Revised Clinical Study Protocol

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00001
Edition Number	1
Date	[redacted]

A Phase III, Multicentre, Randomised, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of Ceftaroline Fosamil (600 mg every 8 hours) Versus Vancomycin Plus Aztreonam in the Treatment of Patients With Complicated Bacterial Skin and Soft Tissue Infections With Evidence of Systemic Inflammatory Response or Underlying Comorbidities

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

[redacted]

Date

[redacted]

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
01	04 March 2014		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
01	25 July 2013		

PROTOCOL SYNOPSIS

A Phase III, Multicentre, Randomised, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of Ceftaroline Fosamil (600 mg every 8 hours) Versus Vancomycin Plus Aztreonam in the Treatment of Patients With Complicated Bacterial Skin and Soft Tissue Infections With Evidence of Systemic Inflammatory Response or Underlying Comorbidities

International Co-ordinating Investigator

[redacted]

Study centres and number of patients planned:

This will be a multicentre study. Country selection will be based on qualifications such as registration requirements, capabilities, access to patient population, and recruitment rates. Approximately 765 patients age 18 years or older with complicated bacterial skin and soft tissues infections (cSSTI) with evidence of systemic inflammatory response or underlying comorbidities will be eligible for participation in this study and will be enroled across approximately 170 sites. There will be 2 treatment groups, with approximately 510 patients in the ceftaroline fosamil treatment group and 255 patients in the vancomycin plus aztreonam treatment group (2:1 randomization).

An MRSA expansion period will recruit approximately 60 patients with confirmed MRSA from selected centres based on surveillance data, data from previous studies and local epidemiological data. Data collected from patients during the MRSA expansion period will be analysed and reported separately and not included in the analysis of the 765 patients recruited during the main study period.

Study period		Phase of development
Estimated date of first patient enroled	[redacted]	III
Estimated date of last patient completed	[redacted]	III

Objectives

Primary Objective

The primary objective is to assess whether ceftaroline fosamil is noninferior to vancomycin plus aztreonam in the clinical cure rate at the Test of Cure (TOC) visit in both the modified intent-to-treat (MITT) and clinically evaluable (CE) analysis sets of adult patients with cSSTI.

Secondary Objectives

The secondary objectives are:

- To evaluate the clinical response at the End of Therapy (EOT) visit
- To evaluate the microbiological response at the EOT and TOC visits
- To evaluate the clinical and microbiological response by baseline pathogen at the TOC visit
- To evaluate clinical relapse and re-infection or recurrence at the Late Follow-Up (LFU) visit
- To evaluate superinfection, colonisation and new infection up to TOC and microbiological recurrence and re-infection at LFU
- To evaluate early response to treatment as defined by cessation of lesion spread at 48 to 72 hours of treatment
- To compare the safety and tolerability of ceftaroline fosamil and vancomycin plus aztreonam in patients with cSSTI
- To characterize the pharmacokinetics (PK) and exposure-response relationship of 600 mg of ceftaroline fosamil administered as a 120-minute intravenous (IV) infusion every 8 hours in patients with cSSTI

Exploratory objectives

The exploratory objectives are:

- To evaluate the length of stay in the hospital and any time spent in the intensive care unit
- To evaluate rate of hospital readmission and emergency room visits between the TOC and LFU visits

Study design

This is a phase III, multicentre, randomised, double-blind, comparative study to evaluate the efficacy and safety of IV ceftaroline fosamil administered as a 120-minute IV infusion every 8 hours versus IV vancomycin administered as a 120-minute IV infusion every 12 hours plus IV aztreonam administered as a 30-minute IV infusion every 8 hours in the treatment of patients with cSSTI with evidence of systemic inflammatory response or underlying comorbidities. To be eligible for the study, patients must be 18 years or older and must meet the definition of cSSTI as defined in the inclusion criteria of the protocol. There will be no switch to oral antibiotic therapy during the study.

The study will also evaluate the PK of ceftaroline in patients with cSSTI following the administration of 600 mg ceftaroline fosamil as a 120-minute IV infusion every 8 hours, whereas in previous studies with ceftaroline fosamil, it was given as a 60-minute IV infusion every 12 hours. The study will also attempt to enrich the recruitment for cSSTI patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections that exhibit high minimum inhibition concentration (MIC) for ceftaroline by the selection of countries and sites with a high prevalence of MRSA. Investigators participating in this study should be familiar with the standard of care for skin infections. A single blinded review will be performed of cure and evaluability rates in the overall population (both treatments combined) after approximately one-third of the patients have completed the study to ensure that the underlying assumptions hold and thus the trial has sufficient power based on the projected sample size.

The study will utilize a blinded evaluability committee to determine whether the patient is evaluable for the CE and microbiologically evaluable (ME) analysis sets. This team will review blinded data prior to database lock by focussing on such areas as microbiology, concomitant medications, minimal disease definition and on-study surgical interventions. Details will be outlined in the committee charter.

The MRSA expansion period will recruit patients with confirmed MRSA infections from selected centres where MRSA isolates with an MIC $\geq$2 mg/L to ceftaroline are known or suspected to be found. Data collected from patients during the MRSA expansion period will be analysed and reported separately and not included in the analysis of the 765 patients recruited during the main study period.

Target patient population

The target patient population will be comprised of male and female adult patients 18 years of age or older who present with cSSTI with evidence of systemic inflammatory response or underlying comorbidities. Patients must have an infection of sufficient severity such that it is expected to require hospitalisation and at least 5 days of IV antibiotic therapy (at least 120 hours of study participation period from the first study dose).

Patients may only be enroled into the MRSA expansion period if a skin infection site culture and/or blood culture, obtained within the 72 hours prior to the first dose, is positive for MRSA.

Investigational product, dosage, and mode of administration

Patients randomised to ceftaroline fosamil will receive 600 mg of IV ceftaroline fosamil administered as a 120-minute IV infusion every 8 hours. Each dose will be infused in a volume of 250 mL over 120 minutes. Doses will be adjusted according to the patient's renal function.

Comparator product, dosage, and mode of administration

Patients who are randomised to the comparator group will receive the combination of vancomycin plus aztreonam. Patients will receive IV vancomycin administered as a 120-minute infusion every 12 hours. The dose will be determined based on the patient's actual weight. Each dose will be infused in a volume of 250 mL over 120 minutes. The vancomycin dose will be adjusted according to the patient's renal function, following local guidelines (Liu et al 2011). The vancomycin dose may also be adjusted based on vancomycin levels according to local practices. All patients will have a trough vancomycin/placebo concentration sample taken at steady state (prior to dosing at Day 3). When vancomycin levels are used for dose adjustments, these levels will be measured locally and captured blindly.

The component of the comparator treatment regimen to provide activity against Gram-negative-bacteria will be aztreonam. Patients will receive 1 gm intravenously every 8 hours. Each dose will be infused in a volume of 100 mL over 30 minutes. The dose of aztreonam will be adjusted according to the patient's renal function. Investigators may discontinue the Gram-negative coverage at their discretion provided the patient meets the criteria for discontinuing aztreonam/aztreonam placebo. Criteria for discontinuing the aztreonam/aztreonam placebo are provided in the dose-adjustment section of the protocol.

Duration of treatment

Patient participation will be approximately 26 to 51 days. The study includes an initial Screening Period that occurs within 24 hours prior to the first dose of study drug, a 5- to 14-day Treatment Period including an EOT visit, and a Follow-up Period consisting of a TOC visit 8 to 15 days after the last dose of study drug and a LFU visit 21 to 35 days after the last dose of study drug. The LFU visit assessments may be conducted via the telephone unless the patient has signs and symptoms of relapse, in which case the patient will be required to come to the study centre for additional LFU visit assessments as indicated in the schedule of assessments.

Discontinuation of investigational product (ceftaroline fosamil or vancomycin plus aztreonam), 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 the main body of the protocol.

Outcome variables:

Primary outcome variable

The primary outcome variable will be the clinical cure rate at the TOC visit in both the MITT and CE analysis sets.

Secondary outcome variables

The secondary outcome variables will include the following:

- Clinical cure rate at the EOT visit in the MITT and CE analysis sets
- Per-patient microbiological response at the EOT and TOC visits in the microbiological modified intent-to-treat (mMITT) and ME analysis sets
- Clinical and per-pathogen microbiological response by baseline pathogen at the TOC visit in the mMITT and ME analysis sets
- Clinical relapse at the LFU visit in patients who were clinically cured at the TOC visit in the CE analysis set
- Re-infection and the recurrence rate in patients who were microbiological successes at the TOC visit in the ME analysis set
- Super-infection rate at the EOT visit and new infection rate at the TOC visit in the ME analysis set
- Colonisation rate in patients who had a clinical assessment performed at the EOT visit or the TOC visit in the ME analysis set
- Evaluation of early response at 48 to 72 hours of treatment in the MITT and CE analysis sets

Safety outcome variables

Safety and tolerability will be assessed by the incidence and severity of adverse events (AEs), evaluation of 12-lead electrocardiogram (ECG) tracings, abnormalities in vital sign assessments, clinical laboratory assessments, physical examinations, and reasons for withdrawal of study drug.

In addition, AstraZeneca will pursue complete data gathering (eg, through questionnaires) to allow proper safety evaluations for the following events: haemolytic anaemia, drug-induced liver disease, renal impairment, and seizures. These events are currently classified as important potential risks for ceftaroline fosamil in the global and regional risk-management plans.

Exploratory healthcare utilisation outcome variables

Exploratory healthcare utilisation outcome variables include the following:

- Length of hospital stay
- Length of any time spent in the intensive care unit
- Rehospitalisation rate between the TOC and LFU visits
- Emergency room visits between the TOC and LFU visits

Pharmacokinetics

It is the intent of the study that the majority of treated patients will have sparse plasma concentration samples taken to determine the population PK of ceftaroline and ceftaroline fosamil in this patient population. In addition, approximately 45 patients will have an intensive plasma sampling (ie, approximately 30 patients from the ceftaroline fosamil treatment group) to determine the PK of ceftaroline, ceftaroline fosamil and ceftaroline M-1 in this patient population by means of traditional noncompartmental PK analysis. It is anticipated that 20 of the 30 selected patients will be evaluable in the ceftaroline fosamil arm for full ceftaroline concentration-time course data. Sites that cannot perform plasma sampling for PK analysis due to staff or equipment issues will not be excluded, but all qualifying sites will be required to participate in the collection of plasma samples for PK analysis. All samples will be taken on Day 3, following administration of 1 of the 3 doses of ceftaroline fosamil, at a time that is convenient for the collection of plasma samples.

Statistical methods

The primary objective is to assess whether ceftaroline fosamil is noninferior to vancomycin plus aztreonam in the clinical cure rate at the TOC visit in both the MITT and CE analysis sets using a 10% margin. Additional analysis sets are defined for the secondary efficacy outcome variables and for the safety analysis.

- Modified Intent-to-Treat Analysis Set

  The MITT analysis set will be a subset of the intent-to-treat analysis set and will include all randomised patients who receive any amount of study drug.

- Microbiological Modified Intent-to-Treat Analysis Set

  The mMITT analysis set will be a subset of the MITT analysis set who meet the minimal disease criteria (patients who meet any of the inclusion criteria for cSSTI [#3 of the inclusion criteria] and #4, #5, and #6 of the inclusion criteria) and will include patients for whom at least 1 bacterial pathogen has been isolated from an appropriate microbiological specimen (blood, tissue, or pus obtained from the cSSTI site) at baseline.

- Clinically Evaluable Analysis Set

  The CE analysis set will be a subset of the MITT analysis set and will include patients who meet all of the following criteria:

  – Met the disease criteria for a cSSTI, as determined by the evaluability committee

  – Did not have a non-eligible infection including those caused exclusively by extended-spectrum β-lactamase producing Gram-negative organisms or monomicrobial *Pseudomonas* spp.

  – Received between 80% to 120% of the prespecified intended dose of study drug therapy. Compliance will be calculated as described in the calculation or derivation of efficacy variables section of the protocol

  – Had an outcome assessment performed at the TOC visit or determined to be a clinical failure at EOT. A patient with an indeterminate outcome (who is not a failure at EOT) will not be included in the CE analysis set

  – Did not receive, from the first dose of study drug through TOC, alternate (nonstudy) systemic antimicrobial therapy that would be effective for the treatment of the cSSTI, for a reason other than treatment failure

  – Did not have a procedure that the evaluability committee determined made the patient unevaluable

  In addition to meeting the above criteria, patients must meet the following specific conditions for inclusion in this analysis set:

  – Received the correct study drug to which they were randomly assigned

  – Received at least 48 hours of therapy in order to be considered an evaluable failure, unless deemed a clinical failure based on a treatment-limiting AE

  – Received at least 72 hours of therapy in order to be considered an evaluable clinical cure

- Microbiologically Evaluable Analysis Set

  The ME analysis set will include patients who meet criteria for both the mMITT and CE analysis sets.

- Safety Analysis Set

The safety analysis set will include all patients who received any amount of study drug irrespective of the treatment arm they were randomised to. The safety analysis set will be grouped according to the actual treatment they received.

- Pharmacokinetic Analysis Set

  The PK analysis set will include all patients who have at least 1 plasma concentration data assessment available for ceftaroline.

The sample size is based on the primary outcome variable of clinical cure rate at the TOC visit and assumes a point estimate for the clinical cure rate of 80% in the vancomycin plus aztreonam group and 80% in the ceftaroline fosamil group in the MITT analysis set, a noninferiority margin of 10% and a power of 90%. This gives a total sample size of 765 patients (510 in the ceftaroline fosamil group; 255 in the vancomycin plus aztreonam group). This sample size also gives greater than 90% power for the CE analysis set assuming an 85% clinical cure rate for both treatments and a 20% nonevaluable rate.

The primary objective is to assess whether that ceftaroline fosamil is noninferior to vancomycin plus aztreonam in the clinical cure rate at the TOC visit in both the MITT and CE analysis sets using a 10% margin. A 2-sided 95% confidence interval for the observed difference in the clinical cure rate between ceftaroline fosamil and vancomycin plus aztreonam will be computed using the unstratified method of Miettinen and Nurminen (Miettinen et al 1985). Noninferiority will be declared if the lower limit of the 95% confidence interval (corresponding to a 97.5% 1-sided lower bound) is greater than –10% for both the MITT and CE analysis sets.

The primary efficacy analysis will be performed for both MITT and CE analysis sets; in addition, data will be presented by subgroups according to baseline characteristics. The detailed subgroups will be described in the statistical analysis plan.

For each secondary efficacy outcome measure, a 2-sided 95% confidence interval will be computed using the unstratified method of Miettinen and Nurminen (Miettinen et al 1985). Subgroup analyses will be conducted on selected secondary outcome measures.

The safety analysis will be performed using the safety analysis set. Safety parameters include AEs, 12-lead ECG, vital sign assessments, clinical laboratory assessments, physical examinations, and reasons for withdrawal of study drug. 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. Conclusions from the safety data will not be based on inferential statistics alone, but the totality of the data. Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment with ceftaroline fosamil but who actually received vancomycin plus aztreonam) will be presented according to the actual treatment group received.

Ceftaroline, ceftaroline fosamil, and ceftaroline M-1 plasma concentrations will be listed and descriptively summarised at each sampling window for patients with sparse plasma sample collection and at each nominal sampling time for patients with intensive plasma sample collection, respectively. For patients with intensive plasma sampling, PK parameters will be determined using standard noncompartmental methods and will be descriptively summarized. Individual compartmental PK parameters of ceftaroline and ceftaroline fosamil for cSSTI patients will be derived via a population modeling approach. The ceftaroline and ceftaroline fosamil concentration, patient demographic, and disease status data will be combined with the data from appropriate previous clinical studies for the population PK analysis. Individual compartmental PK parameters for patients with ceftaroline and ceftaroline fosamil plasma concentration data available will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, C_{max}, t_{max}, AUC, $t_{½}$, λ_z, CL, V_z, V_{ss}, and MRT will be derived from the predicted ceftaroline and ceftaroline fosamil concentration time courses. The appropriate ceftaroline exposure outcome variables predicted by the population PK modeling will be used for a PK/PD modeling for appropriate microbiological or clinical cure outcome variables.

Based on surveillance data, data from previous studies and local epidemiological data, the MRSA expansion period will aim to recruit approximately 60 patients with confirmed MRSA in order to have an adequate number with MIC $\geq$2 mg/L against ceftaroline. This should provide between 12 and 18 patients with the required MIC (approximately 9 to 14 in the clinically evaluable population) and as per the main study they will be randomised 2:1 to ceftaroline vs vancomycin, respectively. Data collected from patients during the expansion period will be analysed and reported separately and do not form part of the original 765 patients recruited during the main study period. Data from the MRSA expansion period will be summarised using similar methods to the main study period but will not be subject to the hypothesis of non-inferiority.

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 (CSP).

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
C	Celsius
CABP	Community-acquired bacterial pneumonia
CE	Clinically evaluable
CI	Confidence interval
CL	Plasma clearance
C_{max}	Maximum plasma concentration
CLSI	Clinical and Laboratory Standards Institute
CrCl	Creatinine clearance
CSA	Clinical study agreement
CSP	Clinical study protocol
cSSSI	Complicated skin and skin structure infections
cSSTI	Complicated bacterial skin and soft tissues infection
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of Therapy
fT	Free drug concentration
gm	Gram
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
INR	International normalized ratio
IV	Intravenous

Abbreviation or special term	Explanation
IVRS	Interactive voice response system
IWRS	Interactive web response system
LFU	Late Follow-Up
MCV	Mean corpuscular volume
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MITT	Modified intent-to-treat
mMITT	Microbiological modified intent-to-treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRT	Mean residence time
MSSA	Methicillin-susceptible *Staphylococcus aureus*
OPAT	Outpatient parenteral antimicrobial therapy
PBPs	Penicillin-binding proteins
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin time
PTA	Probability of target attainment
PTT	Partial thromboplastin time
PVG	Pharmacovigilance
QTc	Corrected QT interval
QTcB	QTc interval corrected by Bazett
QTcF	QTc interval corrected by Fridericia
SAE	Serious adverse event
$t_{½\lambda z}$	Terminal plasma half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to C_{max}
TOC	Test of cure
V_{ss}	Volume of distribution during steady-state
V_z	Volume of distribution during terminal phase

1. INTRODUCTION

1.1 Background

The spectrum of activity of ceftaroline fosamil includes both Gram-positive and Gram-negative bacterial pathogens, many of which are important in skin and skin structure infections and in respiratory disease. Ceftaroline fosamil is a broad spectrum agent active against Gram-positive organisms including resistant isolates such as multidrug-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA). The activity of ceftaroline fosamil against Gram-negative species includes respiratory pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*. Ceftaroline fosamil 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 enzymes or those that hyperproduce AmpC β-lactamase. Consequently, ceftaroline fosamil 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 fosamil is inactive against isolates of *Pseudomonas aeruginosa* and other nonfermentative Gram-negative species.

Ceftaroline fosamil, 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 fosamil has been shown to bind with high affinity to PBPs from methicillin-susceptible *S. aureus* (MSSA) and unlike other available β-lactams, it also binds efficiently to PBP2a, the additional PBP present in MRSA. Ceftaroline fosamil has also been shown to bind with high affinity to PBPs in *S. pneumoniae* including PBP2x, alterations of which are common in penicillin-resistant *S. pneumoniae* isolates.

Ceftaroline fosamil was effective in animal models of infection that included mouse thigh and lung infections with Gram-negative and Gram-positive species, endocarditis models of infection in rat and rabbit with *S. aureus*, and pneumonia studies in rabbit with penicillin-resistant *S. pneumoniae*. Ceftaroline fosamil exhibited short to modest postantibiotic effects in vitro and in vivo, similar to other antibiotics of the cephalosporin class. Ceftaroline fosamil 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.

1.2 Clinical Experience

To date, the highest single doses of ceftaroline fosamil studied were single doses of 1500 mg infused over 1 hour (8 subjects in Study P903-20 and 54 subjects in a thorough corrected QT interval (QTc) study [P903-05]) and 2000 mg infused over 1 hour (8 subjects in Study P903-20). Total daily doses of 1800 mg/day have been assessed in 3 volunteer studies: 600 mg infused over 1 hour every 8 hours for 10 days in P903-020 (8 subjects), 600 mg

infused over 1 hour every 8 hours for 10 days in Study CXL-PK-01 (8 subjects), and 900 mg infused over 1 hour every 12 hours for 10 days in Study CXL PK-01 (9 subjects). In study CXL-PK-01, ceftaroline fosamil was studied in combination with equal doses of the β-lactamase inhibitor NXL104. None of these single- or multiple-dose studies demonstrated noticeable safety concerns. Minor accumulation of ceftaroline fosamil was observed with the 600 mg every 8-hour dose of ceftaroline fosamil when given with concurrent administration of NXL104 (600 mg every 8 hours). Approximately 71 patients are expected to receive ceftaroline fosamil (600 mg every 8 hours) in combination with NXL104 (600 mg every 8 hours) in a Phase 2 study in patients with complicated urinary tract infections (Study CXL-PK-02), which is currently in progress.

Ceftaroline fosamil 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 requiring haemodialysis. 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 cSSSI studies [1378 patients] and 2 community-acquired bacterial pneumonia [CABP] studies [1228 patients]). The safety and efficacy of ceftaroline fosamil has been demonstrated in patients with cSSSI and in patients with moderate-to-severe CABP.

Two Phase II studies were conducted to test the potential efficacy of ceftaroline fosamil in adults with cSSSI: Study P903-03 was a randomised, multicentre, observer-blinded study using ceftaroline fosamil (600 mg given intravenously every 12 hours) versus vancomycin (1 gm given intravenously every 12 hours) plus optional aztreonam (1 gm given intravenously every 8 hours) for 7 to 14 days, and Study P903-19 was a randomised, multicentre, open-label study using ceftaroline fosamil (600 mg intramuscular every 12 hours) versus linezolid (600 mg given intravenously every 12 hours) plus optional aztreonam (1 gm given intravenously every 12 hours) for 5 to 14 days. In Study P903-03, clinical cure rates and by-subject microbiological response for the ceftaroline fosamil group were high and numerically greater than that of the vancomycin group. In Study P903-19, clinical cure rates and by-subject microbiological response rates were >90% in both treatment groups, with linezolid plus aztreonam showing numerically higher cure rates than ceftaroline fosamil.

Two Phase III studies have been conducted in cSSSI (Studies P903-06 and P903-07). The results of the primary endpoint (clinical response at test of cure [TOC] in the co-primary modified intent-to-treat [MITT] and clinically evaluable [CE] populations of the individual studies) demonstrated that monotherapy with ceftaroline fosamil was noninferior to vancomycin plus aztreonam in subjects with cSSSI, as evidenced by the lower limit of the 95% confidence interval (CI) around the difference (ceftaroline fosamil – vancomycin plus aztreonam) in clinical cure rates being greater than the prespecified noninferiority boundary of –10%. In the individual pivotal Phase III cSSSI studies and in the pooled Phase III studies, the clinical cure rates were high and similar between treatment groups in both the CE population (ranging from 91% to 93%) and MITT population (ranging from 85% to 87%).

Four pooled Phase III cSSSI and CABP studies consisted of 1305 adult patients treated with ceftaroline fosamil (600 mg given intravenously every 12 hours) and 1301 adult patients treated with an active comparator. This pooled population included males and females who were 18 to 99 years of age. Of the 1305 patients treated with ceftaroline fosamil, 397 patients (30.4%) were at least 65 years of age, 1072 patients (82.1%) were white, and 862 patients (66.1%) had normal renal function. The characteristics of the patients in the comparator group were similar to the corresponding characteristics in the ceftaroline fosamil group. The incidences of treatment-emergent adverse event (TEAEs) were similar in ceftaroline fosamil and comparator groups (45.7% versus 46.7%, respectively). The most common TEAE system organ class in the ceftaroline fosamil 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 III studies. The most common TEAEs in the ceftaroline fosamil group were diarrhoea, headache, nausea, insomnia, constipation, and vomiting. The most common TEAEs in the comparator group were pruritus, nausea, diarrhoea, headache, insomnia, and hypokalaemia. The incidences of individual TEAEs were similar in the 2 treatment groups.

In summary, in each of these adequate and well-controlled studies, ceftaroline fosamil was well tolerated and demonstrated a safety profile that was compatible with treatment of cSSSI and CABP and known cephalosporin class effects. Further, noninferiority was demonstrated in the Phase III studies for all prospectively defined analyses across all analysis populations.

1.3 Research hypothesis

This study is designed to test the hypothesis that ceftaroline fosamil will be noninferior to vancomycin plus aztreonam in the treatment of patients with complicated bacterial skin and soft tissue infections (cSSTI) with evidence of systemic inflammatory response or underlying comorbidities and that ceftaroline fosamil will be well tolerated in patients with cSSTI.

1.4 Rationale for conducting this study

The purpose of the study is to assess the safety and efficacy of ceftaroline fosamil 600 mg given intravenously every 8 hours infused over 120 minutes in patients with cSSTI.

This therapeutic dose of ceftaroline fosamil was selected based on microbiology surveillance data, MIC distribution, pharmacokinetic (PK)/pharmacodynamic (PD) modelling and simulation of probability of PK/PD target attainment to cover all relevant pathogens, in particular *S. aureus* and MRSA, which are the most commonly isolated pathogens from cSSTIs.

Based on 2008-2009 microbiology surveillance data, the incidence of MRSA with ceftaroline MIC of 2 mg/L is typically 10% (corresponding to an MIC90 of 2 mg/L) worldwide; however, this incidence varies regionally. In Europe, the surveillance data indicate that the overall incidence of MRSA with ceftaroline MIC of 2 mg/L is approximately 17%, with observed incidences as high as 60%, but this varies between European countries. Conversely, in the United States, the incidence of MRSA with ceftaroline MIC of 2 mg/L is approximately 5%.

In other regions and countries the incidence of MRSA with ceftaroline MIC of 2mg/L may be >45% (in-house data).

The dose of ceftaroline fosamil was selected to ensure that an adequate exposure of ceftaroline with a killing target is achieved to cover all relevant pathogens, including MRSA with MIC values of 2mg/L, for this cSSTI study.

A population PK model for ceftaroline was built from 7 Phase I studies, 2 Phase II, and 2 Phase III studies in patients with cSSTI, and Monte Carlo simulation was employed to search for an appropriate ceftaroline fosamil dosing for this study. Ceftaroline is a cephalosporin and the percent time of free-drug concentration (fT) above the MIC over the dosing interval (% *f*T>MIC) is the PK/PD index relating to antimicrobial efficacy. The PK/PD targets (the magnitude of the PK/PD index) for ceftaroline against *S. aureus* have been determined by a preclinical murine thigh infection model with the median values of 26% *f*T>MIC, 36% *f*T>MIC and 51%>MIC for stasis, 1-log kill and 2-log kill respectively (Andes and Craig 2006). Monte Carlo simulations of this dosing regimen (600 mg every 8 hours infused over 120 minutes) indicate that it provides adequate exposure to achieve a probability of target attainment (PTA) of >90% for the PK/PD targets of both 1- and 2-log bacterial killing for *S. aureus,* including MRSA, with an MIC of 2 mg/L (in-house data).

For other relevant pathogens in cSSTI such as *Streptococcus pyogenes*, this dose will provide a PTA of 100 % for the maximum PK/PD target of 100% *f*T>MIC. In the case of *E. coli* and *Klebsiella pneumoniae* (nonextended-spectrum β-lactamase producers*)*, the median PK/PD targets for stasis and 1-log kill were determined to be 48.5% *f*T>MIC and 73% *f*T>MIC, respectively from a murine thigh model. The murine thigh model did not allow an estimate of 2-log kill for Enterobacteriaceae. The proposed dose provides adequate exposures to achieve a 90% PTA for the PK/PD target of 1-log kill (in-house data).

This study will attempt to gain meaningful experience in infections caused by *S. aureus*, including MRSA, with broth microdilution ceftaroline MICs of 2 mg/L by encouraging the participation of countries and sites with high prevalence of MRSA with this characteristic. The MRSA expansion period is expected to increase the number of such patients recruited to the study. Data from patients collected during the expansion period will be analysed and reported separately and not included in the overall analysis of the 765 patients as per the original protocol.

1.5 Benefit/risk and ethical assessment

1.5.1 Potential benefits

Patients enroled in this study will receive effective antibiotic treatment for their underlying infection. The therapeutic benefits of vancomycin plus aztreonam are well established. Based on the previous clinical experience with ceftaroline fosamil and from other cephalosporins, it is expected that patients who are randomly assigned to the ceftaroline fosamil treatment group should experience favourable outcomes.

1.5.2 Known risks

The currently known safety profile of ceftaroline fosamil has been established based on a review of 17 clinical studies (which included 4 Phase III studies in cSSSI and CABP) conducted in the context of the ceftaroline fosamil development program. Most experience originates from ceftaroline fosamil doses of 600 mg every 12 hours, administered in a 60-minute infusion. In studies conducted with ceftaroline fosamil, typical cephalosporin-class effects were seen with a low frequency and severity and generally these events did not warrant treatment other than with conservative measures. The most common adverse reactions were diarrhoea, nausea, and headache. Direct Coombs test seroconversion has been reported with ceftaroline use, as with other cephalosporins; however, no AEs representing haemolytic anaemia have been reported. Ceftaroline fosamil is contraindicated in patients with known hypersensitivity to β-lactam antibiotics. As with all antibiotics, patients who receive ceftaroline fosamil are at risk of developing *Clostridium difficile*-associated diarrhoea. In addition, increased transaminase levels, hypokalaemia, and phlebitis have been reported. The frequency of adverse reactions is presented in Table 1.

Table 1 Frequency of Adverse Reactions

Frequency	System organ class	Event
Very common (≥10%)	Investigations	Direct Coombs test positive
Common (≥1% and <10%)	Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain
	Nervous system disorders	Headache, dizziness
	Skin and subcutaneous tissue disorders	Rash, pruritus
	Hepatobiliary disorders	Increased transaminases
	Vascular disorders	Phlebitis
	General disorders and administration site conditions	Pyrexia
Uncommon (≥0.1% and <1%)	Blood and lymphatic system disorders	Anaemia, thrombocytopenia
	Immune system disorders	Hypersensitivity/anaphylaxis
	Skin and subcutaneous tissue disorders	Urticaria
	Infections and infestations	*Clostridium difficile* colitis
	Investigations	Prothrombin time prolonged, international normalized ratio increased
	Renal and urinary disorders	Blood creatinine increased

Table 1 Frequency of Adverse Reactions

Frequency	System organ class	Event
	General disorders and administration site conditions	Infusion site reactions(erythema, phlebitis, pain)

Currently, limited information is available at a daily dose regimen of 600 mg every 8 hours (see Section 1.2). The available safety data suggest that the safety profile at this dose is similar to that seen at the 600 mg every 12-hours dose.

For further information on ceftaroline fosamil, please refer to [redacted] ([redacted]).

During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body ("redman" syndrome) or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. Phlebitis, hypersensitivity reactions, anaphylaxis, nausea, chills, drug fever, rashes (including exfoliative dermatitis), and rare cases of vasculitis have been seen. Vancomycin has been associated with the bullous eruption disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis, and linear immunoglobulin A bullous dermatosis. In addition, events associated with nephrotoxicity, ototoxicity, and haematology have been seen.

The therapeutic risks of aztreonam include rash, pruritus, urticaria, erythema, petechiae, exfoliative dermatitis, flushing, very rarely toxic epidermal necrolysis, eosinophilia, increase in prothrombin and partial thromboplastin time, phlebitis, and discomfort at the intravenous (IV) injection site. There have been isolated reports of thrombocytopenia, neutropenia, anaemia, bleeding, and pancytopenia. Jaundice and hepatitis, including transient elevations of hepatic transaminases and alkaline phosphatase (without overt signs or symptoms of hepatobiliary dysfunction), anaphylaxis, angiooedema, bronchospasm, diarrhoea, nausea, vomiting, abdominal cramps, mouth ulcer, and altered taste have also occurred. Rare cases of *Clostridium difficile*-associated diarrhoea, including very rarely pseudomembranous colitis or gastrointestinal bleeding have occurred. In addition, rare instances of the following events have been reported: vaginitis, candidosis, seizures, dyspnoea, hypotension, weakness, confusion, dizziness, vertigo, sweating, headache, breast tenderness, halitosis, muscle aches, fever, malaise, sneezing and nasal congestion, and transient increases in serum creatinine.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to assess whether ceftaroline fosamil is noninferior to vancomycin plus aztreonam in the clinical cure rate at the Test of Cure (TOC) visit in both the MITT and CE analysis sets of adult patients with cSSTI.

2.2 Secondary objectives

The secondary objectives are:

- To evaluate the clinical response at the End of Therapy (EOT) visit
- To evaluate the per-patient microbiological response at the EOT and TOC visits
- To evaluate the clinical and per-pathogen microbiological response by baseline pathogen at the TOC visit
- To evaluate clinical relapse and re-infection or recurrence at the Late Follow-Up (LFU) visit
- To evaluate superinfection, colonisation, and new infection up to TOC and microbiological recurrence and re-infection at LFU
- To evaluate early response to treatment as defined by cessation of lesion spread at 48 to 72 hours of treatment
- To compare the safety and tolerability of ceftaroline fosamil and vancomycin plus aztreonam in patients with cSSTI
- To characterize the pharmacokinetics and exposure-response relationship of 600 mg of ceftaroline fosamil administered as a 120- minute IV infusion every 8 hours in patients with cSSTI

2.3 Exploratory objectives

The exploratory objectives are:

- To evaluate the length of stay in hospital and any time spent in the intensive care unit (ICU)
- To evaluate rates of hospital readmission and emergency room visits between the TOC and LFU visits

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a Phase III, multi centre, randomised, double-blind, comparative study to evaluate the efficacy and safety of ceftaroline fosamil versus vancomycin plus aztreonam in the treatment of patients with cSSTI with evidence of systemic inflammatory response or underlying comorbidities. Ceftaroline fosamil at 600 mg will be administered as a 120-minute IV infusion every 8 hours.

Approximately 765 adult patients who are 18 years of age or older will be eligible for this study if they have evidence of systemic inflammatory response or underlying comorbidities and present with cSSTI, as described in Section 3.1.1. Comorbidities include diabetes mellitus requiring drug therapy, stage 2 or 3 human immunodeficiency virus infection, chronic renal impairment, cirrhosis, peripheral vascular disease, malnutrition, use of immunosuppressive agents, and a malignancy (other than nonmelanoma skin cancers). Patients with systemic inflammatory response syndrome and severe sepsis are eligible for the study. Patients with septic shock are not eligible for the study (refer to Appendix G for definitions of sepsis, severe sepsis, and septic shock). As per the acute bacterial skin and skin structure infection guidelines (FDA 2010_FDA_2010), the number of patients with major cutaneous abscesses will be limited to no more than 30% of the total enroled patients. Patient must have an infection of sufficient severity such that it is expected to require hospitalization and at least 5 days of IV antibiotic therapy (at least 120 hours of study participation period from the first study dose). Patients may only be enroled into the MRSA expansion period if a skin infection site culture and/or blood culture obtained within the 72 hours prior to first dose is positive for MRSA.

Patients will be recruited into the MRSA expansion period at selected centres based on surveillance data, data from previous studies and local epidemiological data.

Information regarding the patient's length of stay in the hospital as well as the length of any time spent in the ICU, rehospitalisation, and emergency room visits will be collected.

Patients meeting all of the inclusion criteria and none of the exclusion criteria will be eligible for participation in the study after providing written informed consent. For the expansion period, this will include consent to use the local microbiology cultures and associated data taken in the 72 hr period before enrolment visit that identified the patient as eligible. These cultures/isolates (ie MRSA and any co-infecting isolates) and data will be used to define the baseline microbiology and must be stored and made available to the central laboratory for further analyses. Patients must receive a minimum of 5 days of treatment with study drug (at least 120 hours of study participation period from the first dose). However, the duration of therapy may be adjusted up to 14 days based on the clinical response of the patient. The EOT assessments will be completed at the time the patient completes the study drug therapy. For patients who complete the study drug therapy on Day 14, Day 14 and the EOT visit will be the

same visit. The TOC visit will occur 8 to 15 days after the last dose of study drug and a LFU visit will occur 21 to 35 days after the last dose of study drug. The LFU visit assessments may be conducted via the telephone unless the patient has signs and symptoms of relapse, in which case, the patient will be required to attend the study centre for additional LFU visit assessments as indicated in the schedule of assessments. The duration of patient participation will be approximately 26 to 51 days.

Patients will be randomised in a 2:1 ratio to receive ceftaroline fosamil (approximately 510 patients) or vancomycin plus aztreonam (approximately 255 patients). Patients randomised to ceftaroline fosamil will receive 600 mg of ceftaroline fosamil administered as a 120-minute IV infusion every 8 hours. Each dose will be infused in a volume of 250 mL. Doses will be adjusted according to the patient's renal function (see Section 5.5.3.1). Patients who are randomised to the comparator group will receive the combination of vancomycin plus aztreonam. The dose of vancomycin will be based on the patient's actual weight (see Section 5.5.3.2). Patients will receive vancomycin intravenously every 12 hours. Each dose will be infused over 120 minutes. The vancomycin dose will be adjusted according to the patient's renal function and may be adjusted based on vancomycin levels according to local practices. The component of the comparator treatment regimen to provide activity against Gram-negative bacteria will be aztreonam. Patients will receive 1 gm intravenously in a volume of 100 mL given over 30 minutes every 8 hours. The aztreonam dose will be adjusted according to the patient's renal function (see Section 5.5.3.3). Investigators may discontinue the Gram-negative coverage at their discretion provided that the patient meets the criteria for discontinuing aztreonam/aztreonam placebo. Criteria for discontinuing the aztreonam/aztreonam placebo are provided in Section 5.5.3.3. Creatinine clearance is required at baseline and it is expected that the investigator will continue to monitor the patient's creatinine clearance level as clinically relevant throughout the study.

In order to maintain the blind, patients will also receive either normal saline, 5% dextrose in water, or 5% glucose as placebo. See Section 5.5.2 for details regarding the infusion schedule. There will be no switch to oral antibiotic therapy during the study.

All patients will have a trough vancomycin/placebo concentration sample taken at steady state (prior to dosing at Day 3) and drug concentrations will be assessed via a central laboratory (see Section 6.4.7). Local vancomycin levels will be captured blindly when used for dose adjustments. The study will attempt to enrich for MRSA infections to gain experience with ceftaroline fosamil MICs of 2 mg/L by the selection of countries and sites with high prevalence of MRSA.

On days where electrocardiogram (ECG) recordings, safety laboratory assessments, and vital sign measurements are obtained, the procedures should be collected ±30 minutes from the end of one of the study drug infusions.

A single blinded review will be performed to determine cure and evaluability rates in the overall population after approximately one-third of the patients have completed the study to

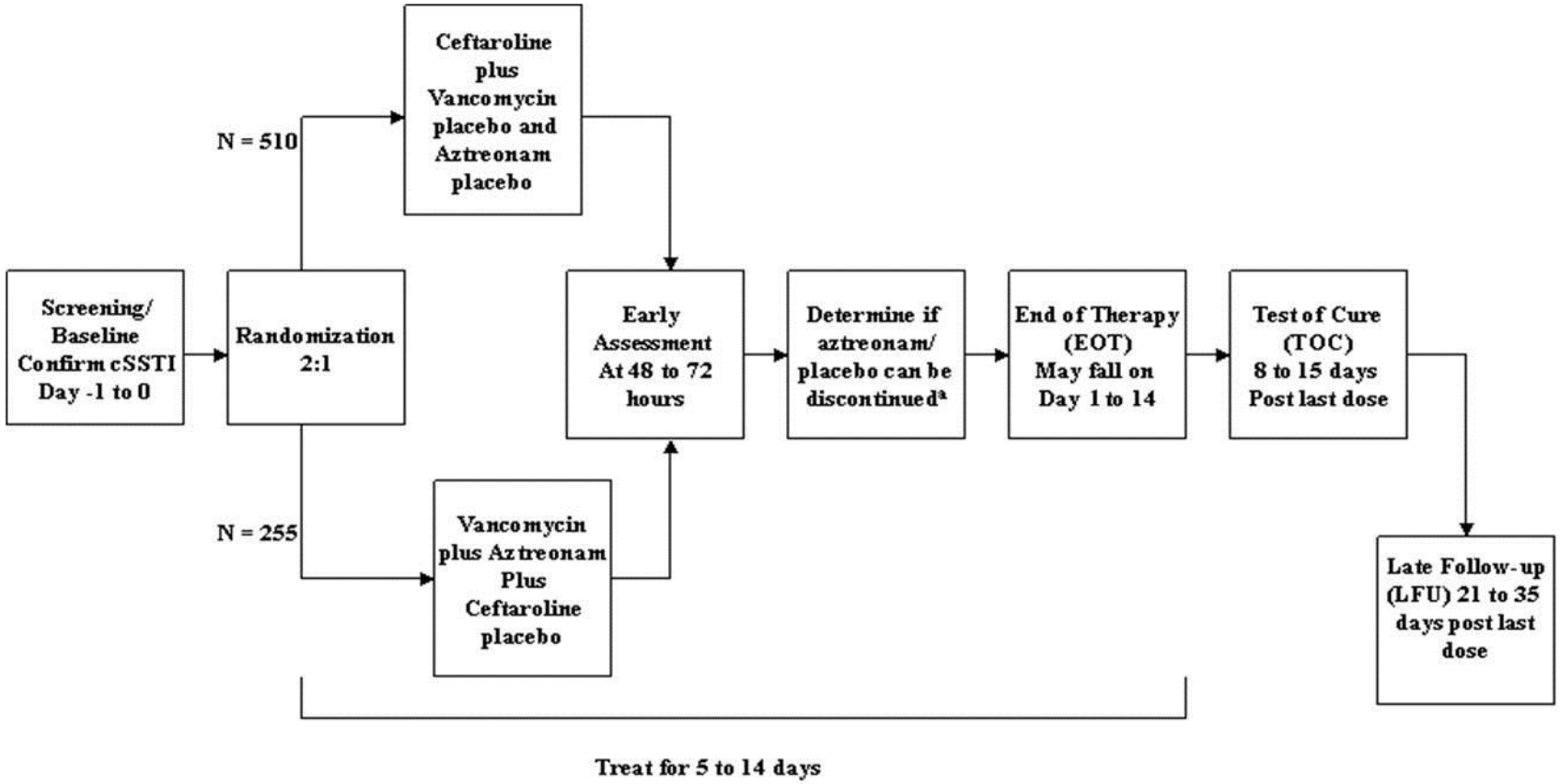
ensure that the underlying assumptions hold and thus the trial has sufficient power based on the projected sample size.

The study will utilize a blinded evaluability committee to determine whether patients are evaluable for the CE and microbiologically evaluable (ME) analysis sets. This team will review blinded data prior to database lock by focussing on such areas as microbiology, concomitant medications, and on-study surgical interventions. Details will be outlined in the committee charter.

In addition, AstraZeneca will pursue complete data gathering (eg, through questionnaires) to allow proper safety evaluations for the following events: haemolytic anaemia, drug-induced liver disease, renal impairment, and seizures. These events are currently classified as important potential risks for ceftaroline fosamil in the global and regional risk management plans.

A study design flow diagram is presented in Figure 1. Details of the study plan are included in Table 2.

Figure 1 Study design Flow Diagram



[a] Investigators may discontinue Gram-negative coverage provided criteria in Section 5.5.3 are met

Table 2 Schedule of Assessments

	Screening Period	Treatment Period					Follow-Up Period	
	Baseline	Study Drug Administration				EOT[d]	TOC[e]	LFU[f]
Day	**–1 to 0**	**1 [a] and 2**	**3[b]**	**4 to 9 (while on study drug)[c]**	**10 to 14 (while on study drug)[c]**	**(may fall on Day 1 to 14)**	**8 to 15 days after last dose of study drug**	**21 to 35 days after last dose of study drug**
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical history, surgical history, and demographics	X							
Prior and/or concomitant medications	X	X	X	X	X	X	X	X[g]
Physical examination[h]	X		X	X (Day 7)	X (Days 10 and 14)	X	X	
Vital sign measurements	X	X	X	X (Day 7)	X (Days 10 and 14)	X	X	
Temperature	X (Highest)	X (3 times/day)	X (3 times/day)	X (Highest)	X (Highest)	X (Highest)	X	
Record height	X							
Record weight	X		X			X		

Table 2 Schedule of Assessments

	Screening Period	Treatment Period					Follow-Up Period	
	Baseline	**Study Drug Administration**				**EOT[d]**	**TOC[e]**	**LFU[f]**
Day	**–1 to 0**	**1 [a] and 2**	**3[b]**	**4 to 9 (while on study drug)[c]**	**10 to 14 (while on study drug)[c]**	**(may fall on Day 1 to 14)**	**8 to 15 days after last dose of study drug**	**21 to 35 days after last dose of study drug**
12-lead ECG[i]	x (triplicate)		x (single)			x (single)	x (single)	
Clinical assessment of cSSTI[j]	x	x	x	x	X	x	X	
Assessment of clinical response[k]						x	X	
PK[b] and vancomycin levels[, m]			x[m]					
Record procedures performed on the cSSTI site	x	x	x	x	x	x	X	
Record adverse events		x	x	x	x	x	X	
Record serious adverse events	x	x	x	x	x	x	X	x
PT/INR/PTT	x		x[l]	x[l] (Day 7)	x[l] (Days 10 and 14)	x[l]	X	
Safety laboratory tests (CBC with differential and comprehensive metabolic panel)	x		x [l]	x [l] (Day 7)	x [l] (Days 10 and 14)	x [l]	X	

Table 2 Schedule of Assessments

	Screening Period	Treatment Period					Follow-Up Period	
	Baseline	**Study Drug Administration**				**EOT[d]**	**TOC[e]**	**LFU[f]**
Day	**–1 to 0**	**1 [a] and 2**	**3[b]**	**4 to 9 (while on study drug)[c]**	**10 to 14 (while on study drug)[c]**	**(may fall on Day 1 to 14)**	**8 to 15 days after last dose of study drug**	**21 to 35 days after last dose of study drug**
Direct Coombs test (local laboratory)	x					x	X	
Urinalysis, microscopy[n]	x		x		x (Day 10)	x	X	
Pregnancy test	x[o]					x[p]		
Estimate creatinine clearance[l]	x	As clinically relevant						
Measure C-reactive protein	x		x			x		
Microbiological assessment	x[q]		x[r]	x[r]	x[r]	x[r]	x[r]	x[r]
Blood culture[s]	x		x[t]	x[t]	x[t]	x[t]	x[t]	x[t]
Study drug randomisation[u]	x							
Study drug administration		x	x	x	x	x		
Record patient location[v]	x	x	x	x	x	x		
Record rehospitalizations and ER visits								x

a Treatment Day 1 is the first day of study drug administration; it starts when the first dose of study drug is started and lasts 24 hours. Subsequent treatment days are consecutive 24-hour intervals. Procedures performed on Day 1 should also be performed on Day 2.

b For sites participating in the PK portion of the study, see Section 6.6.1 Collection of samples. See footnote "m "to ensure adequate samples are taken.

c Visit assessments on Days 4 to 9 and 10 to 14 are only for those patients still on study drug, not those who have stopped and completed the EOT assessments. These visits will have daily assessments unless otherwise noted.

d Perform the EOT assessments within 24 hours of administering the last dose of study drug.

e Perform the TOC assessments 8 to 15 days after administration of the last dose of study drug.
f Perform the LFU assessments 21 to 35 days after administration of the last dose of study drug. The LFU visit assessments may be conducted via the telephone unless the patient has signs and symptoms of relapse, in which case, the patient will be required to attend the study centre for additional LFU visit assessments.
g Record only concomitant antimicrobial agents taken between the TOC and LFU visits.
h Perform complete physical examination at baseline and brief physical examinations on Days (±1 day) 3, 7, 10, 14, EOT and TOC visits.
i Obtain electrocardiogram recordings at baseline (3 times each separated by at least 1 minute within a 15 minute period), Day 3 (±1 day), EOT, and TOC visits. The electrocardiogram recording should be collected ± 30 minutes from the end of one of the study drug infusions.
j Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area indicating with a marker lesion size at the site of infection, level of pus/collection, and pain or tenderness).
k Document both components of the cure, improvement, and resolution of signs and symptoms. See Section 6.3.1 for the definition of clinical response.
l Perform PT/INR/PTT, and safety laboratory tests at baseline, Days (±1 day) 3, 7, 10, 14, EOT, and TOC visits. At the EOT visit, PT/INR/PTT and safety laboratory tests will not be performed if the assessment was performed within the prior 24 hours. Creatinine clearance is required at baseline and it is expected that the investigator will continue to monitor the patient's creatinine clearance level as clinically relevant throughout the study. Safety laboratory assessments should be collected ± 30 minutes from the end of one of the study drug infusions.
m To measure the vancomycin trough levels, there should be an additional tube drawn before the first infusion of the treatment day. The Ceftaroline PK samples can be taken in relation to any infusion.
n Perform the urinalysis and urine microscopy at baseline, Day 3 (±1day), Day 10, 14, EOT, and TOC visits. At the EOT visit, samples for urinalysis and urine microscopy will not be performed if the assessments were performed within the prior 24 hours.
o Urine pregnancy test for women of childbearing potential and those who are fewer than 2 years postmenopausal.
p If the pregnancy test is positive at the EOT visit, follow the reporting requirements in Section 13.3.
q Obtain an appropriate cSSTI site specimen at baseline. In the expansion period this will not be performed if the assessments were carried out within the 72 hours prior to the first dose. The baseline microbiological assessment will use data from the prior sample. Culture the specimen and perform Gram-stain and susceptibility testing.
r Perform microbiological assessment of cSSTI site specimen when medically indicated, but ONLY if a focus of infection is present. Perform a microbiological assessment at EOT if the patient discontinued from the study drug for insufficient therapeutic effect and a focus of infection is present. Perform a microbiological assessment at TOC if a focus of infection is present. Perform a microbiological assessment at the LFU visit in patients experiencing relapse, if clinically appropriate, and if a focus of infection is present.
s Obtain blood for culture at baseline (can be up to 72 hours before the first dose in the MRSA expansion period and pathogens from positive blood cultures must be made available for in vitro susceptibility testing). Blood cultures should be repeated upon receipt of a positive result (rather than daily) until sterilisation is confirmed in those patients with a positive result at baseline (see Section 3.1.2).
t Obtain blood for culture if the previous blood culture was positive. Obtain a blood culture at the TOC visit if any of the previous blood cultures were positive. Obtain blood for culture at the LFU visit if medically indicated and the patient is experiencing clinical relapse.
u Verify the patient meets all study inclusion and exclusion criteria before randomisation.
v Record the location/ward of the patient, ie intensive care unit, etc. each day, but only once per day for the location as of 12:00 h (12:00 pm/noon).

Abbreviations: CBC, complete blood count; cSSTI, complicated skin and soft tissue infection; ECG, electrocardiogram; EOT, End of Therapy; INR, international normalized ratio; LFU, Late Follow-up; PK, pharmacokinetic; PT, prothrombin time; PTT, partial thromboplastin time; TOC, Test of Cure.

3.1.1 Definitions of complicated bacterial skin and soft tissue infections

If patient has multiple lesions, select one as the primary lesion. This lesion must be used for determination of eligibility criteria and all subsequent measurements and assessments. The case definition for cSSTI includes the presence of 1 or more of the following types of infections:

- **Cellulitis**: a diffuse skin infection characterised by spreading areas of erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, minimum length of 10 cm and width of 7.5 cm).

- **Traumatic or surgical wound infection**: an infection characterised by purulent drainage/or collection from an injury-related wound or surgical wound with surrounding erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, the shortest distance of redness, oedema, and/or induration extending at least 5 cm from the peripheral margin of the wound). Appropriate surgical intervention must be completed prior to the first dose of study drug or up to at most, 48 hours after the first dose of study drug.

- **Major cutaneous abscess**: an infection characterised by a collection of pus within the dermis or deeper that is accompanied by erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, the shortest distance of redness, oedema, and/or induration extending at least 5 cm from the peripheral margin of the abscess). The abscess must undergo incision and drainage prior to the first dose of study drug or up to at most, 48 hours after the first dose of study drug. Major cutaneous abscesses will be limited to 30% of the study population.

- **Burn infection**: an infection characterised by purulent drainage, erythema, oedema, and/or induration of a minimum surface area of 75 cm^2. (eg, the shortest distance of redness, oedema, and/or induration extending at least 5 cm from the peripheral margin of the burn infection). Burns must involve less than 15% of the body surface area and the infection must have been acquired within 7 days of hospitalisation. Appropriate surgical intervention must be completed prior to the first dose of study drug or up to, at most, 48 hours after the first dose of study drug.

- Patients may only be enroled into the MRSA expansion period if a skin infection site culture and/or blood culture obtained within the 72 hours prior to the first dose is positive for MRSA.

For further eligibility criteria, refer to Section 4.1.

3.1.2 Microbiological assessments

Sites should refer to the study-specific manual, which will be provided from the central reference laboratory, for specifics regarding microbiological assessments, collection, and reporting.

3.1.2.1 Microbiological supplies

The central reference laboratory will supply to the local laboratory media containing transport vials and instructions for shipment of the specimens. The sites will have the option to do sensitivity testing of the pathogen to the study and comparator drugs by the disk diffusion assay. The antibiotic disks will assess pathogen sensitivity based on zone size. Antibiotic disks used to test ceftaroline fosamil and the comparator drugs will be supplied by the AstraZeneca central reference laboratory. Storage information for antibiotic will be supplied by the manufacturer for the comparator drug (vancomycin) only**.** The central reference laboratory will confirm the susceptibility of all isolates tested at the local laboratory and resolve any discrepancies between the local and central laboratory results.

Upon receipt and identification confirmation of the clinical trial isolates, the central reference laboratory will confirm both the disk diffusion zone size (mm) and the MIC (mg/L) values using the Sensititre frozen broth microdilution MIC panels ([redacted]). The site's local laboratory must also ship the Gram-stained slides to the central reference laboratory to confirm interpretation of results.

3.1.2.2 Specimen collection

Microbiology is a very important part of this protocol and every means possible of obtaining uncontaminated viable specimens that lead to a positive culture result at baseline and a definitive result at all other times is encouraged. To be eligible for the MRSA expansion period, all patients must have a skin infection site culture and/or blood culture obtained within the 72 hours prior to the first dose, which is positive for MRSA. This will be assessed as the baseline culture. The baseline MRSA isolate (and any co-infecting isolates) must be stored and made available to the central laboratory.

An adequate clinical specimen for microbiologic evaluation should be obtained from all patients (for the expansion period this can be within the 72 hours prior to the first dose) and sent to the local laboratory for microscopic evaluation (eg, Gram stain), culture, and in vitro antibacterial susceptibility testing will be performed on the appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods (Murray et al 2007). The Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, these tests may be performed within 24 hours of collection if the specimen is stored at 2°C to 8°C before processing. The specimen for microscopic evaluation (eg, Gram stain) and culture should be collected before administration of antimicrobial therapy. The specimen may be obtained by any one of the following:

- Punch biopsy or needle aspirate of the leading edge of redness (point of maximal inflammation and redness) for patients with cellulitis (see Appendix F for guidance on the needle aspiration technique)

- Biopsy, needle aspiration, or surgically obtained specimens of purulent material from an infected wound or burn (a swab is not recommended)

- Incision and drainage procedure using sterile techniques that minimize potential isolation of normal skin flora, aspiration of purulent material, or tissue from a cutaneous abscess

- If an appropriate microbiological sample is not obtained by the aforementioned means, deep swabs will be accepted as long as they are obtained during significant surgical interventions and/or using the Levine technique (see Appendix F)

Blood cultures: In the expansion period, if no blood samples were taken in the 72 hours before the first dose, these should be taken at the baseline assessment. Blood cultures will also be obtained by direct venipuncture and cultured for aerobes and anaerobes. Two samples should be collected from 2 separate venipuncture sites. If they are obtained from the same site, then an interval of 30 minutes should occur between collections. If the blood culture is positive for a pathogen, it should be repeated until a negative result is obtained. If the culture is negative, repeat culture should be performed if it is clinically indicated.

If treatment is discontinued before the EOT visit or if the patient is withdrawn from the study (if additional/alternate antibacterials are administered), an appropriate specimen for culture should be obtained after stopping the initial treatment but before the new treatment is administered. Specimens for microbiological assessment of cSSTI obtained after baseline should be collected when medically indicated and only if a focus of infection is present.

If the patient presents with relapse at the LFU visit, a specimen for microbiological assessment should be collected if clinically appropriate and if a focus of infection is present; blood cultures should be obtained if medically indicated.

3.1.2.3 Shipment of specimens

The central reference laboratory will supply media containing transport vials and instructions for shipment of clinical isolates from the local laboratory to the central reference laboratory.

3.1.2.4 Specimen analysis

All bacterial pathogens (aerobes and anaerobes) will be identified to the genus and species level using confirmatory not presumptive, identification methods. Gram-stain results are essential. All bacterial organisms identified are to be recorded in the electronic case report forms (eCRFs). The investigator will determine and record whether the organism is considered to be a pathogen. Consult the microbiology laboratory manual for a list of bacteria that are normally considered pathogens for this indication.

All susceptibility testing performed at the local laboratory must be in accordance to CLSI methodology. The central reference laboratory will provide a laboratory manual that will describe pivotal microbiological procedures.

The central reference laboratory will confirm pathogen identifications and susceptibility test results on all clinical isolates reported and shipped by the local laboratory. Definitive

identification of the pathogen and susceptibility test results will default to the central reference laboratory result if there are noted discrepancies.

For the microbiological assessment, the investigator should collect the following information:

- Anatomic location of where the specimen was obtained
- Specimen identification number
- Description of how the sample was obtained, processed, and transported to the laboratory, including the date and time of sample collection
- When appropriate, in vitro susceptibility testing of the isolates to both the study drug and other antibacterial drugs that may be used to treat cSSTI caused by the pathogens targeted by the study drug. In vitro susceptibility for comparator drugs should be performed using standardized methods, as outlined in Section 3.1.2.2, for the study drugs unless otherwise specified (standard methods for in vitro susceptibility testing are developed by organizations such as the CLSI). Investigators should describe the exact methodology used for susceptibility testing if a standardized method was not used
- Gram stain of the specimen and identification of the cultured isolate

Characterization of virulence factors associated with the bacterial pathogens (eg, Panton-Valentine Leukocidin-positive isolates of *S. aureus* or *emm*-types of *S. pyogenes*) will be performed by an external provider identified by AstraZeneca.

3.1.2.5 Isolate storage

All culture isolates maintained at the central reference laboratory will be kept for a period of no longer than 3 months post marketing authorization application approval status. Samples will not be disposed of until approval is obtained from AstraZeneca.

3.1.2.6 Resistance

The central reference laboratory will confirm all resistant (ie, ≥4-fold increase in MIC) isolates reported by the local laboratory. All posttherapy isolates showing a change in MIC ≥4-fold from the baseline pretherapy isolate will be shipped to an AstraZeneca-designated laboratory for further genetic analyses. Other isolates may also be shipped to designated laboratories for further analysis.

3.2 Rationale for study design, doses, and control groups

The purpose of this study is to assess whether ceftaroline fosamil is noninferior to vancomycin plus aztreonam in the clinical cure rate at the TOC visit in the MITT and CE analysis sets of adult patients with cSSTI.

The therapeutic dose of ceftaroline fosamil (600 mg every 8 hours infused over 120 minutes) was selected based on microbiology surveillance data, MIC distribution, PK/PD modelling and simulation of probability of PK/PD target attainment to cover all relevant pathogens, in particular *S. aureus* and MRSA, which are the most commonly isolated pathogens from cSSTIs. For details, see Section 1.4, Rationale for conducting this study. The study will generate safety data for this dose regimen. Ceftaroline fosamil, dosed at 600 mg and infused over 60 minutes every 12 hours, was studied in previously conducted global studies in cSSSI patients in which ceftaroline fosamil was shown to be safe and effective (see Section 1.2).

Vancomycin has been chosen as a component of the comparator treatment regime for its activity against Gram-positive pathogens. Ceftaroline has bactericidal activity against MRSA; therefore, the comparator regimen should include a bactericidal anti-MRSA agent. Vancomycin, unlike linezolid, is bactericidal and is widely acceptable as standard of care for initial treatment of suspected MRSA-associated cSSTI (Stevens et al 2005, Dryden 2010, Liu et al 2011).

Similar cSSTI registration studies of daptomycin (Arbeit et al 2004), tigecycline (Breedt 2005, Sacchidananda 2005) ceftobiprole (Noel et al 2008a, Noel et al 2008b), and telavancin (Stryjewski et al 2008) used vancomycin as an active comparator and employed a similar approach as this cSSTI study (eg, noninferiority design, duration of therapy, timing of clinical assessments).

The predictability, reproducibility, and consistency of efficacy results for vancomycin, as well as its global therapeutic acceptance for the treatment of cSSTI caused by Gram-positive pathogens support the sensitivity-to-drug effect requirement as an active control agent for this noninferiority study. The proposed vancomycin dosage regimen is based on the patient's weight and will be given every 12 hours infused over 120 minutes (Liu et al 2011). After the initial dose, subsequent doses of vancomycin will be adjusted for those with renal impairment. This dosing regimen has been selected to be inline with current guidances and to attempt to achieve minimum trough levels of 10 mg/L. Vancomycin trough levels will be measured on all patients at steady state. Those sites who routinely adjust vancomycin based on trough levels in accordance with their local practice may do so, and stringent blinding plans will be in place at such sites.

The component of the comparator treatment regimen to provide activity against Gram-negative pathogens is aztreonam. Aztreonam is a monobactam antibiotic with activity against common Gram-negative pathogens involved in cSSTI (eg, *Citrobacter* spp, *E. coli*, *Enterobacter* spp, *Klebsiella* spp, and other members of the Enterobacteriaceae family) and has no overlapping activity with the Gram-positive activity of vancomycin. Aztreonam is a recommended therapy for Gram-negative cSSTI in expert guidelines (Stevens et al 2005). The dose of aztreonam will be 1 gm given intravenously every 8 hours with adjustment based on renal function. Many of the cSSTI studies referenced in Section 1.2 used vancomycin plus aztreonam as the comparator study drug regimen. This combination (vancomycin and aztreonam) is considered to be a suitable comparator for the proposed study.

4. PATIENT SELECTION CRITERIA

Investigators should keep a record, the patient screening log, of patients who entered prestudy 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. Patient must provide a signed written informed consent prior to any study-specific procedures

2. Patient must be a male or female, aged 18 years and older

3. Patient must have one of the following cSSTIs:

- **Cellulitis**: a diffuse skin infection characterised by spreading areas of erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, minimum length of 10 cm and width of 7.5 cm)

- **Traumatic or surgical wound infection**: an infection characterised by purulent drainage/or collection from an injury-related wound or a surgical wound with surrounding erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, the shortest distance of redness, oedema, and/or induration extending at least 5 cm from the peripheral margin of the wound). Appropriate surgical intervention must be completed prior to the first dose of study drug or up to, at most, 48 hours after the first dose of study drug.

  Note: in some cases the shortest distance of redness, oedema and/or induration extends less than 5 cm from the peripheral margin of the wound/abscess/burn infection. However, if the surface area of the infection is at least 75cm^2, then the patient will be eligible. Please refer to the Wound Management Guidelines for further clarification.

- **Major cutaneous abscess**: an infection characterised by a collection of pus within the dermis or deeper that is accompanied by erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, the shortest distance of redness, oedema, and/or induration extending at least 5 cm from the peripheral margin of the abscess). The abscess must undergo incision and drainage prior to the first dose of study drug or up to, at most, 48 hours after the first dose of study drug. The number of patients with major cutaneous abscesses will be limited to no more than30% of the study population.

- **Burn infection**: an infection characterised by purulent drainage, erythema, oedema, and/or induration of a minimum surface area of 75 cm^2 (eg, the shortest distance of redness, oedema, and/or induration extending at least 5 cm from the peripheral margin of the burn infection). Burns must involve less than 15% of the body surface area and acquired within 7 days of hospitalisation. Appropriate surgical intervention must be completed prior to the first dose of study drug or up to, at most, 48 hours after the first dose of study drug.

4. (This criterion applies only to the main part of the study and is not required for the MRSA expansion period.)

   Patients must demonstrate at least one of the following criteria (for the first 3 bullets, the criterion must be met within 24 hours prior to first dose of study drug):

- Temperature ≥38.0°C (100.4°F) or ≤36.0°C (96.8°F)

  Note: preconsent axillary, tympanic, oral and rectal temperatures are acceptable as long as they are documented by a health care professional and measured within the 24 hours prior to administration of the first dose of study drug

and/or

- White blood cells >12000 cells/mm^3 or <4000 cells/mm^3 or >10% band forms (immature white blood cells)

and/or

- Heart rate >90 beats per minute and respiratory rate >20 breaths per minute after 10 minutes of rest

and/or

- One or more of the following comorbidities:

  – Diabetes mellitus requiring drug therapy (note: patients with diabetic foot infections are excluded as per exclusion criterion #8)

  – Stage 2 or 3 HIV infection (per Center for Disease control classification 2008) (Schneider et al 2008) (note: patients with a CD4 count <150 cell/microliter within 6 months prior to first dose of study drug or suspected opportunistic infection are excluded)

  – Chronic renal impairment (estimated creatinine clearance ≥20 mL/min to <50 mL/min) as calculated by the Cockcroft-Gault formula (Cockcroft et al 1976) provided in Appendix D

- Cirrhosis with Child-Pugh Stage A or B (note: patients with Child-Pugh Stage C are excluded)

- cSSTI below the knee associated with peripheral vascular disease diagnosed on the basis of any of the following: claudication at a distance of at least 20 meters; resting ankle-brachial index 0.3 to 0.8; prior femoral artery bypass grafting; or prior aortic aneurysm repair (note: patients with ulcers due to peripheral vascular disease are also excluded)

- Albumin <2.5 g/dL or prealbumin <11 mg/dL in the absence of liver disease

- Use of immunosuppressive agents, including a glucocorticoid (Note: patient who is receiving or has received >40 mg per day of prednisone or equivalent for more than 1 week within the 2 weeks prior to study enrolment is excluded)

- Malignancy, other than nonmelanoma skin cancers, with a life expectancy of >3 months

5. Patient must have an infection of sufficient severity to warrant hospitalisation

6. Patient must have an infection of sufficient severity such that it is expected to require at least 5 days of IV antibiotic therapy (at least 120 hours of study participation period from the first study dose)

7. Female patients of childbearing potential may be entered if pregnancy testing is negative and the patient agrees to abstain from procreational sexual intercourse or must use double-barrier contraceptive measures for the duration of the study, unless the subject is a female already using effective oral contraceptives, in which case she must continue to use the oral contraceptive and will use one additional barrier method.

8. For the MRSA expansion period, patients must have a positive culture for MRSA that has been obtained from the skin infection site and/or blood samples at any time within the 72hrs before the first dose.

4.2 Exclusion criteria

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

1. Patient is involved in the planning or conduct of the study (applies to both AstraZeneca/[redacted] staff and staff at the study site)

2. Patient has previously enroled or been randomly assigned into the present study

3. Patient has participated in another clinical study with an investigational drug or investigational device during the last 30 days

4. Patient has received systemic antibacterial drugs for 24 hours within 96 hours prior to first dose of study drug. (Note that for the MRSA expansion period patients are only to be excluded if they have received systemic drugs that are active against MRSA for >24 hours within the 96 hours prior to first dose of study drug. Patients who have received prior antibiotic that is not active against MRSA are eligible).

   Patients who have received antibiotics for >24 hours may be enroled under the following circumstances:

- The clinic notes objectively document the clinical progression of cSSTI (ie, not by patient history alone), and for the MRSA expansion period the patient has not received either ceftaroline or vancomycin, OR

- Patient recently completed a treatment course with an antibacterial drug for an infection other than cSSTI and the drug does not have antibacterial activity against bacterial pathogens that cause cSSTI

5. Patient has uncomplicated skin and skin structure infections such as a simple abscess, impetigo, furunculosis, or folliculitis or other uncomplicated infections (eg, patients with infections expected to improve with simple incision and drainage)

6. Patient has skin and skin structure infection suspected to be caused by viral pathogens (eg, varicella, herpes zoster, or herpes simplex) or fungal pathogens

7. Patient has skin and skin and soft tissue infection suspected to be caused by anaerobic pathogens (eg, perirectal abscess)

8. Patient is diabetic and the skin and soft tissue infection is inframalleolar (ie, diabetic foot infections). cSSTIs in other locations in a diabetic patient are permitted.

9. Patient has decubitus ulcers, ulcers due to peripheral vascular disease.

10. Patient has an infection caused by human bites (ie secondary infected arthropod stings and bites are permitted)

11. Patient has necrotizing skin infection including necrotizing fasciitis, Fournier's gangrene, clostridial myonecrosis, or ischemic gangrene

12. Patients has sternal wound infections

13. Patient is likely to require amputation of the primary site of infection, preventing evaluation of the clinical and microbiologic response to treatment

14. Patient has an infection that involves prosthetic materials, a catheter, or other foreign body material that will not or can not be removed

15. Patient has another focus of bacterial infection requiring concomitant antibiotics that would interfere with evaluation of the response to study drug (for the MRSA expansion period, only antibiotics known to be active against MRSA are excluded)

16. Patient has ecthyma gangrenosum

17. Patient has clinical (eg, visible bone or positive probe-to-bone test) or radiographic evidence of osteomyelitis or septic arthritis

18. Patient has critical limb ischemia of the affected limb, defined as resting ankle-brachial index <0.3. Patients with ulceration or gangrene of the foot are also excluded

19. Patient has evidence of an immediate life-threatening disease including, but not limited to, respiratory failure, acute congestive heart failure, acute coronary syndrome, or unstable arrhythmias

20. Patient is receiving or has received >40 mg per day of prednisone or equivalent for more than 1 week within the 2 weeks prior to study enrolment.

21. Patient has sustained shock, defined as systolic blood pressure <90 mm Hg for >2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure

22. Patient is pregnant or lactating and intends to continue breastfeeding

23. Patient has burns of >15% of total body surface area

24. Patient's body weight is >130 kg

25. Patient has severe neutropenia (defined as an absolute neutrophil count <500 cells/mm^3) or is expected to be severely neutropenic within the next 14 days

26. Patient has known or suspected exclusive monomicrobial infections with extended-spectrum β-lactamase positive Gram-negative organisms, or monomicrobial *Pseudomonas* infections

27. Patient has documented history of hypersensitivity or allergic reaction (urticaria, angiooedema, anaphylaxis, desquamative rash) to any β-lactam antimicrobial, vancomycin, or aztreonam

28. Patients has Child-Pugh Stage C chronic liver disease

29. Patient has a history of failure of or prior use of vancomycin or aztreonam as therapy for the current cSSTI, or prior isolation of an organism with in vitro resistance to vancomycin or aztreonam

30. Patient requires significant surgical intervention that cannot be performed within 48 hours after initiating study drug therapy

31. Patient has severe impaired renal function (creatinine clearance <20 mL/min) estimated by the Cockcroft-Gault formula (Cockcroft et al 1976)

32. Patient has previously participated in a study of ceftaroline fosamil

33. Patient is unable or unwilling to adhere to the study-specified procedures and restrictions

34. Patient has any condition that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the data

See Section 5.3 for procedures for withdrawal of incorrectly enroled patients.

5. STUDY CONDUCT

5.1 Restrictions during the study

Given the severity of illness for eligible patients, it is expected that all patients enroled in the study will be hospitalised until the EOT visit. In the unusual event that a patient is able to be discharged from the hospital prior to EOT, OPAT is permitted provided qualifications outlined in Section 5.5.4 are met. There are no specific dietary or activity restrictions other than those typical for a patient with cSSTI.

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Patient enrolment, randomisation, and initiation of investigational product

The investigator will:

- Obtain signed informed consent from the potential patient before any study-specific procedures are performed. For the expansion period, this includes consent to use the local microbiology cultures and associated data taken in the 72 hr period before the first dose, which identified the patient as eligible.

- Assign the 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).

- Determine patient eligibility (see Sections 4.1 and 4.2). For questions regarding patient eligibility, please contact your [redacted] medical monitor to discuss the case

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

5.2.1 Procedures for randomisation

The study will include patients with a mixture of cellulitis, traumatic or surgical wound infections, major cutaneous abscess, or burn infections. The number of patients with major cutaneous abscesses will be limited to no more than 30% of the clinical trial population.

Randomisation codes will be assigned strictly sequentially, as patients become eligible for random assignment into the study. Eligible patients will be randomly assigned in a 2:1 ratio to ceftaroline fosamil (approximately 510 patients) or vancomycin plus aztreonam (approximately 255 patients).

The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the interactive voice response system (IVRS)/interactive web response system (IWRS) database. The randomisation scheme will be produced by a computer software program called GRand (AstraZeneca Global Randomisation System) that incorporates a standard procedure for generating randomisation numbers.

Patient eligibility will be established before patients are randomly assigned to treatment. 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 identification numbers for that patient's supply of drug.

5.3 Procedures for handling patients incorrectly enroled, randomised, or initiated on investigational product

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

Where patients who 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 after initiation, a discussion should occur between the AstraZeneca physician or delegate and the investigator regarding whether to continue or discontinue the patient from treatment.

The AstraZeneca physician or delegate is to ensure that 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

AstraZeneca, [redacted], 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 that all infusion bags or bottles are appropriately labeled and masked according to the Handling Instructions. The dose of investigational product (ceftaroline fosamil, vancomycin, and aztreonam) may be adjusted based on the patient's renal function.

In order to maintain the blind, patients randomised to receive ceftaroline fosamil will receive vancomycin placebo and aztreonam placebo and patients randomised to receive vancomycin plus aztreonam will receive ceftaroline fosamil placebo. The unblinded pharmacy staff or unblinded study staff will cover the infusion bag and tubing so that the study drug solution will not be seen by the blinded staff or patient.

The vancomycin dose may also be adjusted based on vancomycin trough levels according to local practices. The unblinded pharmacy staff or unblinded study staff will be responsible for managing dose adjustments.

AstraZeneca/[redacted] will assign an unblinded monitor to confirm drug accountability. Additional details regarding blinding of the investigational products can be found in the Handling Instructions.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigators 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 that this documentation is maintained and reporting the action to AstraZeneca/[redacted], without revealing the treatment given to the patient to the blinded AstraZeneca/[redacted] 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 products

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 of L-arginine/gm of ceftaroline prodrug) is added as an alkalizing agent to control pH of the constituted solution to pH 4.8 to 6.2. 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%, 5% dextrose in water, or 5% glucose for dilution of the infusion. Refer to the Handling Instructions for preparation details.

Vancomycin hydrochloride is a lyophilised powder for preparing IV infusions. Each vial contains the equivalent of 500 mg or 1 gm vancomycin base. Refer to the Handling Instructions for preparation details.

Aztreonam is presented as a sterile powder containing approximately 1 gram of aztreonam per vial. Following constitution, the product is for IV use. Refer to the Handling Instructions for preparation details.

Information on the investigational product (ceftaroline fosamil and vancomycin plus aztreonam) dosage, form, and strength is provided in Table 3.

Table 3 Investigational Product

Investigational product	Dosage form and strength
Ceftaroline fosamil	Sterile crystalline powder in a single-dose, clear glass 20-mL vial, intravenous, 600 mg every 8 hours
Vancomycin	Lyophilized powder, intravenous, dose strength (based on patient's actual weight) every 12 hours
Aztreonam	Sterile powder containing approximately 1 gram of aztreonam per vial, intravenous, 1 gm every 8 hours

5.5.2 Doses and treatment regimens

Patients are required to be hospitalised during treatment with study drug. Patients are to receive a minimum of 5 days of study drug. However, the duration of therapy may be adjusted up to 14 days based on the clinical response of the patient. Note: 1 day of treatment is considered to be a 24-hour period starting from the time the first study dose is started.

This trial will be double-dummy to maintain the blind given the different dosing regimens, ie, patients randomised to receive ceftaroline fosamil will receive vancomycin placebo and aztreonam placebo and patients randomised to receive vancomycin plus aztreonam will receive ceftaroline fosamil placebo. Table 4 illustrates how placebo will be used in each

treatment group to maintain the blind. There will be no switch to oral antibiotic therapy during the study. In the unusual event that a patient is able to be discharged from the hospital prior to EOT, OPAT is permitted provided qualifications outlined in Section 5.5.4 are met.

Table 4 Dosing Regimens

Hour	Ceftaroline Fosamil treatment arm[a]	Vancomycin plus Aztreonam treatment arm[a]
0 1	Ceftaroline fosamil in 250 mL over 120 minutes	Vancomycin[b] in 250 mL over 120 minutes
2	Aztreonam placebo in 100 mL over 30 minutes	Aztreonam in 100 mL over 30 minutes
3 4 5 6 7		
8 9	Ceftaroline fosamil in 250 mL over 120 minutes	Ceftaroline fosamil placebo in 250 mL over 120 minutes
10	Aztreonam placebo in 100 mL over 30 minutes	Aztreonam in 100 mL over 30 minutes
11		
12 13	Vancomycin placebo in 250 mL over 120 minutes	Vancomycin[b] in 250 mL over 120 minutes
14 15		
16 17	Ceftaroline fosamil in 250 mL over 120 minutes	Ceftaroline fosamil placebo in 250 mL over 120 minutes
18	Aztreonam placebo in 100 mL over 30 minutes	Aztreonam in 100 mL over 30 minutes
19 20 21 22 23		

a Refer to the study drug Handling Instructions for guidance on study drug dosing windows.
b A placebo should be given if the patient is on a 24-hour or 48-hour dosing regimen of vancomycin. Note: q8h regimens of vancomycin are not allowed in this study.

Patients randomly assigned to the ceftaroline fosamil group will receive ceftaroline fosamil in a volume of 250 mL infused over 120 minutes followed by aztreonam placebo in a volume of 100 mL infused over 30 minutes every 8 hours. In addition, vancomycin placebo will be given in a volume of 250 mL infused over 120 minutes every 12 hours. Dose adjustments are discussed in Section 5.5.3.1.

Patients randomly assigned to the vancomycin plus aztreonam group will receive vancomycin, in a volume of 250 mL infused over 120 minutes every 12 hours and aztreonam in a volume of 100 mL infused over 30 minutes every 8 hours. In addition, ceftaroline fosamil placebo will be given in a volume of 250 mL infused over 120 minutes every 8 hours. Dose adjustments are discussed in Section 5.5.3.2 for vancomycin and Section 5.5.3.3 for aztreonam.

Investigators may discontinue the Gram-negative coverage at their discretion provided the patient meets the criteria for discontinuing aztreonam/aztreonam placebo. Criteria for discontinuing the aztreonam/aztreonam placebo can be found in Section 5.5.3.3.

As there are many infusions to be given each day, it will be critical to adhere to the infusion schedule. All doses are to be administered within a +/- 60-minute window.

Investigators should take into account the approximately 1300 mL of IV fluid that patients will receive when assessing the patient's daily fluid intake.

5.5.3 Initial dose determination and adjustments

All dose adjustments during the study must be made by the unblinded pharmacy staff or unblinded study staff. Measurement of estimated creatinine clearance is required at baseline and it is expected that the investigator will continue to monitor the patient's creatinine clearance level as clinically relevant throughout the study. The vancomycin dose may also be adjusted based on vancomycin trough levels according to local practices.

Table 5 Initial Dose and Subsequent Dosing Adjustments

	Initial Dose (Day 1, Infusion 1)	**Subsequent Infusions (Infusion 2 and later)**
Ceftaroline fosamil (in 250 mL)	Initial dose determined upon baseline Creatinine Clearance. 1) >50 mL/min = 600mg 2) value >30 mL/min and ≤50 mL/min = 400mg 3) value ≥20 mL/min and ≤30 mL/min = 300mg 4) less than 20 mL/min = excluded	Based upon follow-up creatinine clearance[a] results 1) >50 mL/min = 600mg 2) value >30 mL/min and ≤50 mL/min = 400mg 3) value ≥20 mL/min and ≤30 mL/min = 300mg 4) less than 20 mL/min = discontinued from study drug therapy

Table 5 Initial Dose and Subsequent Dosing Adjustments

	Initial Dose (Day 1, Infusion 1)	Subsequent Infusions (Infusion 2 and later)
Vancomycin (in 250 mL)	Initial dose determined upon Actual Body Weight (ABW) only. 1) <55 kg, the initial dose will be 15 mg/kg 2) ≥55 kg and ≤75 kg, the initial dose will be 1 gm 3) >75 kg and ≤130 kg, the initial dose will be 15 mg/kg 4) >130 kg will be excluded from the study	<u>Based upon baseline creatinine clearance or follow-up creatinine clearance[a] results</u> Dose adjustment if creatinine clearance < 75 mL/min and ≥ 20 mL/min. Determined by local guidance (recommended guidance is provided in handling instructions). Patients with creatinine clearance < 20 mL/min are to be withdrawn from study drug therapy <u>AND Changes due to local trough level results</u> Determined by local guidance (recommended guidance is provided in handling instructions) Note: Target trough level recommended to be at least 10 mg/L
Aztreonam (in 100 mL)	Initial dose 1gm	<u>Change due to baseline creatinine clearance or follow-up creatinine clearance[a] results.</u> 1) >30 mL/min, no dose adjustment will be made 2) ≥20 mL/min and ≤30 mL/min, the dose should be reduced to 500 mg. 3) less than 20 mL/min while on study must discontinue all study drug therapy Minimum aztreonam dose: 0.5gm (500mg).

a Creatinine Clearance estimate is required at baseline and then as clinically relevant

5.5.3.1 Ceftaroline fosamil initial dose and adjustments

The initial and all subsequent doses of ceftaroline fosamil will be determined by renal function, estimated by the Cockcroft-Gault formula, as follows:

- For patients with an estimated creatinine clearance value of 50> mL/min, the dose of ceftaroline fosamil will be 600 mg every 8hours.
- For patients with an estimated creatinine clearance value >30 mL/min and ≤50 mL/min, the dose of ceftaroline fosamil will be reduced to 400 mg every 8 hours.

- For patients with an estimated creatinine clearance value ≥20 mL/min and ≤30 mL/min, the dose of ceftaroline fosamil will be reduced to 300 mg every 8 hours.

Patients with an estimated creatinine clearance value of less than 20 mL/min will be excluded from the study, and patients whose creatinine clearance value decreases below 20 mL/min while on therapy will be discontinued from study drug therapy. These patients will be followed for safety and clinical outcome of the underlying infection.

Information regarding dose adjustments is included in the Handling Instructions.

5.5.3.2 Vancomycin initial dose and adjustments

The first dose of vancomycin will be given at a dose based on actual body weight as measured at baseline. This initial dose of vancomycin will be:

- If the patient's actual weight is <55 kg, the initial dose will be 15 mg/kg.
- If the patient's actual weight is ≥55 kg and ≤75 kg, the initial dose will be 1 gm.
- If the patient's actual weight is >75 kg and ≤130 kg, the initial dose will be 15 mg/kg.

Patient's with an actual weight of >130 kg will be excluded from the study. The dose will not be changed based on body weight measurements taken after baseline.

Subsequent doses may be adjusted for 2 reasons:

1) Renal function via creatinine clearance estimated by the Cockcroft-Gault formula
2) Vancomycin trough levels according to local practices. If dose adjustment is made based on vancomycin trough levels, target trough level is recommended to be at least 10 mg/L.

If the patient's estimated creatinine clearance result is within the normal range (eg, >75 mL/min), the patient's dose of vancomycin will be determined based on his or her actual weight (as described above) and no dose adjustment will be necessary. If the patient's estimated creatinine clearance results are not within the normal range, the dose of vancomycin should be adjusted according to local guidelines. References to assist with vancomycin dosage both in normal patients as well as those with renal impairment are provided in the Handling Instructions.

Patients with an estimated creatinine clearance value of less than 20 mL/min will be excluded from the study, and patients whose creatinine clearance value decreases below 20 mL/min while on study will be no longer receive study drug. These patients will be followed for safety and clinical outcome of the underlying infection.

5.5.3.3 Aztreonam initial dose and adjustments

Aztreonam will be given to provide activity against Gram-negative infections to those patients randomized to the vancomycin arm. The patients randomized to ceftaroline fosamil will receive aztreonam placebo.

For all patients randomized to the vancomycin/aztreonam arm, the initial dose of aztreonam will be 1 gm intravenously administered as a 30-minute infusion every 8 hours in 100 mL of normal saline, 5% dextrose in water, or 5% glucose.

For subsequent dosing, the dose of aztreonam will be adjusted for renal function, via creatinine clearance estimated by the Cockcroft-Gault formula, as follows:

- For patients with an estimated creatinine clearance >30 mL/min, no dose adjustment will be made.

- For patients with an estimated creatinine clearance ≥20 mL/min and ≤30 mL/min, the dose should be reduced to 50% of the initial dose (50% = 500 mg).

Patients with an estimated creatinine clearance value of less than 20 mL/min will be excluded from the study, and patients whose creatinine clearance value decreases below 20 mL/min while on study must discontinue all study drug therapy. These patients will be followed for safety and clinical outcome of the underlying infection.

Investigators may discontinue aztreonam at their discretion, provided the following circumstances are met:

  - Gram-positive bacteria have been isolated by culture.

  - Gram-negative bacteria have not been identified by either microscopy or culture.

  - The patient completed a minimum of 3 days of Gram-negative therapy.

5.5.4 Outpatient Parenteral Antimicrobial Therapy

Intravenous study drug may be provided on an outpatient basis if the following criteria are met:

- The Sponsor or delegate has verified the certification of the OPAT site or home health agency that will administer the study drug the subject

- The Investigator continues performing face-to-face assessment of the patient at all visits

- The Investigator considers the patient a good candidate for outpatient therapy

- The patient has shown adequate improvement on study medication to warrant hospital discharge

- The personnel administering the study drug to the patient as an outpatient are trained in GCP and protocol procedures and this training is documented in study files

- The outpatient facility (if applicable) and relevant personnel managing the patient are listed on the site level blinding plan and delegation of authority log and (for US sites) Form FDA 1572

- The Investigator can ensure adherence to the blinding plan, drug storage, stability and infusion schedule.

5.5.5 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labeling. The patient kit label text will be translated into the local language.

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

- Study code
- Kit identification number
- Drug name, dosage form, dosage quantity
- Route of administration
- Sponsor name
- Expiry date

Refer to the Handling Instructions for the information contained on the label attached to the infusion bag/bottle.

5.5.6 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. For a description of the appropriate storage conditions for ceftaroline fosamil, vancomycin and aztreonam, refer to the Handling Instructions document.

5.6 Concomitant treatments

All antimicrobial and nonantimicrobial therapy administered within 4 weeks prior to baseline will be documented in the eCRF. Patients who received systemic antibacterial therapy for the

treatment of the current cSSTI within 96 hours prior to the first dose of study drug 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/[redacted] before administration.

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 eCRF.

The following adjunctive therapies are permitted for patients with wounds, major abscesses, and burn infections:

- Initial surgical management to control the infection must be performed prior to the first dose of study drug or up to, at most, 48 hours after the first dose of study drug. These procedures include such interventions as incision and drainage, removal of foreign bodies, and operative debridement of necrotic tissue.

- After 48 hours of receipt of the first dose of study drug, any unplanned surgical intervention to control ongoing infection will be considered evidence of treatment failure.

- Patients may continue to have expected adjunctive wound care procedures involved in the healing process such as dressing changes, use of topical solution including nonspecific antimicrobial drugs such as povidone-iodine, minor bedside debridement, whirlpool treatments, delayed primary closure, skin grafting, suture removal, re-vascularization procedures, hyperbaric oxygen treatments, or surgical interventions planned at the initiation of treatment.

Topical treatments with specific antibacterial activity and Negative Pressure Wound Therapies (NPTW) are **not** allowed.

Patients likely to require an amputation of the primary site of infection will be excluded from the trial. Patients will be excluded from the CE analysis set if an amputation of the primary site of infection occurs after receipt of the first dose of study drug and is not done to control an ongoing infection.

5.7 Treatment compliance

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

The qualified study centre personnel at the investigative study centre will administer IV study therapy and treatment compliance will be assured. For those patients who are discharged from the hospital but continue on IV therapy, IV study therapy will be administered by a qualified

health care provider (see Section 5.5.4). The dose, date, exact start and stop time, and volume of administration of the IV study therapy will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

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

Study drug will be dispensed in a blinded manner by the unblinded site pharmacist or unblinded study staff to the qualified blinded investigator or blinded medically qualified delegate (as documented per blinding plan and delegation of authority log). 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 is 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.

The drug accountability will be verified by the AstraZeneca/[redacted] unblinded study monitor 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.

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

Refer to the Handling Instructions 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) for discontinuation and the presence of any AEs. The EOT assessments should be performed within 24 hours of administering the last dose of study drug and all other visits occurring after the EOT should be performed (see Table 2). Adverse events should also be followed, as appropriate (see Sections 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 noncompliance 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 breast feeding 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)

Refer to Section 5.9 for details if a patient is withdrawn from the study.

5.8.1 Guidance to investigators on when to end study drug therapy

Patients who are improving clinically will receive at least 5 days (at least 120 hours of study participation period from the first study dose) but not more than 14 days of study drug therapy (ceftaroline fosamil and vancomycin). Patients may have their aztreonam/aztreonam placebo discontinued provided the criteria in Section 5.5.3.3 are met. Study drug 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 demonstrate at least the following:

- Cessation of the spread of the redness, oedema, and/or induration of the lesion as defined by a reduction in the size (length, width, and area) of redness, oedema, and/or induration and

- Resolution (absence) of fever (ie, body temperature less than 37.7°C) for 48-72 hours before study drug is discontinued.

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 is 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 therapy.

- **Resistant Pathogens:** In the event that an organism resistant to 1 or more of the potential study drugs is isolated, the investigator will determine whether the patient should remain on study drug therapy. The investigator may decide to continue study drug therapy if, in the investigator's opinion, there is clear and continuing clinical improvement while on therapy. But, if it is the investigator's opinion that the patient is not benefiting from the study drug, the investigator may decide to prematurely discontinue study drug therapy and to initiate an alternative and appropriate therapy. Investigators should be cautious in making decisions based on local ceftaroline susceptibility results since breakpoints for ceftaroline have not been determined at the doses administered in this study.

5.9 Withdrawal from study

Patients may be withdrawn from the study (ie, investigational product and assessments) at the request of the investigator or AstraZeneca. Patients are also, at any time, free to withdraw from the 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 Sections 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 noncompliance, defined as refusal or inability to adhere to the CSP requirements

- Investigator determines that it is in the best interest of the patient to withdrawal from the study due to reasons other than an AE

Withdrawn patients will not be replaced.

6. COLLECTION OF STUDY VARIABLES

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

6.1 Recording of data

For this study, patient data will be collected by electronic data capture (EDC). Where EDC is not possible, the study data will be recorded on paper CRFs.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The investigator or designee will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.1.1 Electronic data capture

Data will be collected electronically for each study patient by an EDC data management and workflow system. Source data supporting all EDC entries will be recorded in the study patient's medical records as per the site's standard practice. Investigators and study personnel will be responsible for the data capture and will respond to queries within the EDC data management system. For patients who discontinue or withdraw from the study, the site personnel will complete a termination screening that clearly documents the reason for termination on the end of study screens.

The EDC collected data will be real time data collection and reflect the latest observations on the patients participating in the study. Correction of any data errors and other such changes will be made by changing or updating the data in the system, which requires the entry of the user's name and a password for each change that will be captured in the electronic audit trail.

Clinical data (including AEs and concomitant medications) will be entered into a Title 21 Code of Federal Regulations Part 11 compliant data management system provided by AstraZeneca/[redacted]. The data system includes password protection and internal quality checks, such as automatic verification range checks, to identify data that appear to be out of the specified ranges. Programmed edit specifications identify discrepancies in the data, which may be addressed by the 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 2 within 24 hours prior to administration of the first dose (Day 1) of study drug.

6.2.1 Screening Period/baseline assessment (Days -1 to 0)

Screening Period/baseline assessments must be completed within 24 hours prior to randomising the patient into the study.

1. Obtain written informed consent prior to initiating any study-related assessments or procedures. For the MRSA expansion period, this includes consent to use the local microbiology cultures and associated data taken in the 72 hr period before the first dose, which identified the patient as eligible.

2. Following informed consent signature, complete the enrolment call in IVRS/IWRS

3. Verify the patient meets all of the study eligibility procedures by reviewing the inclusion and exclusion criteria with the patient

4. Obtain a complete medical and surgical history including demographic data and documentation on how the infection was acquired (eg, community acquired or hospital acquired)

5. Record all prior and concomitant medications, including all antimicrobial and antiseptic agents administered within 4 weeks prior to Screening/baseline

6. Perform a complete physical examination as defined in Section 6.4.8.

7. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate

8. Record the highest daily temperature (oral, rectal, or tympanic)

9. Record height and weight

10. Obtain three baseline 12-lead electrocardiograms (ECG), each separated by at least one minute, within a 15-minute period. See Section 6.4.9

11. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area - original lesion should be drawn around with a marker to establish baseline) of the site of infection, level of pus/collection.

12. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

13. After obtaining written informed consent, record SAEs

14. Obtain blood samples for prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) as required by the Schedule of Assessments in Table 2. Reference the laboratory manual for specific information on the collection, processing, handling, storage, and shipping of samples. See Section 6.4.5 for the list of laboratory tests and Section 7.1 for the blood volumes

15. Obtain blood samples for safety laboratory tests (complete blood count with differential and comprehensive metabolic panel)

16. Obtain a blood sample for a direct Coombs test

17. Obtain a urine sample for urinalysis and microscopy

18. For women of childbearing potential and those who are fewer than 2 years postmenopausal, obtain a urine pregnancy test

19. Estimate the creatinine clearance using the Cockcroft-Gault formula found in Appendix D

20. Measure C-reactive protein

21. Obtain an appropriate microbiological specimen from the cSSTI site and provide to the local laboratory for culture and perform Gram staining and sensitivity testing (see Section 3.1.2 for information regarding microbiological specimens).
For the MRSA expansion period, microbiology cultures and assessments taken in the 72 hrs before the first dose will be used as baseline.

22. Obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility. Cultures that are positive must be followed until negative

23. After obtaining written informed consent and verifying the patient meets all of the inclusion criteria and none of the exclusion criteria, randomise the patient using the IVRS/IWRS

24. Record the location/ward of the patient, ie intensive care unit, etc. each day, but only once per day for the location as of 12:00 h (12:00 pm/noon).

    For patients who are screen failures, if blood samples have been taken and ECGs performed prior to the patient being screen failed, these should be sent to and analysed by local laboratory/Covance/eRT as appropriate in order to detect possible

SAEs. Blood samples or ECGS should not be taken or performed if the patient has already been screen failed.

6.2.2 Days 1 to 2 assessment procedures

Day 1 is the first dose of study drug. Subsequent visit days are based off of Day 1. Vital sign measurements should be collected ± 30 minutes from the end of 1 of the study drug infusions.

1. Record all new concomitant medications

2. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate daily while the patient remains on study drug

3. For the first 72 hours of the study, measure body temperatures 3 times daily, approximately every 8 hours with a consistent method of temperature measurement.

4. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area - indicating with a marker lesion size at 48 and 72 hours) of the site of infection, decrease in any pus/collection, and change in pain or tenderness.

5. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

6. Assess the patient for AEs and SAEs (see Section 6.4)

7. Administer blinded study drug (see Section 5.5.2 for the doses and treatment regimens)

8. Record the location/ward of the patient, ie intensive care unit, etc. each day, but only once per day for the location as of 12:00 h (12:00 pm/noon).

6.2.3 Day 3 assessment procedures

On days where ECG recordings, safety laboratory assessments, and vital sign measurements are obtained, these procedures should be collected ± 30 minutes from the end of 1 of the study drug infusions.

1. Record all new concomitant medications

2. Performing a brief directed physical examination as defined in Section 6.4.8

3. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate daily while the patient is on study drug

4. For the first 72 hours of the study, measure body temperatures 3 times daily, approximately every 8 hours with a consistent method of temperature measurement.

5. Record weight

6. Obtain a standard 12-lead ECG recording around the end of one of the study drug infusions. See Section 6.4.9.

7. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area) of the site of infection, decrease in any pus/collection, and change in pain or tenderness.

8. For sites participating in PK sampling, obtain blood samples for PK analysis. Record the date and time the sample was actually obtained. See Section 6.6.1 for the schedule of collection PK samples. The date and time of all dose administration will be also recorded.

9. Obtain blood sample for vancomycin trough measurement (see Section 6.4.7) Record the date and time the sample was actually obtained.

10. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

11. Assess the patient for AEs and SAEs (see Section 6.4)

12. Obtain blood samples for PT, PTT, and INR as required by the Schedule of Assessments in Table 2. Reference the laboratory manual for specific information on the collection, processing, handling, storage, and shipping of samples. See Section 6.4.5 for the list of laboratory tests and Section 7.1 for the blood volumes

13. Obtain blood samples for safety laboratory tests (complete blood count with differential and comprehensive metabolic panel)

14. Obtain a urine sample for urinalysis and microscopy

15. Estimate the creatinine clearance using the Cockcroft-Gault formula found in Appendix D if clinically relevant. It is expected that the investigator will continue to monitor the patient's creatinine clearance level as clinically relevant throughout the study.

16. Measure C-reactive protein

17. Obtain an appropriate microbiological specimen from the cSSTI site when medically indicated but ONLY if a focus of infection is present with culturable material

18. If the previous blood culture was positive, obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If

the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility.

19. Administer blinded study drug (see Section 5.5.2 for the doses and treatment regimens and Sections 5.5.3.1 and 5.5.3.2 for dose adjustments)

20. Record the location/ward of the patient, ie intensive care unit, etc. each day, but only once per day for the location as of 12:00 h (12:00 pm/noon).

6.2.4 Days 4 to 9 assessment procedures

Patients must receive a minimum of 5 days of treatment with study drug. The maximum treatment duration is 14 days. After 3 days of treatment with aztreonam/aztreonam placebo, the patient should be assessed to determine whether aztreonam/aztreonam placebo needs to be continued. Criteria for discontinuing the aztreonam/aztreonam placebo are in Section 5.5.3.3. Specimens for laboratory assessments should be obtained on Day 7. Study assessments should be completed while the patient is receiving study drug. On days where safety laboratory assessments and vital sign measurements are obtained, these procedures should be collected ± 30 minutes from the end of 1 of the study drug infusions.

1. Record all new concomitant medications

2. Performing a brief directed physical examination as defined in Section 6.4.8 on Day 7

3. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate

4. Record the highest daily temperature (oral, rectal, or tympanic) while the patient remains on study drug

5. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area) of the site of infection, decrease in any pus/collection, and change in pain or tenderness.

6. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

7. Assess the patient for AEs and SAEs (see Section 6.4)

8. Obtain blood samples for PT, PTT, and INR as required by the Schedule of Assessments in Table 2 on Day 7. Reference the laboratory manual for specific information on the collection, processing, handling, storage, and shipping of

samples. See Section 6.4.5 for the list of laboratory tests and Section 7.1 for the blood volumes

9. Obtain blood samples for safety laboratory tests (complete blood count with differential and comprehensive metabolic panel) on Day 7

10. Estimate the creatinine clearance using the Cockcroft-Gault formula found in Appendix D if clinically relevant. It is expected that the investigator will continue to monitor the patient's creatinine clearance level as clinically relevant throughout the study.

11. Obtain an appropriate microbiological specimen from the cSSTI site when medically indicated but ONLY if a focus of infection is present with culturable material

12. If the previous blood culture was positive, obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility.

13. Administer blinded study drug (see Section 5.5.2 for the doses and treatment regimens and Sections 5.5.3.1 and 5.5.3.2 for dose adjustments)

14. Record the location/ward of the patient, ie intensive care unit, etc. each day, but only once per day for the location as of 12:00 h (12:00 pm/noon).

6.2.5 Days 10 to 14 assessment procedures

Patients must receive a minimum of 5 days (at least 120 hours of study participation period from the first study dose) of treatment with study drug. The maximum treatment duration is 14 days. After 3 days of treatment with aztreonam/aztreonam placebo, the patient should be assessed to determine whether aztreonam/aztreonam placebo needs to be continued. Study assessments should be completed while the patient is on study drug. On days where safety laboratory assessments and vital sign measurements are obtained, these procedures should be collected ± 30 minutes from the end of 1 of the study drug infusions.

1. Record all new concomitant medications

2. Performing a brief physical examination as defined in Section 6.4.8 on Days 10 and 14

3. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate

4. Record the highest daily temperature (oral, rectal, or tympanic) while the patient is on study drug

5. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area) of the site of infection, decrease in any pus/collection, and change in pain or tenderness.

6. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

7. Assess the patient for AEs and SAEs (see Section 6.4)

8. Obtain blood samples for PT, PTT, and INR as required by the Schedule of Assessments in Table 2 on Days 10 and 14. Reference the laboratory manual for specific information on the collection, processing, handling, storage, and shipping of samples. See Section 6.4.5 for the list of laboratory tests and Section 7.1 for the blood volumes

9. Obtain blood samples for safety laboratory tests (complete blood count with differential and comprehensive metabolic panel) on Days 10 and 14

10. Obtain a urine sample for urinalysis and microscopy on Days 10.

11. Estimate the creatinine clearance using the Cockcroft-Gault formula found in Appendix D if clinically relevant. It is expected that the investigator will continue to monitor the patient's creatinine clearance level as clinically relevant throughout the study.

12. Obtain an appropriate microbiological specimen from the cSSTI site when medically indicated but ONLY if a focus of infection is present

13. If the previous blood culture was positive, obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility.

14. Administer blinded study drug (see Section 5.5.2 for the doses and treatment regimens and Sections 5.5.3.1 and 5.5.3.2 for dose adjustments)

15. Record the location/ward of the patient, ie intensive care unit, etc. each day, but only once per day for the location as of 12:00 h (12:00 pm/noon).

6.2.6 End of Therapy assessment procedures

The end of therapy assessments will be completed at the time the patient completes study drug. For patients who complete study drug on Day 14, Day 14 and the EOT will be the same visit. 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.

1. Record all new concomitant medications

2. Performing a brief physical examination as defined in Section 6.4.8

3. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate

4. Record the highest daily temperature

5. Record weight

6. Obtain a standard 12-lead ECG recording ±30 minutes from the end of the study drug infusion if drug is administered at EOT. See Section 6.4.9

7. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area) of the site of infection, decrease in any puss/collection, and change in pain or tenderness.

8. Assess the clinical response (see Section 6.3.1 for the definition of clinical response).

9. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

10. Assess the patient for AEs and SAEs (see Section 6.4)

11. Obtain blood samples for PT, PTT, and INR as required by the Schedule of Assessments in Table 2. Reference the laboratory manual for specific information on the collection, processing, handling, storage, and shipping of samples. See Section 6.4.5 for the list of laboratory tests and Section 7.1 for the blood volumes. If the Days 3, 7, 10 and 14 assessments are within the prior 24 hours, a blood sample for PT, PTT, aPTT and INR will not be collected.

12. Obtain blood samples for safety laboratory tests (complete blood count with differential and comprehensive metabolic panel). If the Days 3, 7, 10 or 14 assessments are within the prior 24 hours, a blood sample for safety laboratory test will not be collected

13. Obtain blood sample for direct Coombs test

14. Obtain urine sample for urinalysis and microscopy. A urine sample will not be obtained if study Day 3 or 10 are within the prior 24 hours

15. For women of childbearing potential and those who are fewer than 2 years postmenopausal, obtain a urine pregnancy test. If the pregnancy test is positive at the EOT visit, follow the reporting requirements in Section 13.3.

16. Measure C-reactive protein

17. Obtain an appropriate microbiological specimen from the cSSTI site when medically indicated but ONLY if a focus of infection is present with culturable material. Perform a microbiological assessment at EOT if the patient was discontinued from study drug for insufficient therapeutic effect and a focus of infection is present with culturable material.

18. If the previous blood culture was positive, obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility.

19. Record the location/ward of the patient, ie intensive care unit, etc.

20. Make the patient completion call in the IVRS/IWRS system.

6.2.7 Test of Cure assessment procedures

The TOC assessments should be obtained 8 to 15 days after administration of the last dose of study drug.

1. Record all new concomitant medications

2. Perform a brief directed physical examination as defined in Section 6.4.8

3. Record vital sign measurements including heart rate, blood pressure, body temperature, respiratory rate

4. Record the highest daily temperature (oral, rectal, or tympanic)

5. Obtain a standard 12-lead ECG recording. See Section 6.4.9

6. Evaluate and record the clinical assessment of cSSTI including but not limited to measuring the extent of erythema, oedema, and/or induration (the length, width, and area) of the site of infection, decrease in any pus/collection, and change in pain or tenderness.

7. Assess the clinical response (see Section 6.3.1 for the definition of clinical response). Document both components of the cure, improvement, and resolution of signs and symptoms

8. Record procedures performed on the cSSTI site (e.g. debridement or incision- and-drainage)

9. Assess the patient for AEs and SAEs (see Section 6.4)

10. Obtain blood samples for PT, PTT, and INR as required by the Schedule of Assessments in Table 2. Reference the laboratory manual for specific information on the collection, processing, handling, storage, and shipping of samples. See Section 6.4.5 for the list of laboratory tests and Section 7.1 for the blood volumes

11. Obtain blood samples for safety laboratory tests (complete blood count with differential and comprehensive metabolic panel)

12. Obtain blood sample for direct Coombs test

13. Obtain a urine sample for urinalysis and microscopy

14. Obtain an appropriate microbiological specimen from the cSSTI site when medically indicated but ONLY if a focus of infection is present with culturable material

15. If any previous blood culture was positive, obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility.

6.2.8 Late Follow-Up assessment procedures

The LFU assessments should be obtained 21 to 35 days after administration of the last dose of study drug. The LFU visit assessments may be conducted via the telephone unless the patient has signs and symptoms of relapse, in which case, the patient will be required to attend the study centre for additional LFU visit assessments as indicated the schedule of assessments.

1. Record all new concomitant medications. Record only concomitant antimicrobial agents taken between the TOC and LFU visits.

2. Assess the patient for SAEs (see Section 6.4)

3. Obtain an appropriate microbiological specimen from the cSSTI if the patient is experiencing relapse, if clinically appropriate, and if a focus of infection is present

with culturable material, an appropriate specimen from the cSSTI site should be obtained

4. Obtain a blood culture if the previous blood culture was positive. Obtain 2 sets of blood culture 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites for a total of 4 bottles. If the 2 sets of blood samples are obtained from the same site, then an interval of 30 minutes should occur between collections. Perform culture and sensitivity testing at the local laboratory and send the isolates to the central reference laboratory for confirmation of organism identity and susceptibility. Obtain the culture if it is medically indicated and the patient is experiencing a clinical relapse.

5. Record any rehospitalisations and emergency room visits due to the cSSTI under investigation.

6.3 Efficacy

6.3.1 Clinical response definitions

6.3.1.1 Clinical response assessments at the EOT and TOC visits

Clinical response (see Table 6) will be made by the investigator at the EOT and TOC visits. Clinical response will be classified as cure, failure, or indeterminate based on the clinical outcome. A favourable clinical response is "clinical cure." A clinical failure occurring at the EOT visit will be carried forward to the TOC visit.

Table 6 Clinical Response Assessments at the EOT and TOC Visits

Clinical response	Definition
Clinical Cure	Resolution of signs and symptoms of skin infection or improvement of signs and symptoms of skin infection to such an extent that no further antimicrobial therapy is necessary.
Clinical Failure	Any of the following: • persistence or worsening in signs or symptoms of the acute skin infection • requirement for concomitant antibiotic therapy for persistence or worsening of the skin infection • requirement of an unplanned surgical intervention > 48 hours after the first dose of study drug for management of progressive skin infection • death caused by skin infection • an adverse event leading to study drug discontinuation when the patient requires alternative antimicrobial therapy to treat the cSSTI

Table 6 Clinical Response Assessments at the EOT and TOC Visits

Clinical response	Definition
	• diagnosis of osteomyelitis 8 or more days after the first dose of study drug
Indeterminate	Any of the following:
	• unable to determine response because the subject is lost to follow-up • treatment change prior to completing at least 48 hours of study drug • death not due to skin infections prior to the visit • diagnosis of osteomyelitis <7 days after the first dose of study drug

Abbreviations: cSSTI, complicated bacterial skin and soft tissue infection; EOT, End of Therapy; TOC, Test of Cure

6.3.1.2 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 cSSTI 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.

6.3.2 Microbiological response definitions

The microbiological response will be assessed per pathogen and per patient according to the definitions listed in the following sections. Microbiological response per patient is assessed in a blinded manner. It is based on the response per pathogen isolated at the baseline visit and on the isolation of pathogens during the course of treatment or the posttreatment period.

6.3.2.1 Per-pathogen microbiological response

The microbiological responses for each pathogen isolated at baseline will be categorized according to the definitions in Table 7.

Table 7 Microbiological Response Categories

Microbiological response category[a]	Definition
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.
Persistence	An adequate source specimen[b] 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	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 Test of Cure (TOC) are only applicable to patients who are not clinical failures at End of Therapy (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 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 at TOC.

b An adequate source specimen is defined as any sample that may yield the growth of a complicated bacterial skin and soft tissue infection (cSSTI) pathogen, eg, blood, pus, or tissue obtained from the cSSTI site.

6.3.2.2 Per-patient microbiological response

Per-patient microbiological response at the EOT and TOC visit will be determined in the mMITT and ME analysis sets 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.

6.3.2.3 Microbiological categories for pathogens identified after the baseline assessment

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

Table 8 Categorization of Bacterial Pathogens Identified After the Baseline Assessment

Microbiological category	Definition
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 cSSTI, or a new cSSTI 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) causing a skin infection (other than original site) determined at TOC regardless of susceptibility to study drugs, in a patient who has signs and symptoms of infection requiring alternative antimicrobial therapy.
Colonisation	Isolation of an organism from the original cSSTI site that is not associated with signs and symptoms of active infection and does not require antimicrobial therapy. Colonisation will be determined only at EOT and TOC when an assessment of clinical response is performed.
Re-infection or recurrence	Isolation of a baseline pathogen (recurrence) or a new pathogen (re-infection) from the original cSSTI site, at the LFU visit, in patients who had favourable clinical and microbiological responses at TOC. To be defined as a recurrent infection or re-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.

Abbreviations: cSSTI, complicated bacterial skin and soft tissue infection; EOT, End of Therapy; LFU, Late Follow-Up. TOC, Test of Cure

6.3.2.4 Early response at 48 to 72 hours of treatment

Early response assessment will be classified as success or failure as defined in Table 9.

Table 9 Early Response at 48 to 72 Hours of Treatment

Early Response	Definition
Success	Cessation of the spread of the redness, oedema, and/or induration of the lesion as defined by a reduction in the size (length, width, and area) of redness, oedema, and/or induration at 48 to 72 hours after enrolment.
Failure	Any of the following: • death • increase in the size (length, width, and area) of redness, oedema, and/or induration of the lesion; administration of rescue antibacterial drug therapy, or administration of any other antibacterial drug therapy (topical or systemic) for treatment of cSSTI before the early response endpoint assessment

Abbreviations: cSSTI, complicated bacterial skin and soft tissue infection

6.3.3 Primary efficacy outcome variable

The primary efficacy outcome measure will be the clinical cure rate at the TOC in both the MITT and CE analysis sets.

6.3.4 Secondary efficacy outcome variables

Secondary efficacy outcome variables include the following:

- Clinical cure rate at the EOT visit in the MITT and CE analysis sets
- Per-patient microbiological response at the EOT and TOC visits in the mMITT and ME analysis sets
- Clinical and per-pathogen microbiological response by baseline pathogen at the TOC visit in the mMITT and ME analysis sets
- Clinical relapse at the LFU visit in patients who were clinically cured at the TOC visit in the CE analysis set
- Re-infection and the recurrence rate in patients who were microbiological successes at the TOC visit in the ME analysis set

- Super-infection rate at the EOT visit and new infection rate at the TOC visit in the ME analysis set
- Colonisation rate in patients who had a clinical assessment performed at the EOT visit or the TOC visit in the ME analysis set
- Evaluation of early response at 48 to 72 hours of treatment in the MITT and CE analysis sets

6.3.5 Exploratory healthcare utilisation variables

Exploratory healthcare utilisation outcome variables include the following:

- Length of hospital stay
- Length of any time spent in the ICU
- Rehospitalisation rate between the TOC and LFU visits
- Emergency room visits between the TOC and LFU visits

6.3.6 Pharmacokinetic outcome variables

Ceftaroline and ceftaroline fosamil compartmental PK parameters derived from population PK analysis and potential PK/PD relationships will be reported separately. Following summary statistics will be reported: plasma concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 at specified sampling windows for those patients with the sparse plasma sample collection; plasma concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 at each nominal sampling time for those patients with the intensive plasma sample collection; noncompartmental PK parameters derived from those patients with the intensive plasma sample collection.

6.4 Safety

The 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 AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, 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. Adverse events may also include complications that occur as a result of protocol-mandated procedures and are distinguished as such.

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, treatment, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life threatening
- Requires inpatient 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.

Cases of liver dysfunction that meet Hy's Law criteria will be defined and reported as SAEs, using the "important medical event" serious criterion if no other criteria are applicable (see Appendix E).

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from time of administration of first dose of study drug throughout the treatment period up to and including the TOC visit. Serious AEs 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 AEs that are unresolved at the LFU visit should be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca/[redacted] retains the right to request additional information for any patient with ongoing AEs or SAEs at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date and time when the AE started and stopped

- Maximum Intensity (rating scale for inpatients)
  - 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 SAE
- Date investigator became aware of SAE
- Cause of SAE
- 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 an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Additional information is required for AEs of haematolytic anaemia, acute renal failure, seizure and convulsion, and symptomatic liver injury (eg, hepatitis and hepatic failure) irrespective of seriousness.

Causality collection

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

For SAEs, causal relationship will also be assessed for other medication, 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 on the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared with baseline in protocol-mandated laboratory values, vital sign measurements, 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 or vital sign measurements is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign measurement will be considered as additional information. Wherever possible, the reporting investigator should use 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 nonmandated parameters should be reported as AEs.

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 is being studied. It may be an increase in the severity of the disease under study 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 procedures. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel will inform the appropriate AstraZeneca/[redacted] pharmacovigilance (PVG) representatives (see Table 13) 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/[redacted] PVG representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca patient safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 3 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform the AstraZeneca/[redacted] PVG representatives (see Table 13) of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than the end of the next business day,** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated e-mail alert will be sent to the designated AstraZeneca/[redacted] PVG representative.

If the EDC system is not available, then the investigator or other study site personnel report should report the SAE to the appropriate AstraZeneca/[redacted] PVG representative by telephone (see Table 13).

The AstraZeneca/[redacted] PVG representative will advise the investigator or study site personnel how to proceed.

6.4.5 Laboratory safety assessment

Laboratory tests required for eligibility will be performed locally, as will tests of coagulation and Direct Coombs test. Other blood and urine samples will be sent to the central reference laboratory, Covance Central Laboratory Services, Inc. Information regarding the transfer of samples and how samples will be labeled, stored, and shipped can be found in the laboratory procedures manual. Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 2.

Table 10 presents the safety laboratory variables that will be measured:

Table 10 Laboratory Variables

Clinical Chemistry	Haematology	Urinalysis
Alanine aminotransferase	Haematocrit	Appearance (color, clarity. odor)
Albumin	Haemoglobin	Bilirubin
Alkaline phosphatase	Platelet count	Glucose
Aspartate aminotransferase	Red blood cell count	Ketones
Blood urea nitrogen	Reticulocytes	Leukocyte esterase
Calcium	White blood cell count (total and differential)	Nitrite
Chloride		pH
Creatinine		Protein
Glucose (nonfasting)		Specific gravity
Inorganic phosphorus		Urobilirubin
Haptoglobin		Microscopic examination
Potassium		Red blood cells
Sodium		White blood cells
Total bilirubin		Casts
Total protein		Crystals
		Bacteria, yeast cells, or parasites

Table 10 Laboratory Variables

Clinical Chemistry	Haematology	Urinalysis
Other Vancomycin trough level to be done by central laboratory for all patients and by local laboratory if needed C-reactive protein to be measured by central laboratory	**Coagulation (local)**	Samples to be analysed by local laboratory: Clinical chemistry at eligibility screening Haematology at eligibility screening International normalized ratio Partial thromboplastin time OR activated partial thromboplastin time Prothrombin time Direct Coombs test Creatinine (as clinically mandated) Vancomycin trough level (if site normal routine)

For the blood volume that will be drawn, see Section 7.1.

6.4.6 Actions required in cases of increases in liver chemistry values

The investigator is responsible for, without delay, determining whether the patient meets potential Hy's law criteria: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal **and** total bilirubin ≥2 × upper limit of normal at any point during the study, irrespective of the value of the patient's alkaline phosphatase. The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe. Details regarding the actions required in the cases of increases in ALT, AST, and total bilirubin can be found in Appendix E.

6.4.7 Vancomycin trough levels

All patients will have a trough vancomycin/placebo concentration sample taken at steady state before dosing on day 3. This trough level sample will be sent to a central laboratory and the data will not be returned to the site in order to ensure that the blind is maintained.

When local practices require vancomycin levels to be used for dose adjustments these levels will be measured locally by the site. Sites must ensure that the blind is maintained as per the site blinding plan.

6.4.8 Physical examination

Physical examinations will be performed according to the schedule specified in Table 2.

A complete physical examination will include an assessment of the following:

- General appearance including skin and measuring height and weight
- Resting vital signs, including heart rate, blood pressure (after in a supine position for 5 minutes), respiratory rate, and temperature (oral, rectal, or tympanic)
- Head and neck
- Lymph nodes
- Thyroid
- Musculoskeletal and extremities, including spine
- Cardiovascular system
- Lungs
- Abdomen
- Neurological symptoms

A brief directed physical examination will be performed according to the schedule specified in Table 2 and include the following:

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

6.4.9 Electrocardiogram

Standard 12-lead ECGs will be recorded and assessed according to the schedule specified in Table 2. The ECGs should be standard 12-lead ECGs with a lead II rhythm strip with the patient in the supine position after the patient has rested in this position for 5 minutes. The baseline ECG will consist of 3 recordings, each separated by at least one minute, within a 15-minute period. Recordings on Day 3, EOT and TOC will consist of a single recording. The ECG recording should be collected around the end of one of the study drug infusions. On Day 3 and at EOT, the ECG recording should be collected ±30 minutes from the end of one of the

study drug infusions. A single independent third party using uniform techniques will carry out formal analysis of ECG data for purposes of the study.

6.4.10 Vital signs

Record vital sign measurements daily while the patient remains on study drug and at the EOT and TOC visits. At the EOT, vital sign measurements should be collected ± 30 minutes from the end of 1 of the study drug infusions.

6.4.10.1 Heart rate and blood pressure

Heart rate and blood pressure 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 2.

6.4.10.2 Body temperature

Body temperature (oral, rectal, or tympanic) will be measured in degrees Celsius. Record the highest daily body temperature while the patient is on study drug. For the first 72 hours of the study, body temperature will be measured 3 times daily, approximately every 8 hours with a consistent method of temperature measurement to be used for the duration of the study (see Table 2).

6.5 Resource Use

The patient's location within the hospital or as outpatient will be recorded during study participation as well as date of hospital discharge. Location will only be recorded once per day for the location as of 12:00 pm (noon) each day. Rehospitalisation, and emergency room visits will be collected at the LFU visit.

6.6 Pharmacokinetics

6.6.1 Collection of samples

It is the intent of the study that the majority of treated patients will have sparse plasma concentration samples taken to determine the population pharmacokinetics of ceftaroline and ceftaroline fosamil in this patient population. In addition, approximately 45 patients will have an intensive plasma sampling (ie, approximately 30 patients from the ceftaroline fosamil treatment group) to determine the PK of ceftaroline, ceftaroline fosamil and ceftaroline M-1 in this patient population by means of traditional noncompartmental PK analysis. It is anticipated that 20 of the 30 selected patients will be evaluable in the ceftaroline fosamil arm for full ceftaroline concentration-time course data. Sites that cannot perform plasma sampling for PK analysis due to staff or equipment issues will not be excluded, but all qualifying sites will be required to participate in the collection of plasma samples for PK analysis. All samples will be taken on Day 3, following administration of 1 of the 3 doses of ceftaroline fosamil, at a time that is convenient for the collection of plasma samples.

Sparse sampling (for patients enroled into the group with sparse plasma sampling):

- 0 hour (within 15 minutes prior to the start of infusion)
- 120 minutes ± 5 minutes after the start of infusion (within 5 minutes before or after the end of infusion)
- Between 3 and 5 hours after the start of infusion (between 1 and 3 hours after the end of the infusion)
- Between 6 and 8 hours after the start of infusion (between 4 and 6 hours after the end of infusion) and prior to the next infusion

Intensive sampling (for patients enroled into the group with intensive plasma sampling):

- 0 hour (within 15 minutes before the start of the infusion)
- 60 minutes after the start of infusion ± 5 minutes
- 90 minutes after the start of infusion ± 5 minutes
- 115 minutes after the start of the infusion ± 5 minutes
- 125 minutes after the start of the infusion ± 5 minutes
- 135 minutes after the start of the infusion ± 5 minutes
- 2.5 hours after the start of the infusion ± 5 minutes
- 3 hours after the start of the infusion ± 5 minutes
- 4 hours after the start of the infusion ± 15 minutes
- 5 hours after the start of the infusion ± 15 minutes
- 6 hours after the start of the infusion ± 15 minutes
- 8 hours after the start of the infusion (infusion stop at 120 min) ± 15 minutes but prior to start of next infusion.

6.6.2 Processing of samples

The total blood volume collected will not exceed the maximum limits for the study (see Section 7.1). The actual date and time of collection of each sample will be recorded in the appropriate page of the eCRF. The exact date and time of the start and end of each infusion during the study will be recorded in the eCRF. Samples will be collected, labeled, stored, and shipped as detailed in the study-specific manuals.

Venous blood samples (approximately 4 mL) for determination of vancomycin trough, ceftaroline fosamil, ceftaroline, and ceftaroline M1 concentrations in plasma will be taken at the times presented in Table 2 and Section 6.6.1. Plasma samples must be processed immediately and stored at –70ºC (samples are not stable at -20ºC). All samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual.

6.6.3 Sample shipping instructions

The plasma samples must be stored at -70ºC. If the site does not have a freezer capable of storing samples at -70ºC, the samples must be shipped on the same day of collection, on dry ice, to Covance Central Laboratory. Samples must be shipped within 30 days of collection.

Covance Central Laboratory will ship samples to Covance Bioanalytical Laboratory on a regular schedule for the plasma concentration determination of ceftaroline fosamil and its 2 metabolites. Time and temperature are critical to maintain the integrity of the samples for analysis. Refer to the laboratory manual for additional details regarding sample shipping instructions.

6.6.4 Determination of drug concentration

Samples for determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in human plasma will be analysed by Covance Bioanalytical Laboratory on behalf of Regulatory Bioanalysis, Global DMPK–IM, 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.

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 presented in Table 11.

Table 11 Volume of Blood to be Drawn From Each Patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety[d]	Clinical chemistry[a]	2.5	7	17.5
	Haematology[b]	2.0	7	14
Vancomycin trough level (Day 3)		2.5	1	2.5
Direct Coombs test (local)		2	3	6
PT/INR, PTT (local)		1.8	7	12.6
Blood for culture (local)[c]		10	22	220
Total				272.6
Sparse pharmacokinetic samples		4	4	16
Intense pharmacokinetic samples (optional)		4	12	48
Total with sparse PK				288.6
Total with optional intense PK				320.6

Abbreviations: INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time

a Includes haptoglobin (for each sample) and C-reactive protein (for applicable visits)
b Includes reticulocytes, red cell distribution width, and mean corpuscular volume
c If blood culture is positive at baseline the test should be repeated upon positive result (rather than daily) until sterilization confirmed. A culture is obtained a the TOC visit (if any previous cultures were positive) and a culture is obtained at the LFU visit if medically indicated and the patient is experiencing clinical relapse.
d Additional samples 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 Plasma samples

Plasma samples will be analysed and stored within the established stability period of the validated methods.

7.3 Labelling and shipment of biohazard samples

The investigator will ensure that samples are labeled 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.

The central reference laboratory will supply media containing transport vials and instructions for shipment of clinical isolates from the local laboratory to the central reference laboratory.

7.4 Chain of custody of biological samples

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

The 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.

[redacted] keeps oversight of the samples during the study through monitoring and AstraZeneca keeps oversight of the entire life cycle through internal procedures and auditing of external laboratory providers.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of optional plasma samples for PK analysis, 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 plasma samples for PK analysis will be an optional part of the study, then the patient may continue in the study.

The investigator at each site will:

- Ensures patients' withdrawal of informed consent to the use of optional PK samples is notified immediately to AstraZeneca/[redacted]

- Ensure that optional plasma samples for PK analysis from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented

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

- Ensure that the patient and AstraZeneca/[redacted] are informed about the sample disposal

[redacted] will ensure that the biobank or central reference laboratory(ies) holding the optional plasma samples for PK analysis 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 the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): 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 (ICF) 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 ICF 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 study site staff.

The opinion of the ethics committee should be given in writing. The investigator should submit the written approval to AstraZeneca/[redacted] before enrolment of any patient into the study.

The ethics committee should approve all advertising used to recruit patients for the study.

AstraZeneca/[redacted] should approve any modifications to the ICF 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 ICF, must be approved by the national regulatory authority or a notification to the national regulatory authority must be 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 investigators will be provided with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

8.4 Informed consent

The investigator at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study
- Ensure that each patient is notified that he or she is 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 that each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the investigator's study file
- Ensure that a copy of the signed ICF 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 ICF that is approved by an ethics committee.

The intense PK component of this study is optional. An optional PK ICF must be signed and dated by each patient to allow participation. The criteria in this section also pertain 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 coordinating 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 CSP).

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

AstraZeneca/[redacted] will distribute any subsequent amendments and new versions of the protocol to each investigator. For details on the distribution to ethics committee, see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca/[redacted] and the centre's ethics committee are to approve the revised ICF 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 and to determine whether these activities were conducted and whether the data were recorded, analysed, and accurately reported according to the protocol, ICH E6(R1), and any applicable regulatory requirements. The investigator will contact AstraZeneca/[redacted] immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY [redacted]

9.1 Prestudy activities

Before the first patient is entered into the study, it will be necessary for a representative of [redacted] 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 (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of AstraZeneca/[redacted]. This will be documented in a CSA between AstraZeneca/[redacted] and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, a [redacted] representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and the EDC system that will be used.

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

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

The investigator will complete, maintain, and ensure adherence of all staff to the site blinding plan.

Specific investigators required: investigators will be familiar with standard care of skin infections.

Specific site requirements: sites will be able to process wound and blood samples and/or bacterial isolates for shipment to the regional or central microbiology laboratory.

Specific territories required: an attempt will be made to enrich the study for MRSA infections with high ceftaroline fosamil MICs by selection of countries and sites with a high prevalence of MRSA and countries and sites that may potentially have a higher proportion of MRSA with MICs of 1 and 2 based on surveillance data.

9.3 Monitoring of the study

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

The blinded [redacted] representative will:

- Provide information and support to the investigator
- 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 (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 use of the patient's optional PK 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 [redacted] representative will verify study drug accountability from receipt of study drug through declaration of clean file and database lock (see Section 5.7.1).

The [redacted] representative will be available between visits if the investigator 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 centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP 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 CSA shall prevail.

Agreements between [redacted] and the investigator should be in place before any study-related procedures can take place or patients are enroled.

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 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 estimated date the first patient will be enroled in the study is Q1 2012 and the estimated date the last patient completes the study is Q3 2013.

The study may be terminated at individual centres if the study procedures are not being performed according to ICH E6(R1) or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ceftaroline fosamil.

10. DATA MANAGEMENT BY [redacted]

Data management will be performed by [redacted].

The data collected through third party sources will be obtained and reconciled against study data. Adverse events and medical and surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by [redacted].

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

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

When all data have been coded, validated, and verified, the investigator will electronically sign the data, a clean file will be declared by data management, and the data will be locked. Any treatment-revealing data may thereafter be added and the final database will be frozen.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

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, IVRS/IWRS) will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious adverse event 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

11.1 Calculation or derivation of efficacy variables

The primary efficacy variable is the clinical cure rate at the TOC visit in the MITT and CE analysis sets. The primary efficacy variable will be based on the definitions in Section 6.3. A missing clinical response at the TOC visit will be counted as indeterminate in the analyses,

unless the response at EOT was clinical failure, in which case the clinical failure will be carried forward to the TOC visit.

The clinical cure rate is defined as the number of patients with clinical cure divided by the number of patients in the corresponding analysis sets (MITT and CE). The clinical cure rate at the EOT visit will be defined in the same way as the primary endpoint based on their analysis sets.

The clinical cure rate at the TOC visit by each pathogen (isolated at baseline) is defined as the number of patients with a clinical cure for the specific pathogen at the TOC visit divided by the number of patients with the same baseline pathogen in the corresponding analysis sets (mMITT and ME). A patient with more than one pathogen would appear in more than one "by pathogen" group.

The per-patient microbiologic favourable rate at the EOT or TOC visit is defined as the number of patients with a favorable microbiological response (eradication or presumed eradication) divided by the number of patients in the corresponding analysis sets (mMITT and ME). For a patient to be a success for per-patient response, all pathogens must have a favourable microbiological response.

The microbiologic favorable rate by each pathogen (isolated at baseline) is defined as the number of patients with a microbiological favorable response (eradication or presumed eradication) for the specific pathogen divided by the number of patients with the same baseline pathogen in the corresponding analysis sets (mMITT and ME).

For response rates, MRSA and MSSA will be counted uniquely. Patients with both MRSA and MSSA will be counted twice in the overall tabulations of *S. aureus* for per-pathogen microbiological response and counted only once for per patient clinical response and per-patient microbiological response.

Identification of pathogens and susceptibility results will be recorded by both the local microbiology laboratory and the central reference laboratory. The identification and susceptibility results of the central reference laboratory will be regarded as definitive and therefore will be used for the purposes of the summary tables.

The clinical relapse rate at the LFU visit is defined as the number of patients with clinical relapse at the LFU visit divided by the number of patients who were a clinical cure at the TOC visit in the CE analysis set.

The microbiological re-infection or recurrence rate at the LFU visit is defined as the number of patients who have a re-infection or recurrence at the LFU visit divided by the number of patients who had a favourable microbiological outcome at the TOC visit in the ME analysis set.

The microbiological super-infection rate at the EOT visit is defined as the number of patients who have a super-infection (as defined in Table 8) at the EOT visit divided by the number of patients in the ME analysis set.

The microbiological new infection rate at the TOC visit is defined as the number of patients who have a new infection (as defined in Table 8) at the TOC visit divided by the number of patients in the ME analysis set.

The microbiological colonisation rate at the EOT visit is defined as the number of patients with a colonisation (as defined in Table 8) at the EOT visit divided by the number of patients where an assessment of clinical response is performed at the EOT visit in the ME analysis set (and similarly for the TOC visit).

The early response rate at 48 to 72 hours of treatment is defined as the number of patients with success divided by the number of patients in the MITT and CE analysis sets.

Treatment compliance will be calculated as the total number of doses received divided by the total number of expected doses based on the first and last date and time of study drug administration and is applicable for vancomycin and ceftaroline.

11.2 Calculation or derivation of safety variables

Adverse events will be collected from time of the first dose of study drug throughout the treatment period up to and including the TOC visit. Serious AEs will be collected from time of signature of informed consent throughout the treatment period up to and including the LFU visit.

The baseline value will be defined as the last available value before the start of study drug (ceftaroline fosamil or vancomycin plus aztreonam). The change-from-baseline variables will be calculated for the following safety variables, as the posttreatment value minus the value at baseline.

- Clinical laboratory tests including clinical chemistry, haematology, coagulation, and urinalysis as defined in Section 6.4.5.
- Vital sign measurements (heart rate, blood pressure, and respiratory rate) and body temperature.
- ECG tracings including heart rate, RR, QRS, QT, QTc interval corrected by Fridericia (QTcF), and QTc interval corrected by Bazett (QTcB) intervals.

11.2.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinued due to AEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation

with the global patient safety physician, be considered other significant AEs and reported as such in the clinical study report.

A similar review of laboratory, vital sign, and ECG data will be performed for identification of other significant AEs. 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

The PK analyses will be performed at AstraZeneca Research and Development. For patients with sparse plasma sample collection, the ceftaroline fosamil, ceftaroline, and ceftaroline M-1 plasma concentrations will be summarised at each sampling window. For patients with intensive plasma sampling, the ceftaroline fosamil, ceftaroline, and ceftaroline M-1 plasma concentrations will be summarised at each nominal sampling time. In addition, PK parameters for patients with intensive plasma sampling will be determined using standard noncompartmental methods and will be descriptively summarised. The actual sampling times will be used in the PK calculations. The following PK parameters will be determined: maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal plasma half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to infinity (AUC), plasma clearance (CL), volume of distribution during terminal phase (V_z), volume of distribution during steady-state (V_{ss}), and mean residence time (MRT). The compartmental pharmacokinetics of ceftaroline and ceftaroline fosamil will be evaluated by population modeling and will be reported separately

11.4 Calculation or derivation of pharmacodynamic variables

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

A PK/PD target analysis in cSSTI 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 status (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 relationship 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 and a PK/PD relationship analysis can be performed.

11.4.2 Population analysis of pharmacokinetic/pharmacodynamic variables

The population PK analysis and PK/PD analysis for some selected outcome variables, if appropriate, will be reported and listed separately.

11.5 Calculation or derivation of exploratory healthcare utilisation variables

Length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start of study drug plus one. Patients with missing discharge dates will be calculated as the difference between the last day with available inpatient data and the start date of study drug. The length of hospital stay will be censored at the last available date. Patients who stay in the hospital beyond the LFU visit will be censored at the LFU visit. The length of any time spent in the ICU will be calculated in the similar way as the length of hospital stay.

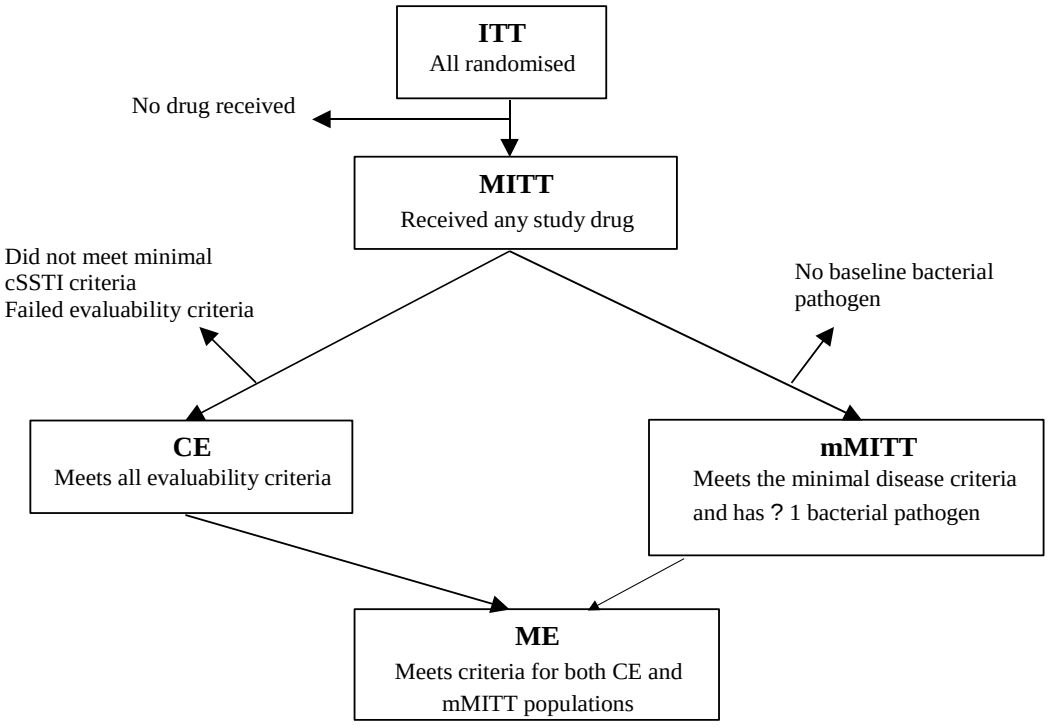
12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

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



Abbreviations: ITT, intent to treat; MITT, modified intent to treat; CE, clinically evaluable; mMITT microbiological modified intent to treat; ME, microbiologically evaluable

12.1.1.1 Intent-to-treat analysis set

The intent-to-treat (ITT) analysis set will consist of all randomised patients. A patient is considered randomised when the unblinded pharmacy staff or unblinded study staff receives the IVRS/IWRS-generated patient number.

12.1.1.2 Modified intent-to-treat analysis set

The MITT analysis set will be a subset of the ITT population and will include all randomised patients who receive any amount of study drug.

12.1.1.3 Microbiological modified intent-to-treat analysis set

The mMITT analysis set will be a subset of the MITT analysis set who meet the minimal disease criteria (patients who meet any of the inclusion criteria for cSSTI [#3 of the inclusion criteria] and #4, #5, and #6 of the inclusion criteria, warranting hospitalization and a minimum of 5 days of IV therapy [at least 120 hours of study participation period from the first study dose]) and will include patients for whom at least 1 bacterial pathogen has been isolated from an appropriate microbiological specimen (blood or tissue obtained from the cSSTI site) at baseline.

12.1.1.4 Clinically evaluable analysis set

The CE analysis set will be a subset of the MITT analysis set and will include patients who meet al of the following criteria:

- Met the disease criteria for a cSSTI, as determined by the evaluability committee
- Did not have a noneligible infections, including those caused exclusively by extended-spectrum β-lactamase producing Gram-negative organisms or monomicrobial *Pseudomonas* spp.
- Received between 80% to 120% of the prespecified intended dose of study drug therapy. Compliance will be calculated as described in Section 11.1
- Had an outcome assessment performed at the TOC visit or determined to be a clinical failure at EOT. A patient with an indeterminate outcome at TOC is not included in the CE analysis set
- Did not receive, from receipt of first dose of study drug through TOC, alternate (nonstudy) systemic antimicrobial therapy that would be effective for the treatment of the cSSTI, for a reason other than treatment failure
- Did not have a procedure that the evaluability committee determined made the patient unevaluable

In addition to meeting the above criteria, patients must meet the following specific conditions for inclusion in this population:

- Received the correct study drug to which they were randomly assigned
- Received at least 48 hours of therapy in order to be considered an evaluable failure, unless deemed a clinical failure based on a treatment-limiting AE
- Received at least 72 hours of therapy in order to be considered an evaluable clinical cure

12.1.1.5 Microbiologically evaluable analysis set

The ME analysis set will include patients who meet criteria for both the mMITT and CE analysis sets.

12.1.2 Safety analysis set

The safety analysis set includes all patients who received any amount of study drug irrespective of the treatment arm they were randomised to. The safety analysis set will be grouped according to the actual treatment they received.

12.1.3 Pharmacokinetic analysis set

The PK analysis set includes all patients who have at least 1 plasma concentration data assessment available for ceftaroline.

12.2 Methods of statistical analyses

12.2.1 General considerations

The primary objective is to assess whether ceftaroline fosamil is noninferior to vancomycin plus aztreonam in the clinical cure rate at the TOC visit in the CE and MITT analysis sets using a 10% margin.

Data collected from patients during the MRSA expansion period will be analysed and reported separately and not included in the overall analysis of the 765 patients as per the original protocol. Data from the MRSA extension period will be summarised using similar methods to the main study period, but will not be subject to the hypothesis of non-inferiority.

Statistical analyses, as specified for each variable, will be conducted and all comparisons will be between ceftaroline fosamil and vancomycin plus aztreonam. The 2-sided 95% CI will be produced for all primary and secondary efficacy analyses. Subgroup analyses will be conducted on selected secondary outcome measures. Descriptive statistics, including number, mean, SD, median, minimum and maximum for continuous variables and number and percentage for categorical variables will be presented by treatment group. For the reporting of descriptive statistics, the mean and median values will be presented to 1 more decimal precision than the source data, SD will be presented to 2 more decimal precision than source data, minimum and maximum values will be presented to the same precision as the source data, and percentages will be presented with 1 decimal precision. Listings of individual patients' data will also be produced.

By definition, indeterminates are included in the MITT analysis set and mMITT analysis set but are excluded from the CE analysis set and ME analysis set. If a patient is a clinical failure at the EOT visit, the patient will be considered a clinical failure at the TOC visit in the analysis of clinical response. A missing clinical response at the TOC visit will be counted as indeterminate in the analyses, unless the response at EOT was clinical failure, in which case the clinical failure will be carried forward to TOC.

For the safety analysis, the patients will be presented under the treatment they actually received. Project standard output templates will be used to produce standard summaries and plots for patient characteristics, safety and tolerability, and efficacy results.

Missing data will result in a reduced sample size for that parameter. No action will be taken to handle missing data for the safety assessment. A patient who withdraws prior to the last planned observation in a study period will be included in the safety analyses up to the time of discontinuation.

Further details on the methods of statistical analysis will be provided via a comprehensive statistical analysis plan to be issued before the unblinding of the data.

12.2.2 Analysis of study population and patient characteristics

The number of patients randomised, protocol deviations, and the number of patients completing and discontinuing from the study drug as well as the study, along with reasons for withdrawal will be tabulated by treatment group. Important protocol deviations are defined as any variations 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. The number of patients in each analysis set will be reported overall and by treatment group.

Demographics (age, sex, and race), medical and surgical history, baseline assessments of clinical signs and symptoms, microbiological assessments, and study drug administration will also be summarised. The summarizations will be presented for the MITT and CE analysis sets overall by treatment group.

12.2.3 Primary efficacy variable

Primary alternative hypothesis

Ceftaroline fosamil will demonstrate clinical efficacy comparable to that of vancomycin plus aztreonam as treatment for patients with cSSTI. The clinical efficacy will be assessed by the clinical cure rate at the TOC visit in the MITT and CE analysis sets.

This hypothesis will assess whether the treatment effect of ceftaroline fosamil, measured by the primary efficacy variable, is noninferior to vancomycin plus aztreonam using a noninferiority margin of 10%. Ceftaroline fosamil will be declared noninferior to vancomycin plus aztreonam if the lower limit of a 2-sided 95% CI is greater than –10%.

Analyses of primary efficacy variable

The clinical response is defined in Section 6.3.1.1 and the clinical cure rate is calculation is specified in Section 11.1. The numbers and percentages in the clinical response category will be tabulated by treatment group.

The primary efficacy variable of the clinical cure rate at the TOC visit in the MITT and CE analysis sets will be presented by treatment group. A 2-sided 95% CI for the observed difference in the clinical cure rate between ceftaroline fosamil and vancomycin plus aztreonam will be computed using the unstratified method of Miettinen and Nurminen (Miettinen et al 1985). Noninferiority will be declared if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) is greater than –10% for both the MITT and CE analysis sets.

If noninferiority is achieved in both the MITT and CE analysis sets and if the lower limit of the 95% CI does not cross zero, the difference in favour of ceftaroline fosamil will be considered statistically significant.

The primary efficacy analysis will be summarised and presented by subgroups according to baseline characteristics. The detailed subgroups will be described in the statistical analysis plan.

12.2.4 Secondary efficacy variables

All of the secondary efficacy variables are defined in Section 6.3.4 and the clinical cure rate and favourable microbiological response rate calculation are specified in Section 11.1. The secondary efficacy outcome variables presented in Table 12 will be analyzed using the method used for primary the primary efficacy outcome variable.

Table 12 Secondary Efficacy Endpoints

Population	Subset(s)	Assessment	Per-patient Evaluation	Outcomes
MITT and CE		EOT	Clinical response	Cure Failure Indeterminate (MITT only)
mMITT and ME	Per pathogen	TOC	Clinical response	Cure Failure Indeterminate (mMITT only)
CE	Clinically cured at TOC	LFU	Clinical response	Continued response Relapse

Table 12 Secondary Efficacy Endpoints

Population	Subset(s)	Assessment	Per-patient Evaluation	Outcomes
mMITT and ME	Per patient Per pathogen	TOC	Microbiological response	Favourable: eradication or presumed eradication Unfavourable: persistence, presumed persistence, or indeterminate (mMITT only)
ME	Microbio-logically favourable outcome at TOC	LFU	Microbiological re-infection or recurrence	No re-infection or recurrence Re-infection or recurrence
ME		EOT	Super-infection	Super-infection No super-infection
ME		TOC	New infection	New infection No new infection
ME	Clinical assessment performed at EOT and TOC	EOT TOC	Colonisation	Colonisation No colonisation
MITT and CE		48 to 72 hours	Early response	Success Failure

Abbreviations: CE, clinically evaluable, EOT, LFU, late follow-up; ME, microbiologically evaluable; MITT, modified intent-to-treat; mMITT, microbiological modified intent-to-treat; TOC, text of cure;

12.2.5 Exploratory healthcare utilisation variables

The healthcare utilisation variable of hospital length of stay will be tabulated by treatment group in the MITT and CE analysis sets. For the unadjusted length of stay comparisons, Kaplan-Meier survival functions will be used to estimate the mean length of stay, median length of stay, and length of stay by discharge quartiles for the 2 treatment groups. Between-treatment differences in survival function will be tested using the Wilcoxon statistic.

An exploratory analysis may be conducted using appropriate methods to determine whether ceftaroline fosamil demonstrates reduced length of hospital stay compared with vancomycin in patients admitted to hospital with cSSTI. The following explanatory variables may be included: antibiotic treatment (ceftaroline fosamil or vancomycin), age, gender, geographic region, pathogen confirmed at the primary site of infection, and hospital location at the time of randomisation (eg, general ward, ICU). Location will also be collected daily post randomisation. For multivariate analysis of length of stay, several accelerated failure time models will be tested to identify the model of best fit according to the Akaike information criterion. Additional details will be provided in the statistical analysis plan.

Rehospitalisation (between the TOC and LFU visits) and emergency room visit (between the TOC and LFU visits) will be presented for each treatment group. Rehospitalisation rate and emergency room visit frequency between the TOC and LFU visits will be computed.

12.2.6 Pharmacokinetic data

Ceftaroline, ceftaroline fosamil, and ceftaroline M-1 plasma concentrations will be listed and descriptively summarised at each sampling window for patients with sparse plasma sample collection and at each nominal sampling time for patients with intensive plasma sample collection, respectively. For patients with intensive plasma sampling, PK parameters will be determined using standard noncompartmental methods and will be descriptively summarized. Individual compartmental PK parameters of ceftaroline and ceftaroline fosamil for cSSTI patients will be derived via a population modeling approach. The ceftaroline and ceftaroline fosamil concentration, patient demographic, and disease status data will be combined with the data from appropriate previous clinical studies for the population PK analysis. Individual compartmental PK parameters for patients with ceftaroline and ceftaroline fosamil plasma concentration data available will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, C_{max}, t_{max}, AUC, $t_{½}$, λ_z, CL, V_z, V_{ss}, and MRT will be derived from the predicted ceftaroline and ceftaroline fosamil concentration time courses. The appropriate ceftaroline exposure outcome variables predicted by the population PK modeling will be used for a PK/PD modeling for appropriate microbiological or clinical cure outcome variables.

12.2.7 Safety and tolerability

Adverse events occurring from the first dose of study drug up to the TOC visit will be summarised by preferred term and system organ class according to MedDRA by treatment group. These summaries will also be presented by relationship to study drug and severity. Adverse events leading to discontinuation will be summarised. The same summarizations will also be presented for SAEs and other significant AEs.

Descriptive statistics of vital sign measurements, clinical laboratory results, and ECG tracings at each time point measured, as well as the change from baseline, will be presented by treatment group. The finding from physical examinations at each visit will be tabulated by treatment group.

For ECG variables, the QT correction factor will be based on the Bazett and Fridericia formulas. Categorical summaries of QTcB and QTcF values (≥450 ms, ≥480 ms, ≥500 ms) and change from baseline values in QTcB and QTcF values (≥30 ms, ≥60 ms) will also be presented.

Shift tables for laboratory tests will be provided by treatment group if necessary. Box plots of selected laboratory tests by treatment group and time point may also be provided.

12.3 Determination of sample size

The study is designed to show noninferiority in the clinical cure rate of ceftaroline fosamil to that of vancomycin plus aztreonam in adult patients with cSSTI. The primary outcome measure is the proportion of patients with a clinical cure at the TOC visit in the MITT and CE analysis sets.

The sample size based on the primary outcome variable of clinical cure rate at the TOC visit assumes a point estimate for the clinical cure rate of 80% in the vancomycin plus aztreonam group and 80% in the ceftaroline fosamil group in the MITT population, a noninferiority margin of 10% and a power of 90%. This gives a total sample size of 765 patients (510 ceftaroline fosamil; 255 vancomycin plus aztreonam). This sample size also gives >90% power for the CE analysis set assuming an 85% clinical cure rate for both treatments and a 20% nonevaluable rate.

The noninferiority margin of 10% is justified on the basis of historical literature related to improvements in lesions from skin infections showing a large treatment effect of antibiotics and a justification that a margin of 10% is a reasonable, clinically acceptable margin for the response endpoint.

Based on surveillance data, data from previous studies and local epidemiological data, the MRSA expansion period will aim to recruit approximately 60 patients with confirmed MRSA in order to have an adequate number with MIC ≥2mg/L against ceftaroline. This should provide between 12 and 18 patients with the required MIC (approximately 9 to 14 in the clinically evaluable population) and as per the main study they will be randomised 2:1 to ceftaroline vs vancomycin, respectively. Data collected from patients during the expansion period will be analysed and reported separately and do not form part of the original 765 patients recruited during the main study period. Full details of the analyses that will be undertaken for the MRSA expansion period will be covered in a specific SAP that will be finalised ahead of DBL for the expansion period.

12.4 Evaluability committee

The study will utilize an evaluability review committee to determine whether the patient is evaluable for the CE and ME analysis sets. This committee will review blinded data prior to database lock by focussing on such areas as microbiology, concomitant medications, and on-study surgical interventions. The committee will be maintained for the MRSA expansion period to classify patients recruited during this part of the study. Details will be outlined in the committee charter.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such (see Section 6.4.4).**

In the case of a medical emergency the investigator may contact the study physician or designee. If the study physician is not available, contact the medical monitor via the numbers listed in Table 13 for the appropriate region.

Table 13 Medical Emergency and AstraZeneca Designee [redacted] Contact Information

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 13 Medical Emergency and AstraZeneca Designee [redacted] Contact Information

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]

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 in the relevant AE modules in the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms is only reported in the Overdose eCRF module.

If an overdose on a study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca/[redacted] 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/[redacted] representative works with the investigator to ensure that all relevant information is provided to [redacted] PVG.

For SAEs associated with an overdose, the designated AstraZeneca/[redacted] representative (see Table 13) works with the investigator to ensure that all the necessary information is provided to the [redacted] PVG 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 nonserious AEs) reporting to [redacted] PVG should be done within 5 calendar days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca or designee.

13.3.1 Maternal exposure

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

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives (see Table 13) 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 [redacted] PVG within 30 calendar days of becoming aware of the pregnancy.

At an appropriate time point, the AstraZeneca representative will follow 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

Andes and Craig 2006
Andes D, Craig WA. Pharmacodynamics of a new cephalosporin, PPI-0903 (TAK-599), active against methicillin-resistant *Staphylococcus aureus* in murine thigh and lung infection models: identification of an in vivo pharmacokinetic-pharmacodynamic target. Antimicrobial Agents and Chemotherapy. 2006; 50(4): 1376–1383.

Arbeit et al 2004
Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI, Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis. 2004; 38 (12): 1673-1681. doi: 10.1086/420818

Breedt 2005
Breedt J, Teras J, Gardovskis J, Maritz FJ, Vaasna T, Ross DP, et al. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind Phase 3 comparison study with vancomycin-aztreonam. Antimicrobial Agents and Chemotherapy. 2005; 49 (11): 4658-4666.

Cerexa Investigator's Brochure 2013
Cerexa, Inc. Ceftaroline fosamil for injection. Investigator's brochure, 11th edition. Oakland (CA); 31 May 2013. 176 p.

Cockcroft et al 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Dryden 2010
Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother. 2010; 65 Suppl 3: iii35–iii44. doi:10.1093/jac/dkq302

FDA 2010
Food and Drug Administration (FDA), Center for Drug Evaluation and Research (US). Guidance for industry: Acute bacterial skin and skin structure infections: Developing drugs for treatment. Draft guidance. Revision 1. August 2010. 38 p.

Liu et al 2011
Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: Executive summary. Clin Infect Dis. 2011; 52(3):285-92.

Miettinen et al 1985
Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

Murray et al 2007
Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, editors. Manual of clinical microbiology. Washington DC; American Society for Microbiology; 2007 (Available upon request).

Noel et al 2008a
Noel GJ, Strauss RS, Amsler K, Heep M. Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. Antimicrob Agents Chemother. 2008 Jan:52(1):37-44.

Noel et al 2008b
Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin structure infections. Clin Infect Dis. 2008 Mar 1:46(5):647-55.

Sacchidananda 2005
Sacchidananda S, Penn RL, Embil JM, Campos ME, Curcioe D, Ellis-Grossef E, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: Results from a Phase 3, randomized, double-blind trial. Int Jr of Infectious Diseases. 2005; 9(5): 251-261.

Schneider et al 2008
Schneider E, Whitmore S, Glynn SK, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years – United States, 2008. MMWR; December 5 2008/57(RR10); 1-8 [cited 2011 Aug 25]. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a1.htm?s_cid=rr5710a1_e.

Stevens et al 2005
Stevens DL, Bisno AL, Chambers HF, Everett DE, Dellinger P, Goldstein EJC, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005; 41 (10): 1373-1406. doi: 10.1086/497143.

Stryjewski et al 2008
Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated Gram-positive skin and skin structure infections (ATLAS study). Clin Infect Dis 2008; 46:1683–93.