independently for each treatment group. Data on drug-related AEs will be collected in the same manner, as required. The number of patients who developed AEs, drug-related AEs, SAEs, AEs that led to withdrawal from the study and other significant AEs will be summarised for each treatment group.

12.2.4.3 Laboratory tests

Quantitative data of laboratory tests will be summarised for each of the two treatment groups using descriptive statistics, and qualitative data will be summarised using frequency table.

Results of laboratory tests will be categorized based on normal limits and clinically significant results, defined by normal limits and percent change from baseline. Shift tables will be provided and the number and percentage of patients with a clinically significant result will be tabulated. Box plots of selected laboratory tests by treatment group and time point may also be provided.

12.2.4.4 Vital signs

Descriptive statistics of vital signs at each time point measured, as well as the change from baseline, will be presented for each treatment group.

12.2.4.5 ECG

The number and percentage of patients in each treatment group that have normal or abnormal result at each time point will be tabulated.

12.2.5 Health Economics and Outcomes Research (HEOR)

Length of hospital stay (LOS) and ICU admission will be summarised by treatment outcome at TOC visit (“clinical cure” versus “clinical failure”).

HEOR data will be analysed in the CE patient population. “Treatment successes” will consist of those patients who are assessed as having an outcome of “clinical cure” (as defined in Section 6.3.2.1) at TOC visit. Treatment failures will consist of those patients who are

assessed as having an outcome of "clinical failure". The methods of these analyses will be fully described in a separate analysis plan and the results will be reported separately.

12.2.6 Patient-based symptom assessments

The CAP-SYM 18 questionnaire has been shown to be a practical, scientifically sound and psychometrically validated patient based outcome measure in a cohort of CAP patients (Lamping D et al 2002). The resolution of patient-based symptoms will be explored and assessed across treatment arms using appropriate statistical methods. These methods will be fully described in a separate analysis plan and the results will be reported separately.

12.2.7 Interim analyses(Not Applicable)

12.3 Determination of sample size

Assuming a point estimate for the clinical cure rate of 85% in the ceftriaxone treatment group, and 85% in the ceftaroline group in the CE population, a non-inferiority margin of 10%, a power of 90%, and a 77.5% evaluability rate, a total sample size of 692 patients is required (346 patients in each treatment group).

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 6.4.4

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

Table 11 Medical Emergency and AstraZeneca Contact Information

13.2 Overdose

Use of study medication in doses in excess of that specified in the protocol is considered an overdose.

In the event of a study drug overdose general supportive treatment will be given as necessary.

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

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within 1 day**, (ie, immediately, but no later than the end of the next business day of when he or she becomes aware of it).

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

For SAEs associated with an overdose, the designated AstraZeneca representative (see Table 11) works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar** day of initial receipt for fatal or life threatening events and **within 4 calendar days** of initial receipt for all other SAEs. For other overdoses (ie, without symptoms or with non-serious adverse events) reporting to the Patient Safety data entry site should be done **within 5 calendar days**.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

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 patient 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 (see Table 11) **within 1 calendar day** (ie, immediately, but no later than the end of the next business day of when he or she becomes aware of it).

The AstraZeneca representative sends pregnancy reports to the AstraZeneca Patient Safety Data Entry Site **within 30 calendar days** of becoming aware of the pregnancy.

At an appropriate time-point, the AstraZeneca representative follows up the outcome of the pregnancy with the investigator/site staff.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal or life threatening events, **within 5 calendar days** of initial receipt for all other SAEs, and **within 30 calendar** days for all other pregnancies (ie, normal birth or elective abortion).

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

Farrington CP and Manning G 1990
Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference of non-unity relative risk. Statistics in Medicine. 1990 9(12):1447-54.

Fine MJ et al 1997
Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk subjects with community-acquired pneumonia. N Engl J Med. 1997;336:243-250.

Lamping D et al 2002
Lamping D, Schroter S, Marquis P, Marrel A, Duprat-Lomon I, Sagnier P. The Community-Acquired Pneumonia Symptom Questionnaire. A new, patient-based outcome measure to evaluate symptoms in patients with community-acquired pneumonia. Chest. 2002;122;920-929

Liu YN et al 2006
A multi-centre study on the pathogenic agents in 665 adult patients with community acquired pneumonia in cities of China; Chin J Tuberc Respir Dis, Jan 2006, Vol.29, No1.

Miettinen O et al 1985
Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine. 1985 4(2) 213-26.

Clinical Study Protocol Appendix B

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00002
Edition Number	1.0

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of important events or medical interventions include but are not limited to the following:

- 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	D3720C00002
Edition Number	1.0

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

Appendix D
Pneumonia Outcomes Research Team (PORT)

1. PNEUMONIA OUTCOMES RESEARCH TEAM (PORT)

1.1 PORT Score Determination

Patient Characteristic	**Point Assignment**
Age	
Male	Age (years)
Female	Age (years) – 10
Nursing home resident[a]	+ 10
Coexisting illnesses	
Neoplastic disease[b]	+ 30
Liver disease[c]	+ 20
Congestive heart failure[d]	+ 10
Cerebrovascular disease[e]	+ 10
Renal disease[f]	+ 10
Physical-examination findings	
Altered mental status[g]	+ 20
Respiratory rate ≥ 30/minute	+ 20
Systolic blood pressure < 90 mmHg[h]	+ 20
Temperature < 35°C (95°F) or ≥ 40°C (104°F)	+ 15
Pulse ≥ 125/minute[i]	+ 10
Laboratory and radiographic findings	
Arterial pH < 7.35[j]	+ 30
Blood urea nitrogen ≥30 mg/dL (11 mmol/L)[f]	+ 20
Sodium < 130 mmol/L	+ 20
Glucose ≥ 250 mg/dL (14 mmol/L)[k]	+ 10
Hematocrit < 30%[l]	+ 10
Partial pressure of arterial oxygen < 60 mmHg (from ABG if medically indicated) or oxygen saturation < 90% (by pulse oximetry)[12]	+ 10
Pleural effusion	+ 10
PORT SCORE	Sum of numbers above

Abbreviations: ABG = Arterial blood gas; PORT = Pneumonia Outcomes Research Team.

[a] Patients that reside in a nursing home or assisted living facility that provides 24-hour medical supervision are excluded from the study and should not be enrolled (See Section 4.2).

[b] Neoplastic disease is defined as any cancer, except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within one year of presentation. Patients with neoplastic lung disease are excluded from the study and should not be enrolled (See Section 4.2).

[c] Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Patients with significant hepatic disease (ie, acute viral hepatitis, elevated liver enzymes, elevated bilirubin, or manifestations of end-stage liver disease) or acute hepatic failure are excluded from the study and should not be enrolled (See Section 4.2).

[d] Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Patients with acute heart failure are excluded from the study and should not be enrolled (See Section 4.2).

[e] Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or CT. Patients with acute cerebrovascular events are excluded from the study and should not be enrolled (See Section 4.2).

[f] Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record. Patients with severely impaired renal function (CL_{CR} ≤ 30 mL/min estimated by Cockroft Gault formula) are excluded from the study and should not be enrolled (See Section 4.2).

[g] Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.

[h] Patients in shock are excluded from the study and should not be enrolled (Section 4.2).

[i] ABG is not required and should be performed only if medically indicated. Add + 0 points if ABG not obtained.

[j] Patients with profound metabolic abnormalities (e.g., diabetic ketoacidosis) are excluded from the study and should not be enrolled (See Section 4.2).

[k] Patients with active gastrointestinal bleeding are excluded from the study and should not be enrolled (See Section 4.2).

[l] Patients with current or impending respiratory failure are excluded from the study and should not be enrolled (See Section 4.2).

1.2 PORT Risk Class Determination

PORT Risk Class	PORT Score
I (ineligible for study)	0 - 50
II (ineligible for study)	51 - 70
III	71 - 90
IV	91 - 130
V (ineligible for study)	≥ 131

Abbreviation: PORT = Pneumonia Outcomes Research Team.

AstraZeneca

Clinical Study Protocol Appendix E

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00002
Edition Number	1.0

Appendix E
Radiographic Studies

RADIOGRAPHIC STUDIES

Radiographic studies should be performed in all patients at baseline, TOC, and LFU visits, as outlined in the Schedule of Assessments (See Table 1), unless the patient was previously deemed a failure. For purposes of the study, acceptable radiographic modalities include CXR or chest CT scan.

General Guidelines for performing imaging studies:

- Investigators should use their clinical judgment to determine whether CXR or chest CT scan is more appropriate for the baseline evaluation
- The same imaging modality (CXR or chest CT scan) should be used for all time points (baseline, TOC visit, and LFU visit) throughout the study period.
- If CXR is being performed, posteroanterior films are preferred to portable anteroposterior films. If the patient's condition does not allow for a standard posteroanterior, a portable anteroposterior CXR is acceptable. If anteroposterior films are obtained at baseline, posteroanterior are preferred at all subsequent time points.

General guidelines for evaluation of radiographic studies:

- Interpretation of radiographic studies and preparation of the radiographic report should be performed by an appropriately qualified (i.e., certified or licensed according to applicable regional requirements) radiologist
- Preferably, the same blinded CXR / CT scan reader will interpret all study-related radiographs per-patient
- Whenever possible, the radiologist should compare the baseline imaging study to any previously obtained imaging studies. Comparison of findings to prior studies should be noted in the radiology report.
- Imaging studies obtained at the TOC and LFU visits should be compared to the baseline imaging study. Comparison of findings to the baseline study should be noted in the radiology report.

Investigators will use the radiographic report as the basis for assigning the radiographic outcome (See Table 6). Radiographic outcome should be recorded by the Investigator on the CRF. A copy of the radiologist's report should be appended to the CRF. The original report will remain at the site as source documentation.

Appendix F
Antibiotics Allowed and Disallowed Prior to Study Drug Administration

APPENDIX F: ANTIBIOTICS ALLOWED AND DISALLOWED PRIOR TO STUDY DRUG ADMINISTRATION

Antibiotics Allowed and Disallowed Prior To Study Drug Administration

Antibiotics Allowed (One dose within 96 hours prior to randomisation)		Antibiotics Disallowed	
Cephalosporins			
Cefaclor	Cefprozil		
Cefadroxil	Ceftazidime		
Cefdinir	Ceftibuten	Cefixime (400 mg)	
Cefepime	Cefditoren	Ceftriaxone	
Cefixime (200 mg)	Cefuroxime		
Cefotaxime	Cephalexin		
Cefpodoxime	Loracarbef		
Fluoroquinolones			
Ciprofloxacin		Gatifloxacin	Levofloxacin
Norfloxacin		Gemifloxacin	Moxifloxacin
		Grepafloxacin	Sparfloxacin
Macrolides and Ketolides			
Clarithromycin		Azithromycin	
Erythromycin		Clarithromycin XL (extended release)	
Roxithromycin		Dirithromycin	
		Telithromycin	
Penicillins and Carbapenems			
Amoxicillin	Nafcillin		
Amoxicillin-Clavulanate	Oxacillin		
Amoxicillin-Sulbactam	Penicillin-G	Ertapenem	
Ampicillin	Penicillin-V	Penicillin-G Benzathine/Procaine	
Ampicillin-Sulbactam	Piperacillin		
Dicloxacillin	Piperacillin-Tazobactam		
Imipenem	Ticarcillin-Clavulanate		
Meropenem			

Antibiotics Allowed (One dose within 96 hours prior to randomisation)	**Antibiotics Disallowed**
Tetracyclines	
Doxycycline (100 mg)	Doxycycline (200 mg)
Minocycline	Minocycline Extended Release
Tetracycline	
Other Antibiotics	
Clindamycin	
Co-trimoxazole	

Clinical Study Protocol Appendix G

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00002
Edition Number	1.0

Appendix G
Schedule of Laboratory Tests

LABORATORY VARIABLES

Haematology[a]
- Haemoglobin
- Hematocrit
- Erythrocyte count
- Mean cell haemoglobin
- Mean cell haemoglobin concentration
- Reticulocyte count
- RDW
- MCV
- WBC
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets
- PT/INR
- PTT

Urinalysis[a,b]
- pH
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Urine microscopy for erythrocyte count, WBC, crystals, and casts

Chemistry[a]

Serum concentrations of:
- Magnesium
- Bicarbonate
- Sodium
- Potassium
- Phosphorus
- Chloride
- Calcium
- Alkaline phosphatase
- Gamma-glutamyl transferase
- ALT (GPT)
- AST (GOT)
- Creatine kinase
- Lactic dehydrogenase
- Total and indirect bilirubin
- Total cholesterol
- Glucose, nonfasting
- Total protein
- Albumin
- Serum creatinine
- Urea nitrogen
- Uric Acid
- Haptoglobin

Other tests[a]
- Direct Coombs' test
- C-Reactive Protein
- Serology for atypicals
- *L.pneumophila* & pneumococcal UAT
- Urine pregnancy test must be sensitive to at least 50 mU/mL of β-hCG

ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), β-hCG (β-Human Chorionic Gonadotropin), INR (International Normalized Ratio), GOT (Glutamic Oxaloacetic transaminase), GPT (Glutamic Pyruvic Transaminase), MCV (Mean Corpuscular Volume), PT (Prothrombin Time), PTT (Partial Thromboplastin Time), RDW (Red Blood Cell Distribution Width), WBC (White Blood Cell Count)

[a] Refer to Laboratory Manual and Schedule of assessments, Table 1, for timings
[b] May be semi-quantitative if standard practice at the respective hospital laboratory

For blood volume see Section 7.1

Clinical Study Protocol Appendix H

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00002
Edition Number	2.0

Appendix H
Study Procedures

1. STUDY PROCEDURES

1.1 Baseline Procedures

Baseline procedures must be fulfilled within 24 hours prior to the start of administration of the first infusion (Day 1) of the study treatment regimen

1. Obtain written informed consent prior to initiating any study-related procedures or assessments

2. Administer CAP-Symptom 18 questionnaire prior to any other study related procedures (see Appendix I). This questionnaire should be read to the patient and the patient is to provide a response without any assistance or interpretation

3. Verify that the patient meets all study eligibility criteria (see Section 4.0)

4. Obtain a complete pertinent medical and surgical history covering the 5-year time frame prior to baseline that includes conditions and procedures from the following categories: allergic; cardiovascular; dermatological; gastrointestinal; genital and reproductive; head, eyes, ears, nose, and throat; haematologic; hepatic; immunological; metabolic and endocrine; musculoskeletal; neurological; psychiatric; renal; and respiratory/pulmonary including smoking history

5. Record all prior and concomitant medications. Ensure all antimicrobial agents within the previous 4 weeks prior to baseline are captured. For patients who have received prior antimicrobials for the current CABP infection, obtain any prior microbiological data that may help determine patient eligibility (see Section 4)

6. Perform a complete physical examination (PE) including:

   – Height and weight measurements

   – General appearance, including skin and height and weight measurements

   – Head and neck (including ears, eyes, nose and throat)

   – Lymph nodes

   – Thyroid

   – Musculoskeletal / extremities, including spine

   – Cardiovascular system

   – Lungs

- Abdomen
- Neurological systems

7. Evaluate and record their CABP signs and symptoms, which include, but may not be limited to, cough, pleuritic chest pain, dyspnoea and sputum production and character.
   - All signs and symptoms from the episode prior to this current CABP diagnosis must also be recorded at baseline.
   - Categorize the symptom intensity by using the AE variables (see Section 6.4.3) of Absent, Mild, Moderate or Severe.
   - For the purposes of this study, also record patient's ability to maintain oral intake and mental status. Categorize their mental status as normal or altered (reference definition of mental status in Appendix D).
8. Assess severity of illness according to the PORT Score Determination and confirm patient has a PORT Risk Class or III or IV (see Appendix D).
9. Record resting vital signs including heart rate, blood pressure (measure after patient has been in a supine position for 5 minutes), respiratory rate, oxygen saturation, and temperature (oral, rectal or tympanic). Measure the patient's temperature (oral, rectal, or tympanic) in the morning and afternoon; record the highest daily temperature (oral, rectal, or tympanic).
10. Obtain three 12-lead ECGs, separated by at least 1 minutes within a 15 minute period
11. Obtain CXR posteroanterior or chest CT scan; if the patient's condition does not allow for a standard posteroanterior, a portable anteroposterior CXR is acceptable
12. Laboratory tests: obtain blood and urine samples as required by the Schedule of Assessments, see Table 1. Reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of samples, Section 7.1 for blood volumes and Appendix G for identification of laboratory tests
13. **NOTE**: Results of *L. pneumophila* urinary antigen test must be available before randomisation. Patients with a positive result are excluded from participation.
14. Additional laboratory tests: obtain additional blood and urine samples as required by the Schedule of Assessments, see Table 1, along with any other medically indicated as determined by the Investigator. Reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of

samples, Section 7.1 for blood volumes, and Appendix G for identification of laboratory tests.

15. Estimate the patient's CL_{CR} using the serum creatinine value (in conventional units) and according to the Cockcroft-Gault formula, if applicable, see Section 5.5.3 for dose adjustment. Severely impaired renal function is defined as $CL_{CR} \leqslant 30$ mL/min

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

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

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

16. If female, conduct a urine pregnancy test, which is sensitive to at least 50 mU/mL of β-hCG. Females of childbearing potential and those who are fewer than 2 years post-menopausal must test negative prior to randomization

17. Obtain microbiological specimens:

- Obtain appropriate sputum specimen and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist). Attempts to collect an adequate sputum sample may be repeated if appropriate. Ensure that all isolates, that are not contaminants, are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.1)

- Obtain pleural fluid specimen only if medically indicated, repeat samples are not required. Collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

- Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing

at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora). Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of all specimens / cultures.

18. Document if anything is bothering the patient, determine if it meets the criteria for an AE or SAE (see Section 6.4) and as applicable contact AstraZeneca

19. Randomise patient according to the IVRS/IWRS instructions and notify the unblinded pharmacist or unblinded study staff. There should be no medically inappropriate delay in randomisation and subsequent administration of the study treatment regimen.

NOTE: Several days may be required before central laboratory results are available; therefore local laboratory results will be used to determine patient eligibility for study randomisation. If local laboratory results are not confirmed by central laboratory results, the patient should be assessed for safety and the AstraZeneca (AZ) study physician contacted

1.2 Study Days 1, 2 and 4

Study Day 1 is defined as the calendar day that the study treatment regimen is first administered and the other Study Days follow consecutively.

1. Administer CAP-Symptom 18 questionnaire (except on Day 1: not applicable), prior to any other study related procedures (see Appendix I). This questionnaire should be read to the patient and the patient is to provide a response without any assistance or interpretation. **This questionnaire is not administered on Day 1**.

2. Unless deemed a failure, obtain and administer blinded study drug therapy: Infusion 1 over 30 (± 10) minutes immediately followed by Infusion 2 over 30 (± 10) minutes, q12h (± 2 hours). If a treatment failure, complete EOT visit assessments.

3. Record any new concomitant medications

4. Evaluate and record their CABP signs and symptoms, which include, but may not be limited to, cough, pleuritic chest pain, dyspnoea and sputum production and character. Categorize the symptom intensity by using the AE variable of Absent, Mild, Moderate or Severe (see Section 6.4.3). For the purposes of this study, also

record patient's ability to maintain oral intake and mental status. Categorize their mental status as normal or altered (reference definition of mental status in Appendix D).

5. Record resting vital signs including heart rate, blood pressure (measure after patient has been in a supine position for 5 minutes), respiratory rate, oxygen saturation, and temperature (oral, rectal or tympanic). Measure the patient's temperature (oral, rectal, or tympanic) in the morning and afternoon; record the highest daily temperature (oral, rectal, or tympanic).

6. Obtain microbiological specimens if medically indicated:

   – Obtain appropriate sputum specimen, if medically indicated, and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist). Attempts to collect an adequate sputum sample may be repeated if appropriate.

   – Obtain pleural fluid specimen only if medically indicated, repeat samples are not required. Collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

   – Repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora) or if medically indicated. Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

7. Assess, identify, and record any AEs or SAEs (see Section 6.4), as applicable contact AstraZeneca

1.3 Study Day 3

1. Unless deemed a treatment failure, administer study drug therapy: Infusion 1 over 30 (± 10) minutes immediately followed by Infusion 2 over 30 (± 10) minutes, q12h (± 2 hours). If a treatment failure, complete EOT visit assessments

2. Obtain written informed consent from those patients who have consented to participate in the optional PK portion of the study. Collect plasma samples during **the dose convenient for plasma samples collection** (see Section 6.5, Table 2):

   – Within 15 minutes prior to the start of Infusion 1 (trough)

   – Within 5 minutes following the end of Infusion 2 (peak)

   – Between 1 and 3 hours after the end of Infusion 2

   – Between 4 and 8 hours after the end of Infusion 2

   Start and stop times of Infusions 1 and 2 for the 1st daily dose must be recorded. The plasma sample, handling and processing instructions will be provided in a separate, detailed Laboratory Manual

3. Record any new concomitant medications

4. Perform a brief physical examination including:

   – General appearance, including skin

   – Cardiovascular system

   – Lungs

   – Abdomen

5. Evaluate and record their CABP signs and symptoms, which include, but may not be limited to, cough, pleuritic chest pain, dyspnoea and sputum production and character. Categorize the symptom intensity by using the AE variable of Absent, Mild, Moderate or Severe (see Section 6.4.3). For the purposes of this study, also record patient's ability to maintain oral intake and mental status. Categorize their mental status as normal or altered (reference definition of mental status in Appendix D)

6. Record resting vital signs including heart rate, blood pressure (measure after patient has been in a supine position for 5 minutes), respiratory rate, oxygen saturation, and temperature (oral, rectal or tympanic). Measure the patient's temperature (oral, rectal, or tympanic) in the morning and afternoon, record the highest daily temperature (oral, rectal, or tympanic)

7. Obtain one 12-lead ECG recording within 60 minutes of the end of Infusion 2

8. Laboratory tests: obtain blood and urine samples as required by the Schedule of Assessments, see Table 1 and reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of

samples, see Section 7.1 for blood volumes and Appendix G for identification of laboratory tests

9. Estimate the patient's CL_{CR} using the serum creatinine value (in conventional units) and according to the Cockcroft-Gault formula, if applicable, see Section 5.5.3 for dose adjustment. Severely impaired renal function is defined as $CL_{CR} \leqslant 30$ mL/min

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

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

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

10. Assess, identify, and record any AEs or SAEs (see Section 6.4), as applicable, contact AstraZeneca

11. Obtain microbiological specimens, if medically indicated:

- Obtain appropriate sputum specimen, if medically indicated, and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist). Attempts to collect an adequate sputum sample may be repeated if appropriate. Ensure that all isolates that are not contaminants are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.1)

- Obtain pleural fluid specimen only if medically indicated, repeat samples are not required. Collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

- Repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora) or if medically indicated.

Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of all specimens / cultures.

1.4 Study Days 5 - 6

1. Unless deemed a treatment failure, administer study drug therapy: Infusion 1 over 30 (± 10) minutes immediately followed by Infusion 2 over 30 (± 10) minutes, q12h (± 2 hours). If a treatment failure, complete EOT visit assessments

2. Record resting vital signs including heart rate, blood pressure (measure after patient has been in a supine position for 5 minutes), respiratory rate, oxygen saturation, and temperature (oral, rectal or tympanic). Measure the patient's temperature (oral, rectal, or tympanic) in the morning and afternoon; record the highest daily temperature (oral, rectal, or tympanic).

3. Assess, identify, and record any AEs or SAEs (see Section 6.4), as applicable, contact AstraZeneca

4. Obtain microbiological specimens, <u>if medically indicated</u>:

   – Obtain appropriate sputum specimen, if medically indicated, and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist), if medically indicated. Attempts to collect an adequate sputum sample may be repeated if appropriate. Ensure that all isolates that are not contaminants are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.1)

   – Obtain pleural fluid specimen <u>only if medically indicated</u>, repeat samples are <u>not</u> required. Collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

- Repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora) or if medically indicated. Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of all specimens / cultures.

1.5 End of Therapy (EOT)

Administration of study drug may occur on the same calendar day as the EOT visit, and if so will be completed before the EOT assessments begin. If the last dose of the study drug or treatment regimen occurs at night, the EOT assessments (with the exception of the ECG recording) can be performed in the morning of the following day.

1. Unless deemed a treatment failure, administer study drug therapy: Infusion 1 over 30 (± 10) minutes immediately followed by Infusion 2 over 30 (± 10) minutes, q12h (± 2 hours). If a treatment failure, complete EOT visit assessments

2. Administer CAP-Symptom 18 questionnaire prior to any other study related procedures (see Appendix I). This questionnaire should be read to the patient and the patient is to provide a response without any assistance or interpretation

3. Record any new concomitant medications

4. Perform a brief physical examination including:

   - General appearance, including skin
   - Cardiovascular system
   - Lungs
   - Abdomen

5. Evaluate and record their CABP signs and symptoms, which include, but may not be limited to, cough, pleuritic chest pain, dyspnoea and sputum production and character. Categorize the symptom intensity by using the AE variable of Absent, Mild, Moderate or Severe (see Section 6.4.3). For the purposes of this study, also record patient's ability to maintain oral intake and mental status. Categorize their

mental status as normal or altered (reference definition of mental status in Appendix D)

6. Record resting vital signs including heart rate, blood pressure (measure after patient has been in a supine position for 5 minutes), respiratory rate, oxygen saturation, and temperature (oral, rectal or tympanic). Measure the patient's temperature (oral, rectal, or tympanic) in the morning and afternoon, record the highest daily temperature (oral, rectal, or tympanic)

7. Obtain one 12-lead ECG recording within 60 minutes of the end of Infusion 2

8. Laboratory tests: Do not obtain EOT laboratory tests if previous laboratory tests were within prior 24 hours. If not, obtain blood and urine samples as required by the Schedule of Assessments, see Table 1 and reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of samples, see Section 7.1 for blood volumes and Appendix G for identification of laboratory tests

9. Additional laboratory tests: obtain additional blood and urine samples as required by the Schedule of Assessments, see Table 1, along with any other medically indicated as determined by the Investigator. Reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of samples, Section 7.1 for blood volumes, and Appendix G for identification of laboratory tests

10. Estimate the patient's CL_{CR} using the serum creatinine value (in conventional units) and according to the Cockcroft-Gault formula, if applicable, see Section 5.5.3 for dose adjustment. Severely impaired renal function is defined as $CL_{CR} \leqslant 30$ mL/min

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

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

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

11. If female, conduct a urine pregnancy test, which is sensitive to at least 50 mU/mL of β-hCG. Females of childbearing potential and those who are fewer than 2 years post-menopausal must test negative prior to randomization

12. Assess, identify, and record any AEs or SAEs (see Section 6.4), as applicable, contact AstraZeneca

13. Obtain microbiological specimens, if medically indicated:

- If deemed a treatment failure, obtain appropriate sputum specimen and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist), if medically indicated. Attempts to collect an adequate sputum sample may be repeated if appropriate. Ensure that all isolates that are not contaminants are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.1)

- Obtain pleural fluid specimen only if medically indicated, repeat samples are not required. Collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

- If deemed a treatment failure, or if results from previous sample test positive (rather than daily), obtain a blood culture until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora). Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of all specimens / cultures.

14. Determine clinical outcome according to Section 6.3.2.

1.6 Test of Cure (TOC)

Perform TOC assessments 8 to 15 days after the last dose of the study treatment regimen is administered.

1. Administer CAP-Symptom 18 questionnaire prior to any other study related procedures (see Appendix I). This questionnaire should be read to the patient and the patient is to provide a response without any assistance or interpretation

2. Record any new concomitant medications

3. Perform a brief physical examination including:

   – General appearance, including skin

   – Cardiovascular system

   – Lungs

   – Abdomen

4. Evaluate and record their CABP signs and symptoms, which include, but may not be limited to, cough, pleuritic chest pain, dyspnoea and sputum production and character. Categorize the symptom intensity by using the AE variable of Absent, Mild, Moderate or Severe (see Section 6.4.3). For the purposes of this study, also record patient's ability to maintain oral intake and mental status. Categorize their mental status as normal or altered (reference definition of mental status in Appendix D)

5. Record resting vital signs including heart rate, blood pressure (measure after patient has been in a supine position for 5 minutes), respiratory rate, oxygen saturation (if medically indicated), and temperature (oral, rectal or tympanic). Measure the patient's temperature (oral, rectal, or tympanic) in the morning and afternoon, record the highest daily temperature (oral, rectal, or tympanic)

6. Obtain one 12-lead ECG recording

7. Obtain CXR posteroanterior or chest CT scan, unless the subject was deemed a failure at the EOT visit. If the patient's condition does not allow for a standard posteroanterior, a portable anteroposterior CXR is acceptable

8. Laboratory tests: obtain blood and urine samples as required by the Schedule of Assessments, see Table 1. Reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of samples, Section 7.1 for blood volumes, and Appendix G for identification of laboratory tests

9. Additional laboratory tests: obtain additional blood and urine samples as required by the Schedule of Assessments, see Table 1, along with any other medically indicated as determined by the Investigator. Reference the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of

samples, Section 7.1 for blood volumes, and Appendix G for identification of laboratory tests

10. Assess, identify, and record any AEs or SAEs (see Section 6.4), as applicable, contact AstraZeneca

11. Obtain microbiological specimens,

- If not previously categorized as a treatment failure at EOT and is now a treatment failure, obtain appropriate sputum specimen, and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist), if medically indicated. Attempts to collect an adequate sputum sample may be repeated if appropriate. Ensure that all isolates that are not contaminants are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.1)

- Obtain pleural fluid specimen only if medically indicated, repeat samples are not required. Collect fluid in one aerobic blood culture bottle and one anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

- If not previously categorised as a treatment failure at EOT and is now a treatment failure, obtain blood cultures or repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora). Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of all specimens / culture

12. If not previously categorised as a treatment failure, determine patient outcome according to Section 6.3

1.7 Late Follow-up Visit (LFU)

A LFU visit should be performed 21 to 35 days after the last dose of the study drug therapy is administered. Patients who were considered clinically cured at the TOC will be reassessed at this visit (see Section 6.3.2.2 and Table 5 for evidence of continuing response, i.e. no relapse)

1. Administer CAP-Symptom 18 questionnaire prior to any other study related procedures (see Appendix I). This questionnaire should be read to the patient and the patient is to provide a response without any assistance or interpretation

2. Record any new concomitant medications.

3. Evaluate and record their CABP signs and symptoms, which include, but may not be limited to, cough, pleuritic chest pain, dyspnoea and sputum production and character. Categorize the symptom intensity by using the AE variable of Absent, Mild, Moderate or Severe (see Section 6.4.3). For the purposes of this study, also record patient's ability to maintain oral intake and mental status. Categorize their mental status as normal or altered (reference definition of mental status in Appendix D)

4. Obtain CXR (posteroanterior) or chest CT scan, unless the patient was deemed a failure at the EOT or TOC visit. If the patient's condition does not allow for a standard posteroanterior examination, a portable anteroposterior CXR is acceptable

5. Additional laboratory tests: obtain additional blood and urine samples as required by the Schedule of Assessments, see Table 1, along with any other medically indicated as determined by the Investigator. Refer to Section 7.1 for blood volumes, Appendix G for identification of laboratory tests and the Laboratory Manual for specific information on the collection, processing, handling, storage and shipping of samples

6. In patients experiencing clinical relapse, a microbiological examination will be performed if clinically appropriate. Obtain microbiological specimens, <u>if medically indicated</u>

   – Obtain appropriate sputum specimen and provide to the local laboratory to culture, perform Gram's stain and susceptibility testing. Sputum induction (eg, via nebulisation) should be performed by appropriately trained personnel (eg, a respiratory therapist), if medically indicated. Attempts to collect an adequate sputum sample may be repeated if appropriate. Ensure that all isolates that are not contaminants are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.1)

   – Obtain pleural fluid specimen <u>only if medically indicated</u>, repeat samples are <u>not</u> required. Collect fluid in one aerobic blood culture bottle and one

anaerobic blood culture bottle for a total of two bottles. Provide specimen to the local laboratory to culture, perform Gram's stain and susceptibility testing Ensure that **all** isolates are sent to the central laboratory for confirmation of organism identity and susceptibility (see Section 6.3.1.2)

– Repeat blood cultures upon receipt of a positive result (rather than daily) until sterilization is confirmed in those patients with a positive result at baseline (ie, baseline blood culture grows an organism other than those judged to be transient or resident skin flora). Obtain one aerobic and one anaerobic bottle of blood from two separate sites for a total of four bottles. Perform culture and susceptibility testing at the local laboratory and send isolates, other than those judged to be transient or resident skin flora, to the central laboratory for confirmation of organism identity and susceptibility. Susceptibility testing of all isolates sent to the central laboratory will be performed by broth microdilution tests and CLSI disk diffusion tests (see Section 6.3.1.4)

Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of all specimens / culture

7. Assess, identify, and record SAEs (see Section 6.4), as applicable, contact AstraZeneca.

8. Capture 'Resource Use' information

Appendix I
CAP-Symptom 18 Questionnaire

1. CAP-SYMPTOM 18 (CAP-SYM 18) QUESTIONNAIRE

The CAP-SYM 18 questionnaire is an interview led Patient Based Outcome measure. It is not an evaluation tool for the investigator and should not duplicate any medical monitoring.

Paper versions of the CAP-SYM 18 questionnaire will be administered via an interview format by an appropriate health care professional at the times indicated in the Schedule of Assessments, Table 1. This paper version will act as the site's source and be used to complete the appropriate information on the eCRFs.

- The CAP-SYM 18 should be administered before any investigations or discussions with the patient about their disease occur with the clinic staff.
- The patient should be reminded that there are no right or wrong answers and the interviewer should read the questions exactly as written on the questionnaire and record the patient's verbatim answers. Under no circumstances should help be given in interpreting the questions or in selecting responses.
- Study staff should record the reason for non-compliance of patients who could not or refused to complete questionnaires.
- Translations of questionnaires will be provided in relevant languages. Where a questionnaire version is not available in a patient's first language, they will not be expected to complete the questionnaire and this reason for non-completion should be recorded.

➢ **Introduction to the CAP-Symptom Questionnaire to be read to the patient.**

Patients with pneumonia sometimes experience symptoms or problems which we are evaluating as part of the study in which you are currently participating. We would therefore like to ask you a few questions about your own current experience in that respect. I am going to read you a list of symptoms or problems. For each of them, I will ask you the extent to which the symptom/problem has bothered you in the past 24 hours: not at all, a little, moderately, quite a bit or extremely. If you have not had the symptom/problem in the past 24 hours, please let me know.

Overall, the interview will only take a few minutes and the questions are simple to answer. Please remember that you should answer in reference to what happened in the past 24 hours. Thank you very much in advance for your participation.

Please read each item to patient and circle the number that corresponds to how much the patient has been bothered by the symptom/problem IN THE PAST 24 HOURS.

In the past 24 hours, how much have you been bothered by:	**Patient did not have the symptom/problem**	**Patient had the symptom/problem and it bothered him/her...**				
		Not at all	**A little**	**Moderately**	**Quite a bit**	**Extremely**
*1. Coughing?	0	1	2	3	4	5
*2. Chest pains?	0	1	2	3	4	5
*3. Shortness of breath?	0	1	2	3	4	5
4. Coughing up phlegm/sputum (secretion from the chest)?	0	1	2	3	4	5
5. Coughing up blood?	0	1	2	3	4	5
*6. Sweating?	0	1	2	3	4	5
*7. Chills?	0	1	2	3	4	5
*8. Headache?	0	1	2	3	4	5
*9. Nausea?	0	1	2	3	4	5
10. Vomiting?	0	1	2	3	4	5
11. Diarrhea?	0	1	2	3	4	5
12. Stomach pain?	0	1	2	3	4	5
*13. Muscle pain?	0	1	2	3	4	5
*14. Lack of appetite?	0	1	2	3	4	5
*15. Trouble concentrating?	0	1	2	3	4	5
16. Trouble thinking?	0	1	2	3	4	5
*17. Trouble sleeping?	0	1	2	3	4	5
*18. Fatigue?	0	1	2	3	4	5

* Indicates items that are included in the CAP-Sym 12.