21 June 2012
EMA/472628/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zinforo

ceftaroline fosamil

Procedure No.: EMEA/H/C/002252

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Zinforo
Applicant:	AstraZeneca AB AstraZeneca European Regulatory Affairs (ERA) Building 411A Floor 4 S-151 85 Södertälje Sweden
Active substance:	ceftaroline fosamil
International Nonproprietary Name/Common Name:	ceftaroline fosamil
Pharmaco-therapeutic group (ATC Code):	Other cephalosporins (J01DI02)
Therapeutic indication(s):	Zinforo is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1): • Complicated skin and soft tissue infections (cSSTI) • Community-acquired pneumonia (CAP) Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strength:	600 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	10 vials

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List of abbreviations

%T>MIC	Percent time above the minimum inhibitory concentration
ABSSSI	Acute bacterial skin and skin structure infection
ADR	Adverse drug reaction
API	Active Pharmaceutical Ingredient
AE	Adverse event
AmpC	*AmpC* beta-lactamase
aPTT	Activated partial thromboplastin time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the plasma concentration time curve
BMI	Body mass index
BRCP	Breast cancer resistance protein
BUN	Blood urea nitrogen
BW	Body weight
CAP	Community-acquired pneumonia
CART	Classification and regression tree
CDC	Clinical Document Control
CE	Clinically evaluable
CFR	Code of federal regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
Cmax	Maximum plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CrCL	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
cSSTI	Complicated skin and soft tissue infection
CURB-65	Confusion, Urea nitrogen, Respiratory rate, Blood pressure, ≥65 years of age
CYP	Cytochrome P450

DAGT	Direct antiglobulin test
DM	Diabetes mellitus
ECG	Electrocardiogram
EOT	End of therapy
EMA	European Medicines Agency
ERS	European Respiratory Society
ERT	Evaluability Review Team
ESBL	Extended-spectrum beta-lactamase
ESRD	End-stage renal disease
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	US Food and Drug Administration
fDCF	Field data clarification forms
GCP	Good Clinical Practice
HAP	Hospital-acquired pneumonia
HHC	Home health care
hERG	Human ether-a-go-go-related gene
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IIR	Integrated Inspection Report
im	Intramuscular
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International Normalised Ratio
Ioc	Intraocular
IR	Infrared
IU	International Units
iv	Intravenous
IVRS	Interactive voice response system
LFU	Late follow-up
MAA	Marketing Authorisation Application
MDRSP	Multidrug resistant *Streptococcus pneumoniae*

ME	Microbiologically evaluable
MIC	Minimum inhibitory concentration(s)
MIC90	Minimum inhibitory concentration(s) required to inhibit the growth of 90% of organisms
mMITT	Microbiological modified intent-to-treat
MITT	Modified intent-to-treat
MITTE	Modified intent-to-treat efficacy
mMITTE	Microbiological modified intent-to-treat efficacy
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NDA	New Drug Application
OAT	Organic anion transporter
OCT	Organic cation transporter
OPAT	Outpatient parenteral antimicrobial therapy
PBP	Penicillin-binding protein
PCS	potentially clinically significant
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PNSP	Penicillin non-susceptible *Streptococcus pneumoniae*
PORT	Pneumonia patient outcomes research team
PT	Prothrombin time
PTA	Probability of target attainment
PVD	Peripheral vascular disease
PVL	Panton-Valentine leukocidin toxin
q8h	Every 8 hours
q12h	Every 12 hours
q24h	Every 24 hours
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SIRS	Systemic inflammatory response syndrome
SmPC	Summary of product characteristics

SOC	System organ class
SOP	Standard operating procedure
SPC	Summary of Product Charactersitics
t½	Half life
TEAE	treatment-emergent adverse event
TEM	*TEM* beta-lactamases
TOC	Test of cure
UAT	Urinary antigen test
ULN	Upper limit of normal
US	United States
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WBC	White blood cell (count)
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 16 December 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zinforo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 December 2009.

The applicant applied for the following indication:

Zinforo is indicated in adults aged 18 years and older for the treatment of the following infections (see section 4.2):

- Complicated skin and soft tissue infections (cSSTI)
- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own studies and bibliographic literature supporting certain studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/158/2010 on the agreement of a paediatric investigation plan (PIP) for the following conditions:

- Treatment of complicated skin and soft tissue infections
- Treatment of community acquired pneumonia

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable.

New active Substance status

The applicant AstraZeneca AB requested the active substance ceftaroline fosamil, contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Ceftaroline fosamil has been granted a marketing authorisation in the USA on 29 October 2010.

Manufacturers responsible for batch release

Facta Farmaceutici S.p.A.
Nucleo Industriale S. Atto
IT-64020 Teramo
Italy

AstraZeneca AB
Gärtunavägen, B674:5,
SE-151 85 Södertälje
Sweden

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **Alar Irs**

- The application was received by the EMA on 16 December 2010.
- The procedure started on 19 January 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 April 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2011(Annex 2)
- During the meeting on 19 May 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 May 2011 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 August 2011.
- The summary report of the inspection carried out between 4 May 2011 and 8 July 2011 was issued on 11 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 September 2011 (Annex 4)
- During the CHMP meeting on 20 October 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 May 2012.
- During the meeting on 18-21 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zinforo on 21 June 2012.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Among the Gram-positive bacterial pathogens *S. aureus*, whether or not it is methicillin-resistant, remains important, especially with the advent of aggressive community-acquired MRSA (CA-MRSA) that express Panton-Valentine Leucocidin (PVL+). In the last decade three non-beta-lactam agents have become available for the management of MRSA infections (daptomycin, tigecycline and linezolid) but there is already some resistance to each of these. These agents have several drawbacks and limitations and there is a need for additional antibacterial agents to manage serious infections due to Gram-positive bacteria. There are currently no licensed beta-lactam agents that are considered to be reliably clinically active against MRSA because they are unable to achieve sufficient binding to PBP2a, which mediates methicillin resistance in almost all cases, to inhibit normal cell wall formation.

The clinical activity of beta-lactam agents that are used to treat community acquired pneumonia may be affected to a variable extent by alterations in pneumococcal PBPs that mediate intermediate or greater degrees of insusceptibility to penicillin. This is because the licensed agents do not bind so efficiently to altered PBPs compared to those in wild-types.

The claimed indication and dosage for Zinforo at submission were:

Indication

"Zinforo is indicated in adults aged 18 years and older for the treatment of the following infections (see section 4.2):

- Complicated skin and soft tissue infections (cSSTI)
- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

Posology

"For the treatment of cSSTI, the recommended dosage of Zinforo is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older for 5 to 14 days. For the treatment of CAP, the recommended dosage of Zinforo is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older for 5 to 7 days. The duration of treatment should be guided by the type of infection to be treated, its severity, and the patient's clinical response.

Special Populations

Renal impairment

The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 ml/min, as shown below (see sections 4.4 and 5.2).

Creatinine clearance (ml/min)	Dosage regimen	Frequency
> 30 to ≤ 50	400 mg intravenously (over 60 minutes)	every 12 hours

There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis.

Hepatic impairment

No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2).

Elderly patients (≥ 65 years)

No dosage adjustment is required for the elderly with creatinine clearance values > 50 ml/min (see section 5.2).

Paediatric population

The safety and efficacy of Zinforo in children aged birth to < 18 years have not yet been established (see section 5.2).

Method of administration

Zinforo is administered by intravenous infusion over 60 minutes (see section 6.6)."

With a few changes, both indication and posology were agreed by CHMP.

The final agreed indication and dosage regimen for Zinforo are:

Indication

"Zinforo is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections (cSSTI)
- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

Posology

"For the treatment of cSSTI and CAP, the recommended dose is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older. The recommended treatment duration for cSSTI is 5 to 14 days and the recommended duration of treatment for CAP is 5 to 7 days.

Special populations

Elderly patients (≥ 65 years)
No dosage adjustment is required for the elderly with creatinine clearance values > 50 ml/min (see section 5.2).

Renal impairment
The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 ml/min, as shown below (see sections 4.4 and 5.2).

Creatinine clearance (ml/min)	Dosage regimen	Frequency
> 30 to ≤ 50	400 mg intravenously (over 60 minutes)	every 12 hours

There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis (see section 4.4).

Hepatic impairment
No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Zinforo in children aged birth to < 18 years have not yet been established. No data are available (see section 5.2).

Method of administration

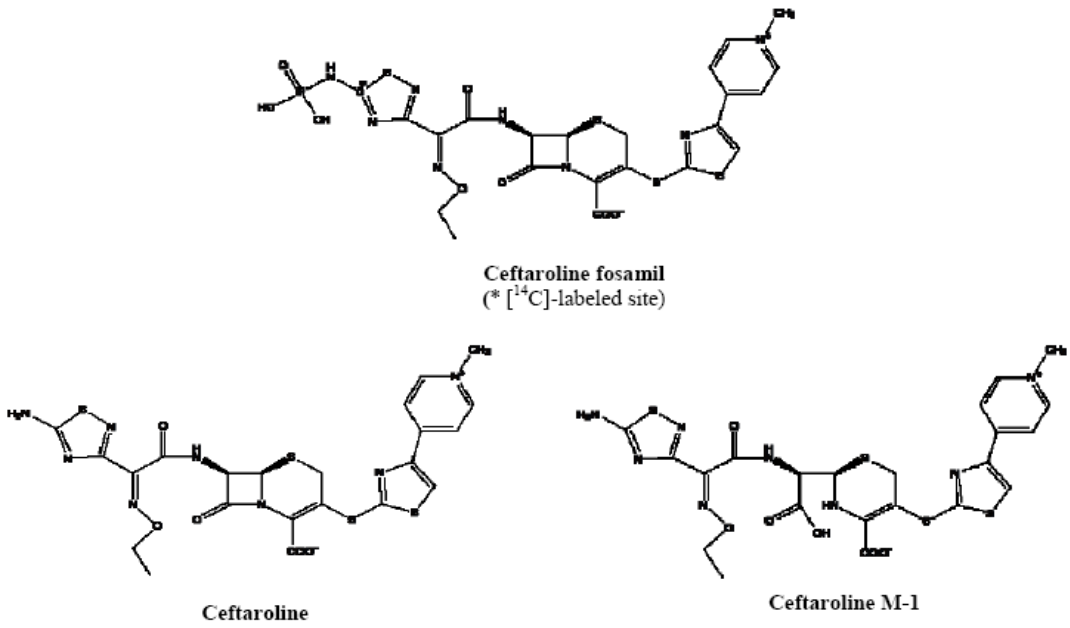
Zinforo is administered by intravenous infusion over 60 minutes (see section 6.6)."

2.1.2. About the product

Ceftaroline is an oxyimino cephalosporin antibacterial agent for intravenous administration by twice daily infusion over 60 minutes. It is presented for clinical use as the more water soluble N-phosphono (fosamil), which is rapidly converted to ceftaroline itself by phosphatases in human plasma. The

structures of ceftaroline fosamil, ceftaroline itself and the inactive ring-opened form, which is designated as ceftaroline M-1, are shown in figure 1.

Figure 1. Chemical Structures of Ceftaroline Fosamil, Ceftaroline, and Ceftaroline M-1



The spectrum of activity of ceftaroline is broadly suited to common pathogens implicated in the indications sought (community-acquired pneumonia [CAP] and complicated skin and soft tissue infections [cSSTI]). Ceftaroline is active *in vitro* against staphylococci, beta-haemolytic streptococci, *Haemophilus* and *Moraxella* spp. and most, but not all, enterobacterial species. The spectrum does not include the non-fermenting Gram-negative rods including *Acinetobacter spp*. and activity against anaerobes is genus- or species-specific.

An inoculum effect was evident on in-vitro testing with several species expressing one or more beta-lactamases that can hydrolyse cephalosporins to some extent. Ceftaroline may be readily hydrolysed by, and is therefore mostly inactive against, organisms that produce ESBLs (including, among others, TEM and SHV lineages), AmpC enzymes or carbapenemases (serine-based and metallo-enzymes).

Unlike the currently licensed cephalosporins ceftaroline shows some ability to bind to and inhibit altered penicillin binding proteins that are associated with methicillin-resistant staphylococci and penicillin-insusceptible pneumococci. For example, most methicillin-susceptible *S. aureus* (MSSA) are inhibited by 0.25-0.5 mg/l ceftaroline. There is an upward shift in MICs against MRSA with MIC_{90} at 1-2 mg/l and occasional isolates require 4-8 mg/l for inhibition. The highest MIC observed from the Phase 3 clinical studies was 2 mg/l, which may not be reliably covered by 600 mg twice daily as 1-h infusions although this regimen is likely suitable up to MICs of 1 mg/l.

Against 50 MRSA with well-characterised resistance phenotypes and genotypes the highest ceftaroline MIC values (2 to 4 mg/l) were observed among strains with SCC*mec* type I with a rank order of susceptibility according to SCC*mec* type of IV > II > III and I.

S. pneumoniae MIC90 values are around 0.12 mg/l but with a shift up from the fully penicillin-susceptible population (MIC90 0.015 mg/l) to non-susceptible (including penicillin-resistant with penicillin MICs ≥ 8 mg/l) strains (ceftaroline MIC90 0.25-0.5 mglL; regardless of serotype). Very few isolates required up to 2 mg/l ceftaroline for inhibition. In the phase 3 studies all pneumococci were

inhibited at 0.12 mg/l and most at < 0.015 mglL. Ceftaroline was very active *in vitro* against a range of *S. pneumoniae* strains including some strains that were non-susceptible to penicillin..

Competition binding assays using *S. aureus* and *S. pneumoniae*, including strains that demonstrate PBP-mediated reduced susceptibility to penicillins, employed a range of methodologies. The IC50 for binding to PBP2a in MRSA was 0.16 mg/l while IC50 values for PBP1a and PBP2x/2a/2b of the pneumococcal strain selected were lower for ceftaroline than for penicillin or ceftriaxone. The effect of ceftaroline on purified transpeptidases derived from strains of both species with different susceptibilities to beta lactam drugs was assessed in several studies. The results supported conclusions that ceftaroline is less active against strains expressing altered PBPs compared to wild-types but was more active than comparator beta-lactam agents.

Ceftaroline fosamil was approved for treatment of cSSTI and CAP in the US on 29 October 2010 under the brand name *Teflaro*® and with a different MAH to that proposed for the EU.

2.2. Quality aspects

2.2.1. Introduction

The medicinal product Zinforo powder for concentrate for solution for infusion is a sterile, pyrogen-free, pale yellowish-white to light yellow powder blend containing 668.4 mg of ceftaroline fosamil acetic acid solvate monohydrate (equivalent to 600 mg of ceftaroline fosamil) and an alkalising agent, L-arginine, aseptically filled into 20 mL sterile vials.

Zinforo is administered by intravenous infusion. The vial presentation is designed for single-dose use.

2.2.2. Active Substance

The drug substance, ceftaroline fosamil, is a sterile, semi-synthetic prodrug of ceftaroline. This form was chosen due to the solubility limitations of ceftaroline. Ceftaroline fosamil is included in the drug product formulation as an acetic acid solvate monohydrate, which is a crystalline solid with good stability.

The chemical name of ceftaroline fosamil is (6R, 7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (monoacetate monohydrate); with molecular formula C24H27N8O11PS4 and relative molecular mass 762.75 g/mol (solvate hydrate form). There is no Ph.Eur. monograph for ceftaroline fosamil.

The chemical structure of ceftaroline fosamil has been confirmed by elemental analysis and spectroscopic methods: UV, IR, ^{1}H-NMR, ^{13}C-NMR, and fast atom bombardment mass spectrometry. All results support the proposed structure.

Ceftaroline fosamil has two chiral centres. The configuration 6R,7R of beta-lactam is defined by the specific optical rotation of one of the starting materials which is obtained by fermentation. Optical rotation is used to confirm the stereochemistry of ceftaroline fosamil.

Polymorphism has been investigated by DSC and XRPD studies. Data provided demonstrate that the same polymorphic form is maintained during the shelf-life of the product.

Manufacture

The manufacturing process of ceftaroline fosamil consists of six chemical transformations and five purification steps.

As ceftaroline fosamil is required as a sterile drug substance it is produced by sterile filtration, and its sterility is maintained by aseptic processing.

The manufacturing process has been adequately described, and satisfactory specifications have been set for reagents, solvents and auxiliary materials used in the process. All critical in-process controls have been well established and justified.

Satisfactory data for process validation and media fill simulation runs for validation of sterile filtration and crystallisation processes have been provided.

The analytical methods have been satisfactorily described and validated according to ICH Q2 (R1).

The drug substance is stored in a packaging system consisting of three sterile bags each sealed within each other. All bags are sterilised before use. The manufacturer has provided specifications for the bags and has confirmed that the material in contact with the drug substance is compliant with EU directive 2002/72/EC as amended and with the European Pharmacopoeia.

Specification

The active substance specification include appropriate tests for appearance (visual inspection), identification (IR spectra and HPLC), clarity of solution (Ph. Eur.), pH (Ph. Eur.), water content (Karl Fischer), specific optical rotation (Ph. Eur.), sulphate ion (IC), acetic acid (IC), sodium ion (ICP), heavy metals (USP), arsenic (ICP), foreign insoluble matter (microscopy), particulate contamination (Ph. Eur.), particle size distribution (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), sterility (Ph. Eur.) and bacterial endotoxin (Ph. Eur.).

A discussion on potential impurities arising from the starting material, the reagents, the route of synthesis or degradation has been provided. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data have been presented and all batches were in compliance with the predefined active substance specification.

Stability

Data from stability studies on four primary batches has been provided. Samples were stored for up to 36 months at 5±3°C (long-term conditions) and for 6 months at 25°C/60% RH (accelerated conditions) in accordance with ICH requirements.

Following the manufacture of the primary stability batches a number of improvements on the processing conditions were made, but no change was made to the synthetic route. It has been demonstrated that in all cases equivalent high quality ceftaroline fosamil has been obtained meeting the proposed specification. Supporting stability data on four batches, manufactured using the current commercial process and, stored for up to 18 months at 5±3°C and for 6 months at 25°C/60% RH, have been provided.

The test parameters evaluated in the stability studies were appearance, identification (HPLC and IR), water content, clarity of solution, acetic acid, assay (anhydrous and acetic acid free), related

substances, sterility and bacterial endotoxins. In all cases the batch analysis data met the predefined specification and no significant changes were observed.

In addition stability data have been provided under stress conditions (heat, acid hydrolysis, base hydrolysis, photo degradation, water hydrolysis and hydrogen peroxide treatment).

The stability data provided justify the proposed retest period in the proposed storage conditions.

Comparability exercise for Active Substance

Not applicable

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The drug product presentation is a sterile, pyrogen-free, powder blend containing ceftaroline fosamil acetic acid solvate monohydrate, and an alkalising agent, L-arginine, filled in 20 mL vials.

Ceftaroline fosamil drug substance is a sterile, semi-synthetic prodrug which is rapidly cleaved upon administration to form ceftaroline. Ceftaroline fosamil was selected for development due to its improved aqueous solubility, as compared with ceftaroline. Ceftaroline fosamil acetic acid solvate monohydrate was selected for development as it can be produced as a crystalline form with good stability.

A preliminar pre-clinical investigation showed that no efficacious plasma concentrations were achieved when ceftaroline fosamil was administered orally, thus the parenteral route of administration was selected.

Initially, the manufacturer's intention was to develop an aqueous ready-to-use solution formulation for infusion. However, this was not feasible due to the limited stability of the prodrug in solution. Consequently, the manufacturer tried to develop a sterile dry powder product that could be reconstituted with a commercially available diluent at time of use.

For the development of the manufacturing process consideration has been given to the possibility of terminally sterilising the finished vials, using the approach outlined in "EMA: Decision Trees for the Selection of Sterilisation Methods". However terminal sterilization was deemed unacceptable for ceftaroline fosamil formulated drug product and assepting processing was chosen for the manufacture of the finished product.

The development of the product has been satisfactorily described. Ceftaroline fosamil is an acidic drug with limited aqueous solubility. Therefore, an alkalising agent was required to aid the dissolution of the drug substance by increasing the pH of the reconstituted solution. L-arginine was chosen.

Adventitious agents

None of the materials used in the manufacture of Zinforo is of animal or human origin.

Manufacture of the product

Ceftaroline fosamil powder for concentrate for solution for infusion is manufactured via an aseptic manufacturing process similar to that used for other parenteral products.

The manufacturing process has been sufficiently described and validated, and adequate in process controls are in place. The manufacturing process involves aseptically blending sterile ceftaroline fosamil powder and sterile L-arginine powder are aseptically blended to form ceftaroline fosamil bulk drug product powder blend, which is then filled into 20 mL vials.

Product specification

Appropriate drug product specifications have been set. The specification for Zinforo is typical for this pharmaceutical form and include tests for appearance (visual examination), identification (HPLC and UV), clarity of solution (Ph. Eur.), constitution time, pH, assay as percent label claim (HPLC), impurities (HPLC), uniformity of dosage units (Ph.Eur.), container/closure integrity, extractable volume (Ph. Eur.), water content (Ph. Eur.), particulate contamination (Ph. Eur.), bacterial endotoxin (Ph. Eur.) and sterility (Ph. Eur.).

The non-compendial analytical methods have been well described and validated in agreement with ICH guidelines. With regards to the method used for the quantitation of related substances in the drug product, the applicant has provided comparative analysis data from two commercial stability batches stored for 15 months at 25°C/60%RH. The levels of related substances were calculated using an area normalisation method and an alternative calculation method. The CHMP recommends that the applicant should use both area-normalisation method and the alternative method to estimate the content of impurities in the first three drug product stability batches in order to determine if both methods give equivalent results. If significant differences in the content of impurities calculated with both methods are observed the analytical methods should be revised. However, this is not expected to be a risk to the patient as in all cases the levels of related substances were below the qualification threshold.

Batch analysis results comply with the predefined specifications and confirm consistency & uniformity of manufacture and indicate that the process is under control.

Stability of the product

The results of long term (up to 24 or 36 months at 5±3°C), intermediate (up to 24 or 36 months at 25°C/60%RH and 30° C/75%RH) and accelerated stability studies (6 months at 40°C/75%RH) have been presented for three production scale batches. Supportive stability data have also been provided on three commercial scale batches stored for up to 18 months at 25°C/60%RH and 30°C/75%RH, and 6 months at 40°C/75%RH.

Results from a photostability study performed as per ICH Q1B guideline have also been provided.

The test parameters evaluated in the stability studies were appearance, clarity of solution, constitution time, pH, assay, degradation products and water content, bacterial endotoxins and sterility. In all cases the parameters tested remained within the proposed specifications and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, excipient, manufacturing process, analytical methods, packaging and control of the drug substance and drug product has been presented in a satisfactory manner.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a

satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following:

The applicant should evaluate both area-normalisation method and an alternative calculation method to estimate the content of impurities in first three drug product stability batches in order to confirm if both methods give equivalent results. If significant differences in the content of impurities calculated with both methods are observed the analytical methods should be revised.

2.3. Non-clinical aspects

2.3.1. Introduction

Ceftaroline is a semi-synthetic cephalosporin which has been developed as the prodrug ceftaroline fosamil because of the low water solubility of the antibacterial agent at physiological pH. Ceftaroline fosamil undergoes rapid biotransformation in plasma. The rationale for the development of ceftaroline was based on the high binding affinity for, and transpeptidase inhibition of, the penicillin-binding protein 2a (PBP2a), the mecA gene product of MRSA, and PBP2x in penicillin-resistant *S. pneumoniae* (PRSP), compared with commonly used beta-lactams.

GLP

The pivotal toxicology and the majority of the safety pharmacology studies conducted by the applicant were reported to be GLP compliant. The safety studies that were not conducted to GLP were conducted to an appropriate scientific standard and justification has been provided by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Ceftaroline inhibits bacterial cell wall biosynthesis through binding to the transpeptidase active site of penicillin-binding proteins (PBPs), which carry out the final steps in cell wall biosynthesis. Ceftaroline has been shown to bind with high affinity to PBP2a in methicillin-resistant *S. aureus* (MRSA), relative to other beta-lactams in the class.

The primary pharmacology of ceftaroline fosamil has been adequately characterised.

In vitro activity of ceftaroline

The spectrum of activity of ceftaroline includes many or most staphylococci, beta-haemolytic streptococci, *Haemophilus* and *Moraxella* spp., *P. multocida* and enterobacterial species but does not include the non-fermenting Gram-negative rods including *Acinetobacter spp*. and activity against anaerobes is genus- or species-specific. An inoculum effect was evident on in-vitro testing with several species expressing one or more beta-lactamases that can hydrolyse cephalosporins to some extent.

Ceftaroline may be readily hydrolysed by, and is therefore mostly inactive against, organisms that produce ESBLs (including, among others, TEM and SHV lineages), AmpC enzymes or carbapenemases (serine-based and metallo-enzymes).

Against *E. coli, Klebsiella spp*. and other enterobacteria (including *Citrobacter spp*., *Enterobacter spp*. and *P. mirabilis*) not over-expressing beta-lactamases or manufacturing enzymes able to readily hydrolyse ceftaroline the MICs are mostly < 2 mg/L. However, the MIC90s for *Morganella morganii, P. vulgaris* and *Serratia marcescens* were all 16 mg/L or higher and these species cannot be considered to fall into the spectrum of activity of ceftaroline. MIC90 values from surveillance studies are highly variable depending on the rates and types of beta-lactamases produced in individual collections of organisms. Isolates of enterobacteria that could be considered within the spectrum of activity of ceftaroline showed that ceftazidime-resistant bacteria usually required at least 16 mg/L ceftaroline for inhibition. However, these isolates were in the minority and there was a large separation evident between the susceptible population (MICs usually 0.5 mg/L or less) and the resistant population (16 mg/L or more). Among the anaerobes, ceftaroline appears likely to be active against *Porphyromonas asaccharolytica* and several *Fusobacteria spp*. and *Veillonella spp*. The Gram-positive anaerobes are more likely to be susceptible, including most *Peptostreptococcus spp.* and *Eubacterium spp*. whereas clostridial species (including *C. perfringens*) appear to have higher MICs and MIC90 values of around 4-8 mg/L. Ceftaroline is not active against *Mycoplasma* or against intracellular *Chlamydia* or *Legionella*.

Ceftaroline demonstrated time-dependent killing. Maximum rates of killing were generally observed at ≥ 2 x MIC. Bactericidal effects (≥ 3-log10 killing) occurred within 8 to 24 hours. Single-point kill rates for 6 *S. aureus* doubled or quadrupled in the presence of 50% human serum. In the presence of serum, the kill-rates for *E. coli* increased by 1/2, while those for *K. pneumoniae* were increased 4-fold.

The post-antiibiotic effects determined in a neutropenic mouse thigh infection model showed short to modest PAE with *S. pneumoniae* or *E. coli*. PAE for *S. aureus* were in the range 0.8 to 7.2 h and for MRSA 3.8 to 4.8 h but there was no PAE against highly penicillin-resistant pneumococci. Variable results have been obtained in other experimental settings and using other strains.

In vivo studies

The activity of ceftaroline has been evaluated *in vivo* in a variety of animal models of infection. In early pre-clinical studies, efficacy was demonstrated in mouse lung, thigh, and peritonitis infection models against Gram-positive and Gram-negative organisms. The murine thigh model was employed to characterize the *in vivo* time course of antibacterial activity of ceftaroline fosamil and determine the PK/PD index and the index magnitude predictive of efficacy to provide guidance for dosing regimen design in human clinical trials. Ceftaroline fosamil efficacy was confirmed in a further murine pneumococcal pneumonia model using human simulated dosing. During the procedure, the applicant informed CHMP that some errors (concerning the free drug % f T >MIC and calculated arithmetic mean values necessary for ceftaroline doses to demonstrate net stasis, 1-log10 kill and 2 log10 kill against the 2 *Klebsiella pneumoniae* and 2 *Escherichia coli* strains tested) in the initial murine thigh and lung models were spotted and have been corrected and that the PK/PD target for Enterobacteriaceae was recalculated. Ceftaroline *in vivo* efficacy was demonstrated in rat endocarditis models against MSSA and staphylococcal (MRSA, GISA, hGISA) and *E. faecalis* (VSE and VRE) endocarditis models in the rabbit, in addition to a rabbit model of staphylococcal (MRSA, GISA) osteomyelitis. Development of ceftaroline resistance *in vivo* was also assessed in the same rabbit endocarditis model using sub-therapeutic doses to induce the emergence of resistant variants. Ceftaroline fosamil *in vivo* efficacy was also evaluated in a rabbit pneumococcal (PSSP, PISP, PRSP) pneumonia model. Finally, ceftaroline fosamil was also studied in an experimental model of meningitis in the rabbit against strains of *E. coli* (ceftaroline MIC of 0.06 mg/L) and *K. pneumonia* (ceftaroline MIC of 1 mg/L).

Secondary pharmacodynamic studies

Ceftaroline fosamil and ceftaroline were tested in a panel of 339 in vitro enzyme, radioligand and electrophysiologic assays in order to assess pharmacological activity unrelated to the therapeutic target.

The secondary pharmacology assays demonstrated that ceftaroline fosamil (but not the metabolite, ceftaroline) possessed inhibitory activity at the Cav1.2 channel; however, the observed effect was not deemed to be clinically relevant. No effects were observed at the 338 other targets tested.

Safety pharmacology programme

The safety pharmacology programme assessed the CNS, cardiovascular, renal and respiratory effects of ceftaroline fosamil and ceftaroline in vitro and single dose *in vivo* studies in the rat and monkey.

Table 1: Safety pharmacology studies performed with ceftaroline fosamil and ceftaroline

Type of Study (Test article)	Dose (mg/kg)/ Concentration (µg/mL)	Test system	Method of administration	GLP status	Study number
Irwin Screen (ceftaroline fosamil)	0, 47, 479, 2000	SD rat (male)	i.v. slow bolus	GLP	DFEW1027
Pro-convulsant Study with PTZ (ceftaroline fosamil)	0, 100, 200, 600, 1000	SD rat (male)	i.v. slow bolus	GLP	DFEW1033
hERG Assay (ceftaroline fosamil)	44.4, 177.7, 711, 1070.3	HEK-293 cells	*In vitro*	GLP	600713-1 (PPI-0903)
hERG Assay (ceftaroline)	50, 200, 400, 600, 800, 1200	HEK-293 cells	*In vitro*	GLP	600713-1 (PPI-0903M)
Action potential assessment (ceftaroline fosamil)	0.77, 7.7, 77 (0, 1, 10,100 µM)	Isolated dog Purkinje Fibers	*In vitro*	GLP	DFEW1029
Action potential assessment (ceftaroline)	18.1, 60.5, 181 (0, 30, 100, 300 µM)	Isolated Dog Purkinje Fibers	*In vitro*	Non-GLP	DFEW1031
Cardiovascular telemetry study (ceftaroline fosamil)	0, 40, 120, 400	Cynomolgus monkey (male)	*1 hour i.v. infusion*	GLP	DFEW1026
Respiratory Assessment (ceftaroline fosamil)	0, 20, 60, 200	SD rat (male)	*i.v. slow bolus*	GLP	DFEW1028a
Renal Assessment (ceftaroline fosamil)	0, 60, 200, 600	SD rat (male)	*i.v. slow bolus*	GLP	B040245

During studies to evaluate the effects of ceftaroline fosamil on the central nervous system, tonic seizures, convulsions and/or pro convulsant activity were observed at ceftaroline exposures (Cmax) that were > 20 fold higher than the proposed clinical Cmax. In addition, a series of safety pharmacology studies were performed to investigate the effects on the cardiovascular system.

Although hERG inhibition was observed with ceftaroline (IC50 656 micrograms/mL), no effect on action potential duration was observed during a dog Purkinje fibre assay and ceftaroline fosamil had no effect

on QT interval *in vivo* (monkey). The results generated did not indicate a potential for QT prolongation in man.

Effects on respiratory function (increased respiration rate and decreased tidal volume) were observed in the rat. As there was no effect on the minute volume and given the transient nature of these effects and the exposures at which they occurred, the observed effects on respiratory function were not considered to be clinically relevant by CHMP.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions have been assessed with ceftaroline in combination with a variety of antibiotics in 3 *in vitro* studies against Gram-positive and Gram-negative pathogens including important drug-resistant strains (study P0903-M-020, study NSR-P0903-M-045, study NSR-P0903-M-043).

The results of these drug interactions studies revealed no instances of antagonism when ceftaroline was combined with the other commonly used antimicrobials. Several antimicrobials, including meropenem, amikacin and piperacillin-tazobactam led to synergistic effects in combination with ceftaroline against the specific strains tested.

2.3.3. Pharmacokinetics

The pharmacokinetic profile following repeated intravenous administration of ceftaroline fosamil was evaluated during the repeated dose toxicity studies conducted in the rat and monkey at up to 1000 and 400 mg/kg/day, respectively. Exposures (Cmax and AUC) to ceftaroline fosamil were significantly lower than those observed for ceftaroline. Exposures to ceftaroline increased in a dose-proportional manner and no accumulation of ceftaroline fosamil or ceftaroline was observed on repeated dosing. Ceftaroline was also readily absorbed following intramuscular administration.

Following intravenous administration of radiolabelled-ceftaroline fosamil, drug related radioactivity was rapidly and widely distributed and the highest tissue/plasma ratio was observed in the kidney, which correlates with the route of elimination and the target organ toxicity observed. Distribution into the lung, bone tissues and cerebrospinal fluid was also observed.

A series of *in vitro* and *in vivo* studies have demonstrated that the transformation of ceftaroline fosamil is mediated by a phosphatase enzyme and that the metabolism of ceftaroline fosamil and/or ceftaroline is not likely to be mediated by CYP enzymes. *In vivo*, ceftaroline and ceftaroline M-1 (its inactive metabolite) have been identified as the predominant metabolites in mice, rats, monkeys and humans and urinary excretion was the principal route of elimination in both animals and humans.

The *in-vitro* data provided to date have shown that at the proposed clinical dose, the potential for pharmacokinetic interactions between ceftaroline fosamil and concomitantly administered medicinal products is low.

Single dose toxicity

Two single dose toxicity studies were conducted: study TAK-599-00012 in the rat and study TAK-599-00014 in monkeys. No mortality was observed following single intravenous doses of ceftaroline fosamil at up to 2000 mg/kg. In the rat, prone position and tonic/clonic convulsions were noted at > 1000 and 2000 mg/kg, respectively. In the monkey, mydriasis was observed at > 200 mg/kg. Discoloured urine was noted in both species.

Repeat dose toxicity

4 repeated dose toxicity studies of up to 13 weeks duration (studies TAK-599-00081, TAK-599-00015, CXL-TX-02 and P0903-T-010) were performed in the rat, whereby ceftaroline fosamil was administered intravenously via either a slow bolus injection or infusion.

5 repeated-dose toxicity studies of up to 13 weeks duration (studies TAK-599-00082 and -00083, TAK-599-00037, CXL-TX-03, P0903-T-011) were performed in the monkey, whereby ceftaroline fosamil was administered intravenously via either a slow bolus injection or a 60 minute infusion.

The CHMP considered that the performed studies were appropriate for the proposed clinical duration, although it was noted that in the majority of the rat studies, ceftaroline fosamil was administered as a slow bolus injection, whereas in humans it will be administered via a 60-minute infusion. The C_{max} values for ceftaroline at the no-effect levels in the rat are 9- to 12-fold higher than the proposed clinical C_{max} which was considered acceptable. However, the corresponding safety margins in terms of AUC were below 1 (0.65 to 0.9).

The exposure margins (C_{max} and AUC) based on the no-effect levels from the monkey studies range from 0.4 to 2.

During the 4-week studies conducted in the rat and monkey, where ceftaroline fosamil was administered either alone or in combination with a β-lactamase inhibitor (which is still in development), ceftaroline fosamil was administered as a 60-minute intravenous infusion. When ceftaroline fosamil was administered alone, in the kidney, no effects were observed in the rat at 200 mg/kg/day, minimal effects were noted in the monkey at 100 mg/kg/day and hence, the NOAELs for these studies were higher than those observed for the pivotal 4- and 13-week studies. The NOAEL variability for the studies in the rat may be linked to observed differences in plasma C_{max}.

The findings were typical of cephalosporins, whereby the main target organs were the kidney (cloudy urine, deposition of granular material (cytoplasmic lysosomes) in the epithelium of the renal collecting tubules in the papillary region accompanied by swelling. dilatation of the renal tubules and pelvic cavity, pigmentation/hypertrophy/regeneration of renal collecting ducts), central nervous system (mydriasis, tonic/clonic convulsions) and the spleen(enlargement of spleen germination centres). The no-effect levels for the pivotal toxicity studies were primarily based upon the histopathological findings in the kidney and it is plausible that the renal effects may be partially responsible for the observed mortality at higher doses. Renal microscopic changes included collecting duct hypertrophy or vacuolation and deposition of foreign material associated with granuloma formation. Renal and urinary disorders (between 1/1000 and 1/100) and hepatobiliary disorders (between 1/100 and 1/10) have been reported in humans. Moreover, other members of this pharmacological class of compounds (cephalosporins) are associated with renal toxicity. Appropriate precautions for patients with renal impairment have been included in Section 4.4 of the SmPC, which was agreed by the CHMP.

Haematuria and yellow cloudy urine were observed during the 4-week intravenous studies in the rat and monkey, respectively and orange urine was observed during the reproductive toxicity studies in the rat. The urinary discolouration was attributed to excretion of the test article or a metabolite. In addition, decreased erythrocyte number, haematocrit and haemoglobin were observed in the monkey and the Coomb's test (often used to detect antibody-mediated destruction of red blood cells) demonstrated that the development of detectable antibodies was higher in patients treated with ceftaroline when compared to ceftriaxone. However, no significant changes in haematology or serum biochemistry parameters were observed to suggest the existence of haemolysis during the phase 2 or phase 3 trials.

Table 2: Summary of repeated dose toxicity studies

Type of Study	Strain/ Species	Method of Admini-stration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Study No.
Repeat Dose Toxicity	Sprague-Dawley Rats	IV slow bolus	2 weeks	0, 40, 120, 400	No	TAK-599-00081
	Sprague-Dawley Rats	IV slow bolus	4 weeks	0, 100, 300, 1000	Yes	TAK-599-00015
	Sprague Dawley Rats	1-hour IV infusion	4 weeks	0, 200	Yes	CXL-TX-02
	Sprague-Dawley Rats	IV slow bolus	13 weeks	0, 30, 90, 270	Yes	P0903-T-010
	Cynomolgus Monkeys	IV slow bolus	2 weeks	0, 40, 120, 400	No	TAK-599-00082
	Cynomolgus Monkeys	1-hour IV infusion	2 weeks	0, 40, 120	No	TAK-599-00083
	Cynomolgus Monkeys	1-hour IV infusion	4 weeks	0, 16, 80, 400	Yes	TAK-599-00037
	Cynomolgus Monkeys	1-hour IV infusion	4 weeks	0, 100	Yes	CXL-TX-03
	Cynomolgus Monkeys	1-hour IV infusion -via implanted catheter	13 weeks	0, 8, 16, 32, 64	Yes	P0903-T-011

Genotoxicity

A series of *in vitro* and *in vivo* genotoxicity studies with ceftaroline fosamil and the active metabolite ceftaroline was conducted. Ceftaroline fosamil and ceftaroline caused an increase in chromosomal aberrations *in vitro*. However, the two compounds were non-mutagenic in the Ames test, did not induce DNA damage in rat hepatocytes and did not cause chromosomal aberrations *in vivo*. Given that other cephalosporins have a similar profile to that observed with the test articles the CHMP agreed that administration of ceftaroline for up to 14 days is not likely to pose a genotoxic risk to humans.

Carcinogenicity

No carcinogenicity studies were performed. The CHMP considered that the absence of carcinogenicity studies was acceptable, as such studies are not required given the proposed duration of treatment and the fact that the ceftaroline fosamil is not considered to pose a genotoxic risk.

Reproduction Toxicity

A series of reproductive toxicity studies in the rat and rabbit was conducted to evaluate the effects of ceftaroline fosamil on fertility and embryofetal development. Ceftaroline fosamil had no effect on male or female fertility (rat) and did not appear to be teratogenic in the rat or rabbit at the doses evaluated. However, during the definitive rat embryofetal development study, there was some evidence of reduced fetal weight at $\geq$ 100 mg/kg/day; it was suggested that the observed fetal weights were within the range observed for historical controls. In addition, although no dose-response relationship was observed, delayed ossification was noted in the rat at $\geq$30 mg/kg/day.

Given that a reduction in fetal weight was observed in both the preliminary and the definitive studies and that the exposures observed at 30 mg/kg day are below the proposed clinical exposures, the CHMP requested the applicant to include the observed effects on fetal weight and ossification in the relevant sections (4.6 and 5.3) of the SmPC. The SmPC was subsequently updated.

No new toxicities were identified during a juvenile toxicity study conducted in the rat.

Toxicokinetic data

Toxicokinetics of ceftaroline fosamil and ceftaroline was evaluated in the toxicology studies in rat and monkey. The analytical methods used for the toxicokinetic analyses for the pivotal toxicity studies were sufficiently validated. Ceftaroline fosamil was administered as repeated iv doses in ranges of 30 to 1000 mg/kg in rats, and 8 to 400 mg/kg in monkeys. The Cmax and AUC of ceftaroline fosamil were significantly lower than those of ceftaroline. In both rats and monkeys, the Cmax and AUC of ceftaroline increased in an approximately dose proportional manner within the dose range studied. No differences were noted in either species with respect to gender in the PK parameters of ceftaroline fosamil, ceftaroline, or ceftaroline M-1. In addition, there was no accumulation of ceftaroline fosamil and ceftaroline after repeated once-daily administration, and only moderate accumulation of ceftaroline M-1 was observed in these studies.

Local Tolerance

During the studies designed to assess local tolerance in the rabbit, no histological changes were observed at the injection site; hence, the local irritancy potential of the formulations evaluated appear to be negligible. The concentration of ceftaroline fosamil evaluated during the local tolerance studies was 4.17 mg/mL. However, according to the proposed SmPC, ceftaroline fosamil (600 mg) may be administered in a total volume of 50, 100 or 250 mL, which corresponds to administration of 12, 6 or 2.4 mg/mL solutions respectively. There is some evidence (from both the repeated-dose non-clinical studies and the clinical studies) to suggest that ceftaroline fosamil may cause irritancy at the injection site (at ≥4.17 mg/mL). Hence in order to support intravenous administration of a 12 mg/mL solution, a Phase 1 clinical study in healthy volunteers is being performed by the applicant to investigate tolerability and irritancy at the injection site.

Other toxicity studies

Although cephalosporins have sensitisation potential, ceftaroline fosamil, when tested alone, had no antigenic potential in both the passive cutaneous anaphylaxis and active systemic anaphylaxis assays in the guinea pig. However, ceftaroline does have the potential to cause sensitisation under conditions of immunostimulation. Moreover, there are clinical data to suggest that ceftaroline may be associated with the risk of hypersensitivity and anaphylaxis.

In the mouse, cephalosporins typically increase immunoglobulin M (IgM) levels due to proliferation of the IgM-producing cells in the splenic germinal centres, causing splenomegaly. In the rat, repeated-administration of ceftaroline fosamil decreased serum IgG levels in the absence of any changes in IgM at exposures that were higher than those proposed clinically. In addition, the splenic changes noted (hypertrophy of the lymphoid follicles) were of minimal to mild severity. In the 13-week monkey study, splenic changes of mild severity were also observed (reversible) at clinical exposures in the absence of any effects on IgG or IgM. Taken together, the decreased serum IgG (rat only) and the observed splenic changes were not considered to be of clinical significance, and hence, further studies to evaluate immunotoxicologic potential were not performed.

The proposed levels of the impurities U1, U2 and U9 as outlined by the drug substance specification (≤0.5, 0.3 and 0.6%, respectively) are considered to be qualified from a toxicological point of view. The limit as outlined by the drug product specification for the ceftaroline fosamil-arginine adduct (≤1.5%) is also acceptable and the applicant has clarified that this impurity does not pose a genotoxic risk.

Phototoxicity studies have not been performed. The absorption spectrum for ceftaroline fosamil indicates that no relevant absorption was observed within the 290 to 700 nm range. Hence, the non-clinical data generated thus far do not suggest that ceftaroline fosamil has the potential to cause phototoxicity. Following repeated intravenous administration of ^{14}C-ceftaroline fosamil, elimination of radioactivity was relatively slow from the kidney, skin and thyroid, whereby radioactivity was still detectable 14 days after the final dose.

2.3.4. Ecotoxicity/environmental risk assessment

The applicant has conducted a series of studies to investigate the potential for ecotoxicity and the results suggest that ceftaroline fosamil will not constitute a risk to the environment. Below a summary of the main results:

Table 3: Summary of main study results-Environmental risk assessment

Substance (INN/Invented Name): Ceftaroline (active compound – focus of the ERA)			
CAS-number: 189345-04-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD 117	log D_{ow} < 0 at pH 5, 7 and 9	Potential PBT - No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	log D_{ow} < 0 at pH 5, 7 and 9	not B
Persistence	DT50 or ready biodegradability	$DT_{50, water}$ = 2 d	not P
Toxicity	NOEC	Lowest NOEC = 1.2 µg/L (blue green alga)	T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0054 (refined)	µg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			No

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS 835.1110	K_{oc} = 21.6 $K_{d(ads)}$ = 8			K_{oc} < 10000 Therefore, terrestrial testing is not triggered
Ready Biodegradability Test	OECD 301	BOD_{28} <5%			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.77 d (HOM), 2 d (LOM) $DT_{50, sediment}$ = not possible to analyse $DT_{50, whole\ system}$ = not possible to analyse % shifting to sediment = Maximum 28% of applied radioactivity (no parent confirmation)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Cyanobacterium	OECD 201	NOEC	1.2	µg/L	*Anabaena flos-aquae*
Algae, Growth Inhibition Test/Green alga	OECD 201	NOEC	33000	µg/L	*Pseudokirch-neriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	7900	µg/L	
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	5000	µg/L	Fathead minnow (*Pimephales promelas*)
Activated Sludge, Respiration Inhibition Test	OECD 209	3 h EC_{50}	> 10^5	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	67	mg/ kg	*Chironomus riparius*

2.3.5. Discussion on non-clinical aspects

The pro-drug, ceftaroline fosamil is hydrolysed to ceftaroline by plasma phosphatases. Ceftaroline is active *in vitro* against staphylococci, beta-haemolytic streptococcocci, *Haemophilus* and *Moraxella* spp. and most enterobacterial species. The spectrum does not include the non-fermenting Gram-negative rods including *Acinetobacter spp*. and activity against anaerobes is genus- or species-specific.

The findings during the safety studies were generally typical of cephalosporins, whereby the main target organs were the central nervous system, kidney and the spleen (for details see above). There were no findings indicative of a genotoxic or teratogenic risk for humans; however, reduced fetus body weight and incomplete ossification were observed during the rat embryofetal development studies. In addition, the studies conducted to date do not indicate a potential to cause local irritancy or haemolysis following intravenous administration of 4.17 and 12 mg/mL formulations, respectively. A Phase I study to investigate tolerability and irritancy at the injection site is ongoing and was deemed by CHMP as sufficient to generate data which could support intravenous administration of the proposed clinical formulation at 12 mg/mL.

2.3.6. Conclusion on the non-clinical aspects

The CHMP agreed that the presented data do not raise any major safety concerns and the non-clinical programmewas considered acceptable. The primary pharmacology of ceftaroline has been adequately characterised. Repeat dose toxicity studies showed that the main target organs were the kidney, the central nervous system and the spleen, as for all cephalosporins. Appropriate precautions for patients with renal impairment have been included in Section 4.4 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Initial application dossier

The application dossier stated in its overview and individual study reports that study protocols and amendments, informed consent forms, information sheets and advertisements were approved by the Institutional Review Board or Independent Ethics Committee at each study centre in conformance with International Conference on Harmonisation (ICH) Guidelines E6 and E3, Code of Federal Regulations (CFR), Part 56, ethical principles stated in the "Declaration of Helsinki," and in accordance with the laws and regulations of the country in which the research was conducted.

There were four Phase 3 efficacy studies in this application – 06 and 07 in cSSTI and 08 and 09 in CAP.

Since ceftaroline had already been approved in the US based on the same clinical studies as included in the EU application dossier, the US FDA had already conducted its own inspection of study sites in accordance with routine practise.

The US inspections included the sponsor (Cerexa) and two study sites from each of the four Phase 3 studies (total 8 sites). These sites were scattered worldwide and several of the highest enrollers were audited on several occasions. Specifically, the US FDA had inspected two sites in the US (contributing to 06 and 07), three sites in Russia (contributing to 06, 07 and 09), two in the Ukraine (contributing to 08 and 09) and one in Georgia (study 08). There were no significant findings reported by the US inspectors. During the course of the studies the sponsor (Cerexa) had also audited 18 sites in study -06, 22 in -07, 19 in -08 and 18 in -09. These sites were scattered worldwide and several of the highest enrollers were audited on several occasions.

EU GCP inspection and findings

During the initial review phase the EMA selected the Zinforo application dossier to be subject to a routine GCP inspection (i.e. this was not triggered by the assessment teams).

The EMA selected two sites from study 07 (one site contributed 22 patients and the other contributed 51 patients) as well as the sponsor (Cerexa) for the GCP inspection. The two sites were not the highest enrolling in the overall study but one site was the highest enroller in the US. Cerexa had itself audited the two sites (on two occasions in one case) during the conduct of the study.

In the GCP inspection report (11 August 2011) the most important conclusions were:

Regarding the US sites inspected:

- At one of the inspected sites, a number of critical and major findings regarding administrative aspects, third party contracts, study management, data handling, storage and accountability of IMP and treatment administration) have been observed.. It was recommended to consider

excluding the data from this site from the overall analyses due to the critical and major findings observed.

- The other inspected site did not have any critical findings and the deficiencies observed did not have an impact on the reliability of the data.

Regarding the US sponsor:

- There is a need for improvement of the quality management system of the sponsor and of the CROs.
- The sponsor did not adequately oversee the activities delegated to the CROs.
- The CRO that managed/monitored US sites did not adequately identify deficiencies at the two sites inspected.
- Given the critical and major findings observed and the possibility that these problems could have been repeated in other investigational sites, a negative impact on the full study could not be excluded.
- The inspectors concluded that it would not be recommended to accept the reported data for the decision about marketing authorisation at this stage.

Consequently, the Rapporteurs, inspectors and EMA held a discussion 16 August 2011 to ensure the findings were fully understood and then held a discussion with the applicant on 24 August 2011 to hear the applicant's plans to address the most important issues raised, while the assessment of the responses to the D120 list of questions (LOQ) was ongoing.

Applicant's actions and responses to the GCP inspection findings

On 24 August 2011 Astra-Zeneca participants stated that they had already held internal discussions regarding how to address the issues, taking into account that many of the observations indicated that Cerexa and/or the CRO that monitored the US sites in study 07 and/or the sites needed to improve their practises but not all had the potential to directly impact on the acceptability of the data. They had already identified five specific inspection findings that, in their view, had the potential to impact on the acceptability of the data from these sites and from the study as a whole. In addition, the applicant had concluded that some of the issues have implications beyond the CRO used to monitor US sites, noting that the US sites together accounted for the majority of patients enrolled into the cSSTI studies but only one site contributing 27 patients participated in the CAP studies. Hence, the applicant had already acknowledged the need to provide reassurance that the data from all four studies (covering five continents and using several different CROs within each study) could be accepted.

The plan proposed by the applicant to address the GCP inspection findings was accepted and the CHMP agreed to allow a prolonged 9-months clock stop to enable the actions to be completed and reported. The applicant's main focus was to conduct a Source Data Verification (SDV) exercise that ultimately comprised an audit of > 80% of all subjects enrolled into the four Phase 3 studies. Briefly, the SDV included:

- The Forest/Cerexa audit programme, which had taken place prior to the ceftaroline US NDA filing in December 2009. These audits involved approximately 40% of the randomised patients for both cSSTI and CAP indications.
- The AstraZeneca audit programme, which was a newly conducted SDV programme by independent auditors involving 34 cSSTI and 68 CAP investigator sites from November 2011 - March 2012. This included some sites that were audited by Forest/Cerexa.

- The combined total number of patient records for which SDV was conducted is 2127, which represented 81.6% of patients randomised into the four Phase 3 studies.
- A committee was convened to adjudicate and classify SDV findings from both SDV programmes. The adjudication committee classified efficacy findings as either critical (inconsistency affecting clinical outcome evaluation of the patient) or non-critical (inconsistency not affecting the clinical outcome evaluation of the patient).

In the report on the SVD the following conclusions were reached:

Monitoring – There were only 7/2127 (0.3%) patients reviewed where the CSR efficacy data for determining the clinical outcome could not be verified in the source records. The rate of critical findings did not exceed 1.2% in any study and the rate of non-critical findings was < 4%. The efficacy results were very robust to any inconsistencies, as confirmed by sensitivity analyses restricted to those patients who had data reviewed. The SDV findings did not call into question the original conclusions from the studies.

Analysis population adjudication process - The applicant identified patients that were excluded from the CE population owing to having received systemic antimicrobials during the excluded window. Sensitivity analyses demonstrated that the inclusion or exclusion of these patients did not significantly affect the overall conclusions of the pivotal studies. In addition, the applicant identified organisms that were inconsistently classified as pathogens or non-pathogens by the Evaluability Committee (EC). Sensitivity analyses were reassuring in that any inconsistent decisions of the EC did not have a significant impact in the overall conclusions on efficacy in the pivotal studies.

Blinding procedures - The applicant reviewed the blinded status of the site personnel and found that 40 personnel were granted inappropriate unblinded status. However, only 4/40 actually accessed unblinded data and all patients randomised during the period that these personnel had inappropriate access were already excluded from the analysis in the original MAA so these findings had no impact on the overall conclusions of the pivotal studies.

Quality control – The Applicant reviewed a high percentage of fDCFs for the pivotal studies and the error rate was found to be very low. The SDV adjudication committee found that these errors had no significant impact on the overall conclusion of the studies. In addition, 31205 non-CRF assessments were reviewed and 118 (0.38%) were found to have dates other than the protocol visit dates. Of these 118 assessments only 14 did not have documentation clarifying why they were conducted outside the protocol specified visit windows. Overall, the error rate for the non-CRF assessments was very low and within SOP targets.

Investigational medicinal product (IMP) handling - The applicant identified the sites where there was the greatest risk of degradation of vancomycin occurring following reconstitution and before administration to the patient i.e. sites employing HHC were considered to be at greatest risk with sites employing OPAT or with off-site pharmacies were considered to be at lesser risk. The sensitivity analyses after excluding either HHC or OPAT using sites did not affect the conclusions regarding non-inferiority. It should be noted that these sensitivity analyses are anyway based on a theoretical worst case scenario assuming that all HHC, OPAT and off-site pharmacy sites mishandled the transportation of vancomycin leading to degradation of the reconstituted product.

CHMP discussion of the inspection and responses from the applicant

The CHMP's remaining concerns that the sponsor oversight and the overall levels of monitoring that occurred in the Phase 3 studies were not optimal were focused on the fact that the initial (Forest-Cerexa) and the applicant's additional audits had identified discrepancies that were scattered across a

range of study sites, indicating that there was an overall sub-optimal oversight of the studies by the CRO and sponsor.

However, the CHMP acknowledged the findings of the applicant's SDV exercise, including the high proportion of patient records audited (81.6%), which took 9 months to complete. Importantly, the CHMP noted the low level of critical and non-critical findings and it was considered that this exercise had to a large extent addressed the doubts raised in the GCP inspection report regarding the data integrity and the validity of the analyses as reported in the CSRs. The CHMP also noted that various sensitivity analyses had been conducted, several of which had excluded patients based on a worse case scenario situation, and even these had supported the initial primary analyses.

The CHMP therefore concluded, following further discussion (including the reporting inspector) that the validity of the individual study databases and the analyses of safety and efficacy could be accepted.

Table 4: Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dose escalation; PK; Safety	P903-01	To evaluate safety and PK of ceftaroline fosamil; to determine highest safe and tolerated dosing regimen of ceftaroline fosamil	Single-center, prospective, randomized, double-blind, single and multiple dose-escalation study	Part 1: ascending regimen of ceftaroline fosamil (50, 100, 250, 500, 750, and 1000 mg), single dose, IV Part 2: ceftaroline fosamil 300 mg q12h for 13 days and a single dose on Study Day 14, IV; ceftaroline fosamil 600 mg q12h for 13 days and a single dose on Study Day 14, IV; and ceftaroline fosamil 800 mg q24h for 7 days, IV	72 enrolled: ceftaroline (N = 54) placebo (N = 18)	Healthy subjects	Part 1: 1 day (single dose) Part 2: 7 or 14 days	Completed; Full
PK; Safety	P903-02	To evaluate PK of ceftaroline fosamil and its metabolites in plasma and urine; to evaluate safety and tolerability	Two-center, open-label, single-dose study	Part A: ceftaroline fosamil 500 mg, single dose, IV (subjects with normal renal function) Part B: ceftaroline fosamil 600 mg, single dose, IV (subjects with normal renal function, or mild or moderate renal impairment)	23 enrolled: ceftaroline (N = 23)	Subjects with normal renal function, mild renal impairment, or moderate renal impairment	1 day (single dose)	Completed; Full
PK; Safety	P903-04	To evaluate PK of ceftaroline fosamil in subjects with normal renal function or severe renal impairment; to evaluate safety and tolerability	Multi-center, open-label, single-dose study	ceftaroline fosamil 400 mg, single dose, IV	12 enrolled: ceftaroline (N = 12)	Subjects with normal renal function or severe renal impairment	1 day (single dose)	Completed; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK; Safety	P903-11	To compare PK of ceftaroline fosamil in healthy elderly subjects (≥ 65 years) to healthy young adult subjects (18-45 years); to evaluate safety and tolerability	Single-center, open-label, parallel-group study	Ceftaroline fosamil 600 mg, single dose, IV	33 enrolled: ceftaroline (N = 33)	Healthy subjects	1 day (single dose)	Completed; Full
PK; Safety	P903-14	To evaluate the effect of ceftaroline fosamil on intestinal microflora of healthy subjects; to determine in vitro susceptibility of intestinal microflora to ceftaroline; to evaluate PK, and safety	Single-center, open-label, multiple-dose study	Ceftaroline fosamil 600 mg, q12h, IV	12 enrolled: ceftaroline (N = 12)	Healthy subjects	7 days	Completed; Full
PK; Safety	P903-15	To evaluate PK and safety of ceftaroline fosamil in adolescents	Multicenter, open-label, noncomparative, single-dose study	Ceftaroline fosamil 8 mg/kg, single dose, IV for subjects weighing < 75 kg (< 165.4 lb) Ceftaroline fosamil 600 mg, single dose, IV for subjects weighing ≥ 75 kg (≥ 165.4 lb)	9 enrolled: ceftaroline (N = 9)	Subjects 12 to 17 years of age receiving antibiotic therapy	Single dose (1 day)	Completed; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK; Safety	P903-17	To evaluate the safety, tolerability, and PK of single and multiple doses of IM ceftaroline fosamil	Single-center, two-part, randomized, parallel-group study Part A (Groups A, B, C, and D) was open-label, single-dose administration Part B (Groups E and F) was double-blind, multiple-dose administration	Treatment Group A: ceftaroline fosamil 400 mg, single dose, IM Treatment Group B: ceftaroline fosamil 600 mg, single dose, IM Treatment Group C: ceftaroline fosamil 600 mg, single dose, IM on Study Day 1 and ceftaroline fosamil 600 mg, single dose, IV, on Study Day 8 Treatment Group D: ceftaroline fosamil 1000 mg, single dose, IM Treatment Group E: ceftaroline fosamil 600 mg q12h, IM on Study Days 1 through 4 and single dose on Study Day 5 Treatment Group F: cefepime HCl 1000 mg IM q12h on Study Days 1 through 4 and single dose on Study Day 5	42 enrolled: ceftaroline (N = 36) cefepime (N = 6)	Healthy subjects	Treatment Groups A, B, and D: 1 day (single dose) Treatment Group C: 1 day (single IM dose) and 1 day (single IV dose) separated by 7 days Treatment Groups E and F: 5 days	Completed; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK; Safety	P903-18	To evaluate safety, tolerability, and PK of ceftaroline fosamil in subjects with ESRD on intermittent hemodialysis and subjects with normal renal function; to determine clearance of ceftaroline by hemodialysis	Single-center, open-label, parallel-group study	Group I (subjects with ESRD on hemodialysis): ceftaroline fosamil 400 mg, single dose, IV (completed 4 hours before start of hemodialysis). After a minimum 7-day washout period, second IV infusion of ceftaroline fosamil 400 mg started ≥ 1 hour after the end of hemodialysis. Group II (subjects with normal renal function): ceftaroline fosamil 400 mg, single dose, IV	12 enrolled: ceftaroline (N = 12)	Subjects with ESRD on intermittent hemodialysis, and subjects with normal renal function	Group I: 1 day (single dose) followed by 1 day (single dose) separated by ≥ 7 day washout period Group II: 1 day (single dose)	Completed; Full
PK; Safety	P903-20	To evaluate safety, tolerability, and PK of single and multiple doses of ceftaroline fosamil in healthy adults	Single-center, sequentially-performed, two-part, randomized, double-blind, placebo-controlled study	Cohort A1: ceftaroline fosamil 1500 mg, single dose, IV Cohort A2: ceftaroline fosamil 2000 mg, single dose, IV Cohort B1: ceftaroline fosamil 600 mg, single dose on Study Days 1 and 10 and multiple doses on Study Days 2 to 9 q8h, IV Cohort B2: ceftaroline fosamil 1200 mg, single dose on Study Days 1 and 10 and multiple doses on Study Days 2 to 9 q12h, IV	30 enrolled: ceftaroline (N = 24) placebo (N = 6) Note: no subjects were enrolled in Cohort B2	Healthy subjects	Cohorts A1 and A2: 1 day (single dose) Cohorts B1 and B2: 10 days	Completed; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK; Safety	CXL-PK-01	To evaluate the safety, tolerability, and pharmacokinetics of ceftaroline and NXL104 following coadministration of a single and multiple (10 days) IV doses of ceftaroline fosamil and NXL104 in healthy subjects	Single-center, 2-part randomized study: Part A was an open-label, 3-way crossover, single-dose study. Part B was a double-blind, placebo-controlled, 10-day, multiple-dose study.	Part A: Subjects received 3 treatments (600 mg ceftaroline, 600 mg NXL104, and 600 mg ceftaroline plus 600 mg NXL104), separated by a 5-day washout period Part B: The following IV infusions for 10 days - 400 mg ceftaroline fosamil and 400 mg NXL104 q8h, 600 mg ceftaroline fosamil and 600 mg NXL104 q8h, 600 mg ceftaroline fosamil and 600 mg NXL104, q12h, and 900 mg ceftaroline fosamil and 900 mg NXL104 q12h	Part A: N = 12 Part B: N = 48; 4 cohorts (9 active, 3 placebo per cohort)	Healthy subjects	Part A: 1 day (single dose) Part B: 10 days	Completed; Full
QTc; PK; Safety	P903-05	To evaluate effects of supratherapeutic dose of IV ceftaroline fosamil versus placebo on QTc, PK, and safety	Single-center, randomized, double-blind, placebo-controlled, three-period crossover study	One dose of each study drug: ceftaroline fosamil 1500 mg, single dose, IV moxifloxacin 400 mg, single dose, IV (positive control) saline placebo, single dose, IV (negative control)	54 enrolled: ceftaroline (N = 54) placebo (N = 54) moxifloxacin (N = 54)	Healthy subjects	1 day (single dose) of each study drug with 5 day washout period between doses	Completed; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Metabolism and Elimination; Safety	P903-13	To evaluate the rates and routes of elimination of radioactivity after IV administration of [14C] ceftaroline fosamil; to characterize and identify the metabolites of ceftaroline fosamil in plasma and excreta; to evaluate safety	Single-center, open-label, single-dose, mass-balance study	Ceftaroline fosamil 600 mg with an additional 15 mg [14C] ceftaroline fosamil, single dose, IV	6 enrolled: ceftaroline (N = 6)	Healthy subjects	1 day (single dose)	Completed; Full
Safety, PK, and efficacy	P903-03	To evaluate ceftaroline clinical response at TOC	Multicenter, randomized, observer-blinded study	Ceftaroline group: ceftaroline fosamil 600 mg, q12h, IV Comparator group: vancomycin 1 g, q12h, IV. If culture indicated PRP-susceptible, gram-positive organism, the Investigator could switch therapy to a PRP within the first 72 hours. Subjects in the comparator group could also receive aztreonam 1 g, q8h, IV if infection with a gram-negative organism was indicated	100 randomized: ceftaroline (N = 67) comparator (N = 33)	Adult subjects with cSSSI	7 to 14 days	Complete; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety, PK, and efficacy	P903-19	To evaluate ceftaroline clinical response at TOC	Multicenter, randomized, open-label, comparative study	Ceftaroline fosamil 600 mg, q12h, IM. Linezolid 600 mg, q12h, IV. Aztreonam 1000 mg, q12h, IV could have been started with linezolid or added up to 72 hours after the first dose of linezolid for subjects with mixed gram-positive and gram-negative infection indicated or suspected at baseline	150 randomized: ceftaroline (N = 103) linezolid ± aztreonam (N = 47)	Adult subjects with cSSSI	5 to 14 days	Complete; Full
Safety and Efficacy	P903-06	To determine noninferiority in clinical cure rate of ceftaroline compared with vancomycin plus aztreonam at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline group: ceftaroline fosamil 600 mg q12h, IV followed by placebo, q12h, IV (Note: ceftaroline fosamil dose could be adjusted based on renal impairment) Comparator group: vancomycin 1 g q12h, IV followed by aztreonam 1 g q12h, IV (Note: vancomycin dose could be adjusted based on local guidelines or weight)	702 randomized: ceftaroline (N = 353) vancomycin plus aztreonam (N = 349)	Adult subjects with cSSSI	5 to 14 days; extension up to 21 days could be approved by Sponsor	Complete; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects Enrolled or Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	P903-07	To determine noninferiority in clinical cure rate of ceftaroline compared with vancomycin plus aztreonam at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline group: ceftaroline fosamil 600 mg q12h, IV followed by placebo, q12h, IV (Note: ceftaroline fosamil dose could be adjusted based on renal impairment) Comparator group: vancomycin 1 g q12h, IV followed by aztreonam 1 g q12h, IV (Note: vancomycin dose could be adjusted based on local guidelines or weight)	694 randomized; ceftaroline (N = 348) vancomycin plus aztreonam (N = 346)	Adult subjects with cSSSI	5 to 14 days; extension up to 21 days could be approved by Sponsor	Completed; Full
Safety and Efficacy	P903-08	To determine noninferiority in clinical cure rate for ceftaroline compared to ceftriaxone at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline group: ceftaroline fosamil 600 mg q12h, IV. (Note: ceftaroline fosamil dose could be adjusted based on renal impairment) Ceftriaxone group: ceftriaxone 1 g q24h, IV followed by saline placebo, q24h, IV Adjunctive therapy for both groups: 2 doses oral clarithromycin starting on Study Day 1	614 randomized: ceftaroline (N = 305) ceftriaxone (N = 309)	Adult subjects with CABP	5 to 7 days	Completed; Full
Safety and Efficacy	P903-09	To determine noninferiority in clinical cure rate for ceftaroline compared to ceftriaxone at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline group: ceftaroline fosamil 600 mg, q12h, IV. (Note: ceftaroline fosamil dose could be adjusted based on renal impairment) Ceftriaxone group: ceftriaxone 1 g, q24h, IV followed by saline placebo, q24h, IV	627 randomized: ceftaroline (N = 317) ceftriaxone (N = 310)	Adult subjects with CABP	5 to 7 days	Completed; Full

[a] Intent-to-treat population.

CABP Community-acquired bacterial pneumonia; cSSSI Complicated skin and skin structure infection; EOT End of treatment; ESRD End-stage renal disease; IM Intramuscular; IV Intravenous; LFU Late follow-up; MRSA Methicillin-resistant Staphylococcus aureus; PK Pharmacokinetic; PRP Penicillinase-resistant penicillin; q8h Every 8 hours; q12h Every 12 hours; q24h Every 24 hours; QTc QT interval corrected for heart rate; TOC Test of cure.

2.4.2. Pharmacokinetics

2.4.2.1. *Introduction*

The PK data are derived from 11 clinical pharmacology studies (phase 1 studies) after administration of ceftaroline fosamil by iv infusion or im injection in healthy volunteers and patients with different degrees of renal impairment and from subsets of patients enrolled in the phase 2 and 3 studies. In addition, *in vitro* studies were conducted to evaluate the protein binding, distribution into blood cells, and in vitro metabolism of ceftaroline, the inhibition and induction potential of ceftaroline on the cytochrome P450 (CYP) enzyme system, as well as studies to determine if ceftaroline fosamil or ceftaroline are substrates or inhibitors of certain transporters. No *in vivo* drug-drug interaction (DDI) studies were performed.

Data from the phase 1 studies were used along with PK data collected in phase 2 and 3 studies to develop population PK models for ceftaroline fosamil and ceftaroline. The final population PK model was then used in the analyses of the PK/PD target values, PK/PD relationships for antimicrobial efficacy, and the probability of target attainment for antimicrobial efficacy in patients with cSSTI and CAP.

PK profile

The initial PK studies were a single dose (50 to 1000 mg) escalation study (P903-01) and a multiple dose (300 or 600 mg twice daily for 14 days or 800 mg once daily for 7 days) escalation study. Ceftaroline fosamil was very rapidly converted to active ceftaroline after iv administration, which is the predominant circulating compound. PK for ceftaroline fosamil, ceftaroline and its inactive metabolite were linear over the dose range and duration tested. Ceftaroline Cmax and AUC values increased approximately in proportion to increases in dose within the dose range of 50 mg to1000 mg, and no accumulation of ceftaroline fosamil or active ceftaroline was observed with twice dailymultiple-dose regimens. The Tmax for ceftaroline generally occurred near the end of the infusion, and the t½ of ceftaroline was 2-3 hours (2.60 ± 0.46 h in study P903-13). These results demonstrated time-independent pharmacokinetics of ceftaroline. The PK of the inactive metabolite (ring opened form) was also independent of dose and duration of dosing over the ranges investigated.

Additional data were obtained on administration of single 600 mg IV doses infused over 60 minutes, twice and thrice daily dosing of 600 mg and twice daily dosing of 900 mg (each over 10 days) in combination with the beta-lactamase inhibitor NXL104 (studyCXL-PK-01**)**. After single 600 mg doses the mean Cmax ceftaroline was around 28,000 ng/ml and AUC 0-t was about 62,000 ng.h/ml. Corresponding values for ceftaroline M1 were about 3,800 ng/ml and 16,500 ng.h/ml. Dose-normalized Cmax and AUC0-24 for ceftaroline and ceftaroline M-1 were comparable across the dosing regimens in this study.

Distribution and metabolism

Following an iv infusion dose, the mean apparent volume of distribution of ceftaroline at steady-state (Vss) or at the terminal phase (Vz) in healthy volunteers ranged from 15.8 – 21.3 L, and 22 – 46 L, respectively (studies P903-01, -02, -11, -13, -18 and -20).

The plasma protein binding of ceftaroline *in vitro* was generally low (approximately 20%, range 14.5%-28%, bound) and concentration independent in human plasma over the clinically relevant concentration range (1 to 50 micrograms/mL).

Ceftaroline and its metabolites are unable to effectively penetrate into red blood cells (mass balance study **P903-13**). The applicant clarified in its responses to the D120 CHMP list of questions that despite some *in vitro* data showing increase in CYP1A2 activity at higher concentrations of the inactive ceftaroline metabolite, in clinical settings the maximum achievable plasma concentration of the metabolite at steady state was approx. 10 times lower and that it was unlikely that any relevant effect on concomitantly administered CYP1A2 substrates (e.g. clozapine or theophylline) would be expected. This was agreed by the CHMP.

Elimination

40%-70% of the ceftaroline fosamil dose was excreted in the urine as ceftaroline (studies P903-01, P903-02, P903-04, P903-11, P903-13, P903-17, P903-18, and P903-20). Additionally, renal clearance of ceftaroline was generally independent of dose and approximately equal to or less than the glomerular filtration rate. Therefore, in conjuction with the *in vitro* results indicating little or no involvement of OAT1, OAT3, or OCT2, active renal transport is not considered to play a major role in renal excretion of ceftaroline.

Following i.v. infusion of [14C] ceftaroline fosamil (Study P903-13), a mean of 87.5%±3.9% of the dose of total radioactivity was excreted in urine and 5.95%±2.93% was excreted in faeces through the last collection interval, confirming that urinary excretion is the principal route of elimination for

ceftaroline and its metabolites. Most of the administered radioactivity was recovered in the first 48 hours (approx.90%). The overall mean recovery of radioactivity in urine and faeces was 93.4%±3.1% over the maximum collection period of 216 hours post-dose, with recovery in individual subjects ranging from 87.5% to 95.9%. The mean percent of dose excreted in urine as ceftaroline was 65.02 ± 8.22. The mean percent of dose excreted in urine as ceftaroline M-1 was 5.66 ± 1.10%.

In study CXL-PK-01 approximately 57% (47.0%-70.8%) of the dose of ceftaroline fosamil was excreted in urine as ceftaroline on Days 1 and 10 and this parameter appeared to be dose independent. Approximately 7% of the dose of ceftaroline fosamil was excreted in urine as ceftaroline M-1 on Day 1 and approximately 8% on Day 10, assuming that ceftaroline was completely metabolised to ceftaroline M-1. Renal clearance for ceftaroline M-1 also appeared to be dose independent.

Dose proportionality and time dependencies

Dose proportionality

The PK for ceftaroline fosamil, ceftraroline and its inactive metabolite were linear over the dose range (single doses 50-1000 mg) and dosing duration (300-600 mg twice dailyfor 14 days) tested (study P903-01). Cmax and AUC increased proportionately with dose and were independent of dose duration. Further data (study P903-20) showed dose-proportionality for single doses of 1500-2000 mg.

Time dependency

Observed t½ is relatively short and there was no appreciable accumulation during multiple dosing with 60-minute infusions of 300 mg and 600 mg twice dailyor 800 mg once daily(study P903-01). There was also no accumulation on dosing with 600 mg thrice dailyor 600 mg twice dailyfollowing 5 days of i.m.dosing (study P903-017).

The estimates of CL and t½ of ceftaroline were generally independent of dose duration and frequency. The mean±SD ceftaroline plasma concentration-time courses following the first and last administrations in P903-01 were generally comparable. These results demonstrated time-independent pharmacokinetics of ceftaroline (study P903-01).

Special populations

Impaired renal function

Ceftaroline is predominately eliminated by the kidney and the PK of ceftaroline has been studied in subjects with varying degrees of renal impairment (studies P903-02, P903-04 and P903-018).

The PK parameters of ceftaroline were altered in subjects with mild (50mL/min<CrCL≤80 mL/min), moderate (30mL/min<CrCL≤50 mL/min), or severe (CrCL<30mL/min) renal impairment compared with subjects with normal renal function (CrCL>80 mL/min). The mean t½ of ceftaroline was increased by 28% and 60% in subjects with mild and moderate renal impairment from an average of 2.87±0.43 hours in subjects with normal renal function. Systemic exposure (AUC) to ceftaroline increased by 22% and 52% in subjects with mild and moderate renal impairment compared to subjects with normal renal function. Ceftaroline renal clearance decreased significantly in subjects with mild and moderate renal impairment by 44% and 64%, respectively; however, Cmax was approximately unaltered in these subjects. In subjects with severe renal impairment, t½ was longer and the systemic exposure was enhanced (after a single IV dose of 400 mg ceftaroline fosamil over 60 minutes, mean values for ceftaroline AUC were 123% greater and Cmax was similar in subjects with severe renal impairment than in subjects with normal renal function. The mean t½ of ceftaroline in subjects with severe renal impairment was 5.05±1.22 hours compared with 2.87±0.43 hours in subjects with normal renal function).

The PK of ceftaroline was also evaluated in subjects with end stage renal disease (ESRD) receiving intermittent haemodialysis (study P903-18). The results showed that the Cmax for ceftaroline in subjects with ESRD was relatively unchanged compared with the Cmax in subjects with normal renal function, while the AUC was increased by 82%. In subjects with ESRD who received ceftaroline fosamil after the end of haemodialysis, the Cmax for ceftaroline was 53% higher and the AUC was 123% higher than in subjects with normal renal function. The t½ of ceftaroline was significantly longer, 113% and 115%, respectively, in subjects with ESRD who received ceftaroline fosamil before or after haemodialysis compared with the t½ in subjects with normal renal function. When haemodialysis was started 4 hours after dosing, about 22% of the administered dose of ceftaroline was removed. High plasma levels of ceftaroline fosamil observed in subjects with ESRD during i.v. infusion may be due to the same arm being used for PK sampling and i.v. infusion, as the other arm was reserved for the haemodialysis procedure. The impact of blood sampling from the arm used for infusion on the PK of ceftaroline is unknown, although the PK parameters of ceftaroline are similar to those of patients with severe renal impairment. There is insufficient information to make specific dosage adjustment recommendations for patients with severe renal impairment and ESRD, including patients undergoing haemodialysis.

The recommendations for dosing in mild and moderate renal impairment in the phase 3 studies and in the SmPC also took into account PK/PD simulations. It was concluded that no dose adjustment was needed (and thus the probability of target attainmentshould be better than for those with normal renal function due to the prolonged $t_{1/2}$).

Monte-Carlo simulations predicted that subjects with severe renal impairment would have AUCs ~100% higher vs. normal renal function and that 300 mg administered twice dailymight be an appropriate dose but such subjects were excluded from clinical studies and so there is no experience that could be used to validate this prediction. At CHMP request the applicant included a plan to obtain the missing data which would support a dose recommendation for patients with CrCl< 30 mL/min in the RMP.

Impaired hepatic function

The effect of impaired hepatic function has not been studied given the lack of evidence of metabolism of ceftaroline and the renal route of excretion.

Gender

The PK of ceftaroline were similar in male and female subjects (study P903-11), although there was a trend toward a slightly higher mean AUC0-∞ (6% to 15%) and Cmax (approx. 17%) in female subjects in both age groups. When ceftaroline clearance (CL) was normalized by body weight (BW), mean values of CL/BW in elderly female and male subjects were within 5% of each other, while mean CL/BW was about 19% higher in young female subjects than in young male subjects. Dosage adjustment based on gender is not necessary.

Elderly

Study P903-011 compared PK profiles between healthy elderly subjects (16 aged ≥ 65 years; including 8 aged ≥ 75 years) and healthy young adult subjects (16 aged 18 to 45 years) following a single dose of 600 mg. The mean CrCl in the elderly subjects in this study was 79.3 ml/min and that for the young adults was 129.95 ml/min. Mean Cmax for ceftaroline was unchanged in elderly subjects but the AUC increased by 33%, which was associated with slower clearance, especially slower renal clearance, vs. young adult subjects. There was a corresponding 41% increase in terminal t½ of ceftaroline in the elderly. An exploratory analysis using linear regression gave negative slopes for AUC0-∞, Cmax and t½ vs. CrCl whereas CL, CLr and Ae0-t were positively correlated with CrCl. The correlations between AUC0-∞, Ae0-t and CrCl were not significant but a statistically significant relationship was detected between t½, CL, CLr and CrCl in healthy elderly and young adult subjects. The Cmax and AUC for

ceftaroline fosamil were both 12% higher in the elderly while the terminal t½ was unchanged. Cmax for ceftaroline M-1 was 11% higher in the elderly and the AUC increased by 48%. Higher systemic exposure to ceftaroline M-1 was associated with reduced renal and overall clearance and the 24% increase in terminal t½. Additional modelling indicated that CrCl was a significant factor for increases in ceftaroline and ceftaroline M-1 systemic exposure in elderly subjects while age alone did not explain the increases observed.

Children

The PK of ceftaroline were evaluated in adolescent subjects aged 12 to 17 years who were hospitalized and receiving antibiotic therapy other than ceftaroline (Study P903-15). P903-15 evaluated PK ceftaroline in nine adolescent subjects aged from 12 to 16 years while being hospitalised and treated with licensed antibacterial agents for infections of any type. Mean BMI was 21.51 kg/m2, mean CrCl was 156.84 mL/minute and actual doses were from 320 to 600 mg. The mean Cmax and AUC0-∞ for ceftaroline were about 10% and 23% less than the values observed in adult subjects following a 600 mg dose. After exclusion of one subject with unusual PK ceftaroline the mean Cmax for ceftaroline M-1 was ~ 7% Cmax ceftaroline and the mean AUC0-∞ was ~ 19% of the AUC0-∞ ceftaroline. Ceftaroline fosamil was rapidly converted to ceftaroline and was generally only measurable in plasma for 0.25 to 1 h after the end of study drug infusion. The mean Cmax was ~ 22% of that for ceftaroline and the mean AUC0-t was ~ 6%. Ceftaroline fosamil was not measurable in any urine samples. The CHMP agreed that the data in this study are confined to nine subjects aged from 12 to 17 years who received a single dose of 8 mg/kg if < 75 kg or 600 mg if ≥75 kg while being hospitalised and treated with licensed antibacterial agents for infections of any type and are therefore too limited to be reflected in the SmPC.

Pharmacokinetic interaction studies

In vitro

The non-clinical studies indicated:

- no inhibition of cytochrome P450 isoenzymes (CYP) (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 & 3A4) *in vitro* by ceftaroline and ceftaroline fosamil
- no induction of CYP450 isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, & CYP3A4/5) *in vitro* by ceftaroline, ceftaroline fosamil and ceftaroline M-1
- ceftaroline is not a substrate or inhibitor of human active renal uptake transporters (OCT2, OAT1 or OAT3), indicating that active tubular secretion of ceftaroline does not contribute significantly to its renal elimination and that ceftaroline is unlikely to inhibit elimination of drugs that are actively secreted in urine by these transporters
- ceftaroline is not a substrate of P-gp or BCRP (breast cancer resistance protein; ABCG2, which is an important efflux transporter) or an inhibitor of P-gp but it is a weak inhibitor of BCRP.

In vivo

Based on the non-clinical findings no drug-drug interaction studies have been performed. The applicant commissioned a review of the data base to explore the impact of concomitant medications on PK. The report considered concomitant medication and PK data from 220 subjects treated with ceftaroline for cSSSI or CAP included in the population PK analyses. Pertinent findings were:

- Inducers or substrates of cytochrome P450 isoenzymes did not alter ceftaroline AUC0-12 or Cmax.

- Use of CYP1A2 inhibitors (p = 0.018) or CYP3A4/5/7 inhibitors (p = 0.005) gave statistically significantly higher ceftaroline AUC0-12 values vs. non-use with increases in median AUC0-12 values of 19.0% and 20.3%, respectively.
- Use of vasodilators or anionic drugs known to undergo active renal tubular secretion gave statistically significantly higher AUC0-12 values (p ≤ 0.001) vs. non-use with increases in AUC0-12 of 16.6% and 17.6%, respectively.

Population PK model

Samples for population PK analyses were obtained from subjects in both treatment groups in phase 2 and 3 studies using a sparse PK sampling schedule on day 3 at selected investigational sites.

- In the cSSTI study 06 the mean (± SD) trough concentration was 0.53 ± 0.69 µg/mL (n = 29). The mean concentration in samples collected within five minutes of the end of infusion was 15.4 ± 6.68 µg/mL (n = 31). In study 07 the mean (± SD) trough concentration was 0.299 ± 0.505 µg/mL. The mean concentration in samples collected within five minutes of the end of infusion was 15.2 ± 8.43 µg/mL (n = 13).
- In the CAP study 08 the mean (± SD) trough concentration was 1.30 ± 4.28 µg/mL (n=63). The mean concentration in samples collected within five minutes of the end of infusion was 20.8 ± 7.74 µg/mL (n=63). In study 09 the mean (± SD) trough concentration was 1.30 ± 2.73 µg/mL (n=73). The mean concentration in samples collected within five minutes of the end of infusion was 21.47 ± 12.35 µg/mL (n=31).

A preliminary 2-compartment model with first-order input (conversion of ceftaroline fosamil to ceftaroline) and both first-order and Michaelis-Menten elimination best characterised the plasma concentrations of ceftaroline in subjects in initial phase 1 studies. The model demonstrated that CrCL was the primary factor predicting clearance of ceftaroline. The effects of dose and sex on CL and the effect of body weight on the volume of distribution V_d of the central and peripheral compartments were also statistically significant.

The final population PK models for ceftaroline fosamil and ceftaroline were based on the phase 1 and cSSTI studies. Subsequently the final model was fit to data from the CAP studies. The model accommodated the phase 3 CAP data showing a relatively unbiased fit. Therefore results were used to predict ceftaroline exposure for PK/PD target, PK/PD modelling and PTA analyses for subjects with either cSSTI or CAP.

A 3-compartment model with zero-order input and first-order elimination, parameterised using clearance and volume, best characterised the plasma concentration-time data for ceftaroline fosamil. The population mean clearance and central volume of distribution of ceftaroline fosamil were estimated to be 228 L/h and 10.8 L, respectively, thus indicating a fairly rapid first-order conversion rate to ceftaroline (21.1 h-1). CrCL was identified as a statistically significant predictor of ceftaroline fosamil clearance and volume of distribution but conversion to ceftaroline still occurred rapidly in subjects with renal insufficiency.

In the PK model for ceftaroline all relevant PK parameters for ceftaroline were conditioned on the fraction of ceftaroline fosamil converted to ceftaroline. A 2-compartment model with first-order input (conversion to ceftaroline) and both first-order and Michaelis-Menten elimination best characterised the plasma concentrations of ceftaroline in phase 1 and phase 2/3 subjects. To assess the extent of the observed dose non-linearity of ceftaroline and its possible impact on the therapeutic dose range, the final ceftaroline PK model (without the M-M elimination component) was fitted to subjects in the limited dose range 250-1000 mg and compared with the full model (with the M-M elimination component fitted

to the same subjects). Both models (linear and nonlinear) presented similar fits to the observed data in the dose range of 250 to 1000 mg, with fits in the therapeutic dose range of 400 and 600 mg twice daily being comparable. Non-linearity was more apparent at the highest doses. The population mean linear clearance (CLlin), likely representing renal clearance of ceftaroline, and intrinsic clearance (CLi) were estimated to be 3.94 L/h and 14.7 L/h, respectively. The steady-state volume of distribution of ceftaroline was determined to be 26 L, indicating that distribution is mostly in extracellular water.

The final population PK model identified a number of covariates affecting ceftaroline PK:

(1) CrCL was the most statistically significant predictor of linear and intrinsic clearance of ceftaroline, both of which decreased with decreasing renal function. For subjects aged 30 years the AUC0-12 was predicted to increase 1.15- to 1.34-fold with mild renal impairment, 1.34- to 1.58-fold with moderate renal impairment and 1.58- to 1.98-fold with severe renal impairment relative to subjects with normal renal function at a dose of 600 mg, suggesting that dosage adjustment might be necessary for subjects with moderate to severe renal impairment. The applicant considered that there was insufficient information to make specific dosage adjustment recommendations for severe renal impairment and ESRD, including haemodialysis and such subjects were not enrolled into phase 3 studies.

(2) Ceftaroline intrinsic clearance decreased with age. After inclusion of the CrCL effect in the model, age was still found to have a statistically significant effect on the overall disposition of ceftaroline. The age effect was more pronounced for those with severely impaired renal function. In subjects aged 65 years vs. those aged 30 years with normal renal function a 1.17- to 1.20-fold increase in steady-state AUC0-12 was predicted at a dose of 600 mg. Similarly a 1.30- to 1.42-fold increase in steady-state AUC0-12 was predicted for subjects aged > 65 years vs. those aged 30 years with severely impaired renal function at a dose of 400 mg. The predicted steady-state AUC0-12 in a 65-year-old subject with severe renal impairment dosed with 400 mg ceftaroline fosamil was comparable to that for a 65-year-old subject with mild renal impairment dosed with 600 mg. However, in the datasets used to build the model only 4 subjects aged > 65 years had moderate renal impairment and only 3 had severe renal impairment. Thus, even though an increase of 42% in AUC0-12 is predicted for a 65-year-old subject with a CrCL of 15 mL/min vs. a 30-year-old subject at a dose of 400 mg, the overall influence of age was not thought to warrant dosage adjustment beyond that recommended for renal impairment. Steady-state Cmax values were not affected by changes in age.

(3) A statistically significant increase in intrinsic clearance and central volume of distribution (1.36- and 1.81-fold, respectively) was estimated for subjects with cSSTI or CAP relative to phase 1 subjects.

(4) Distribution clearance and peripheral volume of distribution were increased for males relative to females. A minor increase in ceftaroline Cmax (≈9% to 11%) and AUC0-12 (≈3%) for female subjects compared with male subjects at a dose of 600 mg was not considered to be of clinical significance.

The population PK analysis identified significant increases in ceftaroline clearance and volume of distribution of the central compartment in patients with cSSTI compared with healthy volunteers. The predicted magnitude of decrease in ceftaroline exposure (Cmax and AUC) in patients with cSSTI or CAP was approximately 20%, which the applicant considered to be not clinically significant.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action of ceftaroline is that of all beta-lactam agents: via inhibition of peptidoglycan synthesis.

Primary and Secondary pharmacology

Primary pharmacology

In-vitro activity by genus/species

The spectrum of activity of ceftaroline includes many or most staphylococci, beta-haemolytic streptococci, *Haemophilus* and *Moraxella* spp., *P. multocida* and enterobacterial species. Ceftaroline is not active against non-fermenting Gram-negative rods including *Acinetobacter spp*. and activity against anaerobes is genus- or species-specific.

An inoculum effect was present on *in vitro* testing with several species expressing one or more beta-lactamases that can hydrolyse cephalosporins. Ceftaroline may be readily hydrolysed by, and is therefore mostly inactive against, organisms that produce ESBLs (including, among others, TEM and SHV lineages), AmpC enzymes or carbapenemases (serine-based and metallo-enzymes).

Most *S. aureus* are inhibited by 0.25-0.5 mg/L but there is an upward shift in MICs against MRSA with MIC90 at 1-2 mg/L and occasional isolates with MICs of 4-8 mg/L. The highest MIC observed from the Phase 3 clinical studies was 2 mg/L. Most other staphylococcal species, including MRSE, show MIC90 values of 1-2 mg/L but *S. lugdunensis* appears more susceptible (MIC90 0.12 mg/L). The surveillance data suggest an ECOFF for *S. aureus* at 1 or more likely 2 mg/L. However, PK/PD analyses suggest that a MIC of 2mg/L may not be adequately covered by dosing at 600 mg twice daily using 1-h infusions.

For *S. pneumoniae* the MIC90 values are around 0.12 mg/L but with a shift up from the fully penicillin-susceptible population (MIC90 0.015 mg/L) to non-susceptible (including penicillin-resistant) strains (MIC90 0.25-0.5 mg/L; regardless of serotype). Very few isolates required up to 2 mg/L for inhibition. In the phase 3 studies all pneumococci were inhibited at 0.12 mg and most at < 0.015 mg/L.

The beta-haemolytic streptococcal species included in surveillance studies and isolated during the phase 2/3 studies were all inhibited by very low concentrations of ceftaroline (MIC90 values < 0.06 mg/L and MICs that did not exceed 0.12 mg/L). Against viridans group streptococci, including those resistant to penicillin, the highest MIC was 1 mg/L and the MIC90 was 0.25 mg/L. As for other cephalosporins, ceftaroline cannot be considered active against enterococci (MIC90 values at least 4-8 mg/L).

Against *E. coli, Klebsiella spp*. and other enterobacteria (including *Citrobacter spp*., *Enterobacter spp*. and *P. mirabilis*) not over-expressing beta-lactamases or manufacturing enzymes able to readily hydrolyse ceftaroline the MICs are mostly < 2 mg/L. However, the MIC90s for *Morganella morganii, P. vulgaris* and *Serratia marcescens* were all 16 mg/L or higher and these species cannot be considered to fall into the spectrum of activity of ceftaroline. MIC90 values from surveillance studies are highly variable depending on the rates and types of beta-lactamases produced in individual collections of organisms.

Isolates of enterobacteria that could be considered within the spectrum of activity of ceftaroline showed that ceftazidime-resistant bacteria usually required at least 16 mg/L ceftaroline for inhibition.

However, these isolates were in the minority and there was a large separation evident between the susceptible population (MICs usually 0.5 mg/L or less) and the resistant population (16 mg/L or more).

Haemophilus influenzae is inhibited with MIC90 0.12 mg/L and mostly by 0.06 mg/L ceftaroline. The highest MICs are often observed for beta-lactamase producers (in this species the enzyme is almost always TEM-1) and isolates with reduced susceptibility to ampicillin due to altered PBPs. The highest MIC observed in Phase 3 studies was 0.5 mg/L. Similarly, *M. catarrhalis* appears susceptible to ceftaroline with MIC90 estimated at 0.25 mg/L overall and only occasional isolates with MICs 0.5 to 1 mg/L. In addition, *P. multocida* is usually inhibited by 0.06 mg/L.

Among the anaerobes, ceftaroline appears likely to be active against *Porphyromonas asaccharolytica* and several *Fusobacteria spp*. and *Veillonella spp*. The Gram-positive anaerobes are more likely to be susceptible, including most *Peptostreptococcus spp.* and *Eubacterium spp*. whereas clostridial species (including *C. perfringens*) appear to have higher MICs and MIC90 values of around 4-8 mg/L.

Ceftaroline is not active against *Mycoplasma* or against intracellular *Chlamydia* or *Legionella*.

PBP-binding studies and activity against well-characterised strains

Competition binding assays have been performed for *S. aureus* and *S. pneumoniae* including strains that demonstrate PBP-mediated reduced susceptibility to penicillins (studies NSR-P0903-M-024, NSR-P0903-M-041, P0903-M-004-011, TAK-599-00055 and TAK-599-00023).

Against 50 MRSA consisting of well-characterised resistance phenotypes and genotypes from various geographical locations the highest ceftaroline MIC values (2 to 4 mg/L) were observed among strains with SCC*mec* type I with a rank order of susceptibility according to SCC*mec* type of IV > II > III and I. The ceftaroline IC50 for binding to PBP2a (as expressed by the majority of MRSA) was 0.16 mg/L (MRSA strain 67-0). Ceftaroline binds equally well to PBPs 1, 2 and 3 of MSSA.

Ceftaroline was very active *in vitro* against a range of *S. pneumoniae* strains (up to penicillin MICs ≥ 8 mg/L). The activity of ceftaroline against 11 prevailing serotypes of *S. pneumoniae* ranged from ≤0.008 - 0.25 mg/L, with an overall MIC90 of 0.12 mg/L. IC50 values for PBP1a and PBP2x/2a/2b of the pneumococcal strain 2039 were lower for ceftaroline than for penicillin or ceftriaxone (study NSR-P0903-M-024).

The effect of ceftaroline on purified transpeptidases from *S. pneumoniae* PBP2X was monitored based on its ability to competitively inhibit hydrolysis of a thioester reporter substrate (S2d) by PBP2X derived from a penicillin-susceptible strain (R6) and a penicillin-resistant strain 5204 (study NSR-P0903-M-026). Against PBP2X derived from R6, inhibition was extremely efficient.

Stability to beta-lactamases from Gram-negative bacteria

The *in vitro* activity of ceftaroline against a collection of molecularly characterised ESBL, AmpC and KPC isolates was low with MIC90 ≥ 128 (study NSR-CXL-M-002).

The kinetics of ceftaroline hydrolysis in the presence of various ESBL and cephalosporinase enzymes was determined; all the β-lactamases tested were able to hydrolyse ceftaroline.

Ceftaroline was generally less susceptible to hydrolysis than benzylpenicillin and was much less stable to hydrolysis than cefepime. Other types of beta-lactamases were not tested(e.g. *M. catarrhalis* beta-lactamases BRO-1 and 2).

Ceftaroline is a weak inducer of AmpC production and therefore it has comparable in-vitro activity against AmpC-inducible *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii, Serratia marcescens*, *P. vulgaris* and *P. aeruginosa* strains as compared to isogenic AmpC-basal (i.e. deficient)

mutant derivatives. However, AmpC-derepressed (high-level constitutive) mutants are resistant to ceftaroline.

Bactericidal activity

Ceftaroline demonstrated time-dependent killing. Maximum rates of killing were generally observed at ≥ 2 x MIC. Bactericidal effects occurred within 8 to 24 hours.

Post-antibiotic effect (PAE)

PAEs determined in a neutropenic mouse thigh infection model (defined as time to 1-log10 increase after decrease in free-drug serum concentration to < MIC minus time to same increase in untreated controls) gave short to modest PAEs with *S. pneumoniae* or *E. coli*. PAEs for *S. aureus* were in the range 0.8 to 7.2 h and for MRSA 3.8 to 4.8 h but there was no PAE against highly penicillin-resistant pneumococci.

Secondary pharmacology

Effects on cardiac conduction

P903-05 was a randomised, double-blind, placebo-controlled, three-period crossover study (minimum 5-day washout) in which 54 subjects (27 per gender) received ceftaroline fosamil (1500 mg administered over 60 minutes), placebo (infusion of saline) and i.v.moxifloxacin (400 mg over 60 minutes) to determine the effect of ceftaroline on the ECG, including the QTc interval.

Mean Cmax ceftaroline was 3.9 times and mean AUC0-∞ was 3.7 times the mean AUC0-τ observed in P903-01 on the last day of dosing with 600 mg twice dailyfor 14 days. In addition, Cmax was 4.6 times and AUC0-∞ was 1.8 times the corresponding mean values observed in P903-04 in subjects with severe renal impairment who received a 400 mg dose. Higher exposures were also documented for ceftaroline fosamil and the M-1 metabolite. There is no clinically meaningful QTcIb interval prolongation due to a supra-therapeutic dose of ceftaroline.

Effects on gut flora

In **P903-14** there were no measurable concentrations of ceftaroline detected with the bioassay in any faecal samples collected.

2.4.4. Discussion on clinical pharmacology

Ceftaroline renal clearance approximates to the glomerular filtration rate and it is not a substrate or inhibitor of human active renal uptake transporters, which supports a conclusion that active secretion in the tubules does not contribute significantly to elimination. The low protein binding and the *in vitro* studies with P-gp and human cytochromes as well as the exploration of the clinical database all suggest a low risk of drug-drug interactions.

The applicant has not made any recommendations for dose adjustment in severe renal impairment and ESRD. There are insufficient data from infected subjects to assist in this matter and the applicant considers that there are insufficient data to underpin reliable modelling. The applicant shall perform a further study in subjects with severe renal insufficiency to support specific dose recommendations (see table 31).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of ceftaroline is straightforward, as per the above. A series of method validation, Pk profile, distribution, metabolism, excretion and pharmacokinetic drug interaction studies have been conducted and are considered to be adequate by CHMP. There is metabolism by opening of the β-lactam ring to form ceftaroline M-1 with 3 additional minor unidentified metabolites/chromatographic peaks detected. These additional minor metabolites were observed in human plasma and excreta and were seen in the rat and monkey.

2.5. Clinical efficacy

There were two phase 2 studies in cSSTI and four phase 3 studies, including two in each indication sought (i.e. cSSTI and CAP). The phase 2 study -19 evaluated only i.m ceftaroline, while all other studies employed intravenous infusions of 600 mg twice daily over 60 minutes.

Table 5: Clinical phase 2 and phase 3 efficacy studies

Phase 2 studies providing design information for Phase 3			
Study	**No. randomised**	**Treatment**	**Objective**
P903-03	Patients with cSSTI Ceftaroline: 67 Vanco/az: 33	vancomycin 1 g q12h plus 1g aztreonam q8h ceftaroline 600 mg q12h IV 7 to 14 days	Per-patient clinical response at the TOC visit in the CE and cMITT populations
P903-19	Patients with cSSTI IM Ceftaroline: 103 Linezolid: 47	linezolid 600 mg q12h plus 1g aztreonam q12h Ceftaroline 600 mg q12h IM 5 to 14 days	Per-patient clinical cure rate at the TOC visit in the CE and MITT populations
Phase 3 studies			
Study	**No. randomised**	**Treatment**	**Primary objective**
P903-06	Patients with cSSTI Ceftaroline: 353 Vancomycin / aztreonam: 349	Vancomycin 1 g q12h plus 1g aztreonam q12h Ceftaroline 600 mg q12h 5 to 14 days	Non-inferiority in clinical cure rate of ceftaroline vs. comparator at TOC visit in CE and MITT populations
P903-07	Patients with cSSTI Ceftaroline: 348 Vancomycin / aztreonam: 346	Vancomycin 1 g q12h plus 1g aztreonam q12h Ceftaroline 600 mg q12h 5 to 14 days	Non-inferiority in clinical cure rate of ceftaroline vs. comparator at TOC visit in CE and MITT populations
P903-08	Patients with CAP Ceftaroline: 305 Ceftriaxone: 309	Ceftriaxone 1 g q24h Ceftaroline 600 mg q12h Each + oral clarithromycin 500 mg q12h on Day 1 only 5-7 days	Non-inferiority in clinical cure rate of ceftaroline vs. ceftriaxone at TOC visit in CE and MITTE populations
P903-09	Patients with CAP Ceftaroline: 317 Ceftriaxone: 310	Ceftriaxone 1 g q24h Ceftaroline 600 mg q12h 5-7 days	Non-inferiority in clinical cure rate of ceftaroline vs. ceftriaxone at TOC visit in CE and MITTE populations

The dose selection for the phase 3 programme was based on Monte Carlo simulations employing a preliminary population PK model.

2.5.1. Dose response studies

Study P903-03

This was a multicentre, randomised, observer-blinded comparative safety and efficacy study of iv ceftaroline versus iv vancomycin with or without adjunctive iv aztreonam for 7 to 14 days. One hundred patients were randomised (ceftaroline to comparator ratio: 2 to 1) in the study. The dose of ceftaroline fosamil was 600 mg over 60 minutes q12h. The active comparator regimen was iv vancomycin 1 g over 60 minutes q12h, initially then either continued or shifted to a PRP, with or without adjunctive iv aztreonam 1 g over 30 minutes every 8 hours (q8h). The primary outcome measure was the clinical response at TOC, which was defined as 7 days to 20 days after EOT.

Of 100 patients enrolled, 88 were CE (61 in the ceftaroline group and 27 in the vancomycin plus aztreonam group) and 63 were ME (42 in the ceftaroline group and 21 in the vancomycin plus aztreonam group).

In patients with cSSTI, ceftaroline therapy resulted in a clinical cure rate that was numerically greater than that of the vancomycin plus aztreonam regimen for both the co-primary cMITT population: 88.1% (59/67) vs 81.3% (26/32) and the CE population (cMITT patients with an outcome assessment): 96.7% (59/61) vs 88.9% (24/27). Microbiological success rates were consistent with the clinical success rates. Ceftaroline therapy resulted in a high microbiological success rate that was numerically greater than that of the vancomycin plus aztreonam regimen for both the mMITT population (cMITT patients with ≥1 baseline pathogen, 84.3%, 43/51 vs 77.8%, 21/27) and the ME population (CE patients with ≥1 susceptible pathogen, 95.2%, 40/42 vs 85.7%, 18/21).

Study P903-19

This was a multicentre, randomised, open-label, comparative efficacy and safety study of intramuscular (im) ceftaroline versus iv linezolid for 5 to 14 days in adult patients with cSSTI. A total of 150 patients were randomised (ceftaroline to comparator ratio: 2 to 1) in the study. The dose of im ceftaroline fosamil was 600 mg q12h. The comparator regimen was iv linezolid 600 mg over 60 minutes q12h with or without adjunctive iv aztreonam 1 g over 60 minutes q12h. The primary outcome measure was the clinical response at TOC, which was defined as 8 days to 15 days after EOT.

Of 150 patients enrolled, 125 were CE (86 in the ceftaroline group and 39 in the linezolid plus aztreonam group) and 96 were ME (63 in the ceftaroline group and 33 in the linezolid plus aztreonam group). The clinical cure rates in ceftaroline and linezolid plus aztreonam groups at TOC after the final dose of study drug for the CE population were 90.7% (78/86) vs 97.4% (38/39) and for the MITT population were 84.7% (83/98) vs 88.9% (40/45). Cure rates were lower for ceftaroline in both populations, but the confidence intervals (CIs) for the 2 treatment groups overlapped.

The dose selection for the phase 3 programme was based on Monte Carlo simulations employing a preliminary population PK model and from murine thigh and lung infection models that suggested that the median free drug %T>MIC to achieve 1-log kill was 44% for *S. pneumoniae* and for (susceptible) enterobacteria compared to 36% for *S. aureus*. The corresponding median values needed to achieve 2-log kill were 51%, 54% and 51%, respectively. Simulations predicted that 600 mg ceftaroline fosamil infused over 60 minutes twice daily (q12h) in subjects with normal renal function would provide a mean free drug %T > MIC of ~51%. This regimen was predicted to give a PTA of 90% for %T >MIC 40% at MIC 2 mg/L.

The PK/PD analyses for enterobacteria were revised during the assessment period. The mean free drug (*f*) %T>MIC values applicable to susceptible enterobacteria were re-calculated. Revised estimates of *f* %T>MIC for ceftaroline required for stasis (45%, 47% and 48.5% for geometric mean, arithmetic mean and median, respectively) and 1 log kill (64%, 69%, 73% for geometric mean, arithmetic mean and median, respectively) are slightly higher than those previously observed with other cephalosporins against enterobacteria.

A final population PK model was developed to allow estimates of exposure in the phase two cSSTI and phase three cSSTI and CAP studies and the dose selected for the phase 3 programme was supported by the final model based on Monte Carlo simulations.

2.5.2. Main studies

The four phase 3 studies were double blind with respect to the investigators and the study participants. For the purposes of drawing up appropriate solutions and achieving appropriate dose adjustments there were designated study personnel at each site who were unblinded to the treatment assignment. Solutions were enclosed in yellow bags to otherwise maintain the blind.

Study P903-06 in cSSTI: A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in adult subjects with complicated skin and skin structure infection

Methods

Study Participants

The study was conducted between February and November 2007 in 55 centers from 10 countries (Europe, Latin America and the US).

The demographic and baseline characteristics between treatment groups were similar. Subjects were predominately male (63%), non-Hispanic (77%), white (75%), and had a mean age of 48 years. Relevant medical and surgical histories were comparable between treatment groups for recent trauma (25%), diabetes mellitus (19%), previous skin infection (14%), and PVD (14%). Infection sizes (lengths, widths, areas) were similar in both treatment group and indicative of severe infections with a median area of 180 cm2 and a mean area of 315 cm2 for all subjects.

Important inclusion criteria

Eligible adults were to have infections that met ***either*** of the following criteria:

- Involved deeper soft tissue or required significant surgical intervention such as a wound infection (surgical or traumatic), a major abscess, an infected ulcer or deep and extensive cellulitis:
    - *Deeper soft tissue* was defined as sub-dermal tissue
    - *Significant surgical intervention* was defined as a major operative procedure
    - *Wound infection* was defined by the presence of either purulent or seropurulent discharge from a surgical/traumatic wound or ≥ 5 cm erythema surrounding the wound margin with onset within 7 days before randomisation and within 30 days of incurring the wound
    - *Abscess* was defined by the presence of a loculated fluid collection with ≥ 2 cm erythema and onset within 7 days before randomisation
    - *Cellulitis* was defined by the presence of advancing erythema, oedema, and heat with onset within 7 days before randomisation. Deep and extensive cellulitis had a surface area ≥ 10 cm2

OR

- Cellulitis or abscess of a lower extremity in subjects with diabetes mellitus or well documented peripheral vascular disease (PVD). In this regard:

- Eligible diabetics had to be on specific treatment
- Well documented PVD was defined as arterial or venous
- vascular disease resulting in ischemia of the lower extremity as manifest by ulceration, poor wound healing,
- or the absence of readily palpable dorsalis pedis and posterior tibial pulses. For the purpose of this study,
- PVD did not include microvascular or lymphatic drainage abnormalities

In addition, they were to have ≥ 3 of the following: purulent or seropurulent drainage or discharge, erythema, fluctuance, heat or localised warmth, pain or tenderness to palpation, fever > 38ºC oral (> 38.5ºC rectal or tympanic) or hypothermia (< 35ºC), WBC > 10,000/mm3, > 10% immature neutrophils (bands) irrespective of WBC count. Subjects were to be in need of hospitalisation or ER treatment except that subjects suitable for OPAT could be enrolled if they met pre-specified conditions and had infections expected to require at least 5 days of IV antimicrobial therapy.

Important exclusion criteria*:*

- More than 24 h systemic treatment with an antimicrobial expected to be effective for cSSTI within 96 h of randomisation unless subjects had failed after at least 48 h of treatment and had microbiological evidence of failure (positive Gram's stain and/or culture of an organism resistant *in vitro* to the prior therapy
- Failure of vancomycin or aztreonam or isolation of an organism resistant *in vitro* to vancomycin or aztreonam
- SSTI known or suspected to be due to anaerobes, fungi, parasites or viruses and infections at least partly due to *Pseudomonas aeruginosa,* involving decubitus or diabetic foot ulcer or an ulcer associated with PVD accompanied by osteomyelitis and likely to require surgical intervention within 60 days
- Need for significant surgical intervention that could not be performed < 48 h post-randomisation
- Any infection associated with a third-degree burn or burn covering > 5% of total BSA, underlying inflammatory skin disease, human or animal bites, rapidly necrotizing processes, gangrene, prosthetic materials that were not to be removed, known or suspected endocarditis, osteomyelitis or septic arthritis
- Severe renal insufficiency (CrCl ≤ 30 mL/min)

Treatments

Ceftaroline fosamil 600 mg was administered IV over 60 minutes every 12 h. The dose was adjusted to 400 mg in case of moderate renal insufficiency (CrCl >30 and up to 50 ml/min). The comparator was vancomycin 1 g administered over 60 minutes every 12 hours plus (followed by) aztreonam 1 g administered over 60 minutes every 12 hours. The vancomycin dose could be adjusted according to body weight. The duration of therapy was from 5-14 days with up to 21 days allowed (sponsor approval for individual subjects).

Objectives

Primary:

To determine the noninferiority (using a pre-specified 10% margin) in clinical cure rate of ceftaroline treatment compared with that of vancomycin plus aztreonam treatment at the test of cure (TOC) visit in clinically evaluable (CE) and modified intent-to-treat (MITT) populations of adult subjects with a complicated skin and skin structure infection (cSSSI). Cure required resolution of all signs and symptoms or improvement such that no further antimicrobial therapy was considered to be necessary. In the final SAP the TOC visit window was defined as 7-20 days post-therapy and the LFU visit window was set to occur between 21-45 days post-therapy.

Secondary:

1. To evaluate the microbiological success rate at the TOC visit

2. To evaluate the clinical response at the end of therapy (EOT) visit

3. To evaluate the clinical and microbiological response by pathogen at the TOC visit

4. To evaluate clinical relapse at the late follow-up (LFU) visit

5. To evaluate microbiological reinfection or recurrence at the LFU Visit

6. To evaluate safety

Outcomes/endpoints

The coprimary efficacy outcome measures were the per-subject clinical cure rate at the TOC visit in the CE and MITT Populations. Subjects were considered clinically cured at the TOC Visit if they had total resolution of all signs and symptoms of the baseline infection, or improvement of the infection such that no further antimicrobial therapy was necessary.

The secondary efficacy outcome measures were:

- Per-subject clinical cure rate at the TOC visit in the cMITT population
- Per-subject clinical cure rate at the EOT visit in the MITT, cMITT, and CE populations
- Per-subject microbiological response at the TOC visit in the mMITT and microbiologically evaluable (ME) populations
- Per-subject clinical and microbiological response by pathogen at the TOC Visit in the mMITT and ME populations
- Per-subject relapse rate at the LFU visit in those subjects who were clinically cured at the TOC visit
- Per-subject reinfection or recurrence rate at the LFU visit in those subjects

Sample size

Assuming a point estimate for the primary outcome measure of clinical cure rate of 85% in the vancomycin plus aztreonam group and 85% in the ceftaroline group, and a noninferiority margin of 10%, power of 90%, and a 20% nonevaluable rate, a total sample size of 690 subjects was required (345 subjects in each treatment group).

Randomisation

Computer-generated block randomization (in groups of four), stratified by country, via an IVRS was used to assign subjects (1:1) to the ceftaroline or vancomycin plus aztreonam group.

Blinding (masking)

This study had a double-blind design. The investigator, study personnel, clinical research organizations (including data management personnel), the sponsor (including analysis personnel), and subjects were blinded. Maintenance of the study blind at both investigative centers and the Sponsor and CROs was implemented according to prospectively written blinding plans. The blinding plans required that the Sponsor and CRO study management team and site investigative personnel be divided into blinded and unblinded teams. The blinding plans specified procedures that would prevent blinded site personnel and blinded study management personnel from access to subject treatment group assignments or subject data that could lead to unblinding.

Statistical methods

Five study populations were analyzed:

1. The MITT Population included all randomized subjects who received any amount of study drug;

2. The cMITT Population was a subset of the MITT Population that included subjects who met the minimal clinical disease criteria for a cSSSI;

3. The mMITT Population was a subset of the cMITT Population that included subjects for whom at least one bacterial pathogen was isolated from an appropriate microbiologic specimen (blood or tissue obtained from the cSSSI site) at baseline;

4. The CE Population was a subset of the cMITT Population that included subjects who received at least the prespecified minimum amount of the intended dose and duration of study drug therapy, for whom sufficient information regarding the cSSSI site was available to determine the subject's outcome, and for whom there were no confounding factors that interfered with the assessment of that outcome;

5. The ME Population was a subset of the CE Population that included subjects for whom at least one bacterial pathogen was isolated from an appropriate microbiologic specimen (blood or tissue obtained from the cSSSI site) at baseline.

A two-sided 95% confidence interval (CI) for the observed difference in the primary outcome measure between ceftaroline and vancomycin plus aztreonam was calculated. Noninferiority was concluded if the lower limit of the 95% CI was higher than –10%. Assuming a point estimate for the primary outcome measure of clinical cure rate of 85% in the vancomycin plus aztreonam group and 85% in the ceftaroline group, and a noninferiority margin of 10%, power of 90%, and a 20% nonevaluable rate, a total sample size of 690 subjects was required (345 subjects in each treatment group).

Secondary efficacy outcomes were analyzed by determining two-sided 95% CIs for the observed difference in the outcome rates between the ceftaroline group and the vancomycin plus aztreonam group. Analyses of baseline characteristics and safety outcomes were conducted using, as appropriate, a Fisher's exact test for dichotomous and categorical variables, and a Wilcoxon Rank-Sum (Mann-Whitney) test for continuous variables. Statistical significance was defined as $p < .05$ using two-sided tests.

Results

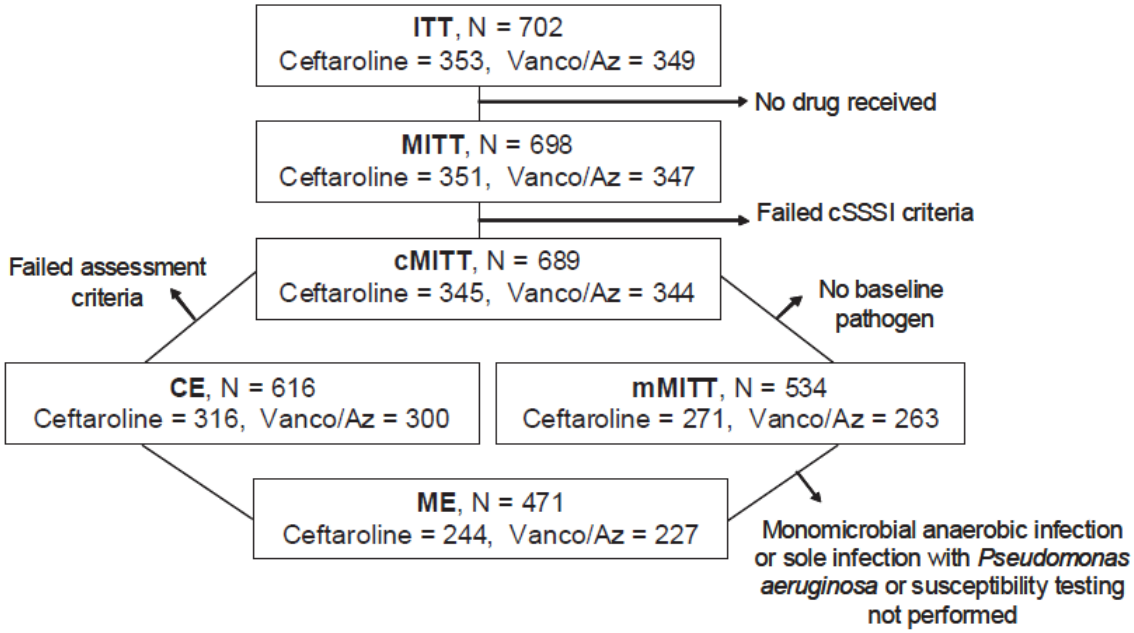
Of 702 patients enrolled, 616 were CE (316 in the ceftaroline group and 300 in the vancomycin plus aztreonam group) and 471 were ME (244 in the ceftaroline group and 227 in the vancomycin plus aztreonam group).

- the primary endpoint of the non-inferiority of ceftaroline compared with vancomycin plus aztreonam was demonstrated for the treatment of cSSTI. Clinical cure rates were high and similar in both treatment groups at TOC in the MITT population (86.6% for ceftaroline vs 85.6% for vancomycin plus aztreonam) and in the CE population (91.1% for ceftaroline vs 93.3% for vancomycin plus aztreonam).
- Clinical cure rates within clinically relevant subgroups, including patients with PVD, DM, polymicrobial infections, and MRSA infections, were favourable and comparable to the overall cure rates in the CE population at TOC.
- Per-subject microbiological responses at TOC were favourable and similar in both treatment groups in the ME and mMITT populations. Clinical cure rates for patients in the MITT, cMITT, and CE populations at EOT were similar in both treatment group and slightly greater than those at the TOC visit.
- Clinical cure rates by baseline pathogen were high and similar in both treatment groups in the ME population at TOC, including patients with infections due to MSSA and MRSA.
- Clinical relapse at LFU in those patients who were clinically cured at TOC was rare in both treatment groups. No microbiological recurrences were observed in this study.

Participant flow

In the ITT population 91% completed therapy and about 4% discontinued therapy due to AEs.

Figure 2: Participant flow for study P903-06



Abbreviations: CE = clinically evaluable; cMITT = clinical modified intent-to-treat; ITT = intent-to-treat; ME = microbiologically evaluable; MITT = modified intent-to-treat; mMITT = microbiological modified intent-to-treat; Vanco/Az = vancomycin plus aztreonam.

Recruitment

A total of 702 patients were randomised: 353 to ceftaroline and 349 to vancomycin plus aztreonam in the ITT population; 351 to ceftaroline and 347 to vancomycin plus aztreonam in the MITT and safety populations. The demographic and baseline characteristics between treatment groups were similar. Patients were predominantly male (63%) and white (75%) with a mean age of 48 years. Treatment groups were well balanced with respect to relevant medical and surgical histories (recent trauma, 25%; DM, 19%; previous skin infection, 14%; and PVD, 14%); infection sizes (lengths, widths, and areas); description and locations of the primary infection site (over 50% occurred in lower extremities followed by 19% in upper extremities); pathogens that grew from cSSTI specimens (majority due to monomicrobial Gram-positive pathogens, with S. aureus the most common pathogen isolated). Demographics and baseline characteristics in the cMITT, CE, and ME populations were similar to those in the MITT population.

Conduct of the study

Protocol amendments

The study design was amended twice.

Amendment 1 more clearly defined disease and enrolment criteria and safety laboratory measurements, changed co-primary analysis population from clinical modified intent-to-treat (cMITT) to modified intent-to-treat (MITT), revised secondary outcome measures and sample size calculations, and expanded conditions for receipt of OPAT.

Amendment 2 implemented recommended changes in the statistical assumptions (power) and increased flexibility in dosing of vancomycin according to the institutional guidelines, which included weight-based dosing (for heavy subjects) and/or reduced dosing for subjects with impaired renal function.

The changes in study conduct were considered necessary to provide clarity and consistency to the multinational study and were not considered to have any meaningful influence on the safety or efficacy outcomes of the study.

Baseline data

The mean/median age was 48 years (range 18-90 years) and 63% were male subjects. About 18% were diabetic and 14% had PVD. Severe erythema was reported in 60%, severe swelling in 40%, severe tenderness in 57% and severe discharge in 40%. The mean lesion size was 315 cm^2 but the median was 180 cm^2. The distribution of lesion types was follows:

Table 6: Description and location of primary site of cSSTI at baseline (MITT population)

Description of Infection	*Ceftaroline (N = 351) n (%)*	*Vancomycin plus Aztreonam (N = 347) n (%)*	*Total (N = 698) n (%)*
Type of infection			
Deep/extensive cellulitis	121 (34.5)	120 (34.6)	241 (34.5)
Major abscess	99 (28.2)	101 (29.1)	200 (28.7)
Infected wound	54 (15.4)	43 (12.4)	97 (13.9)
Infected burn	25 (7.1)	20 (5.8)	45 (6.4)
Infected ulcer	23 (6.6)	31 (8.9)	54 (7.7)
Lower extremity SSSI in subject with diabetes mellitus or PVD	21 (6.0)	20 (5.8)	41 (5.9)
Cellulitis	17 (4.8)	19 (5.5)	36 (5.2)
Abscess	4 (1.1)	1 (0.3)	5 (0.7)
Infected bite[a]	7 (2.0)	7 (2.0)	14 (2.0)
Other	1 (0.3)	5 (1.4)	6 (0.9)

At least one pathogen was obtained from 75% of subjects and 75% of pathogens were S. aureus (32% MRSA and 43% MSSA) while 11% were S. pyogenes. Overall 7.4% in the ceftaroline group had a pathogen isolated from blood cultures compared to 3.8% in the vancomycin group.

In each treatment group 40% of subjects had received prior antibacterial therapy for the target infection, although mostly for < 24 h and most of those treated for > 48 h had evidence of failure. In addition, about 7% per group received another antibacterial agent between randomisation and TOC, including 13/25 ceftaroline and 9/26 for reason of failure. The median duration of study treatment was 7 days in each group and only 1% had treatment extended beyond Day 14. Aztreonam was given for a median of 4.5 days in the comparative group.

Outcomes and estimation

The primary analysis demonstrated non-inferiority of ceftaroline vs. comparator in the co-primary populations with lower limit of the 95% CI within -7%. The higher number of comparator group

subjects with indeterminate outcome was due primarily to more subjects being LTFU. Clinical cure rates in the cMITT Population were nearly identical to those in the MITT Population. In the CE Population the median infection area was zero in both treatment groups at TOC. Similar results were found in the MITT Population.

At TOC the failure rates were 28 (8.9%) for ceftaroline and 20 (6.7%) for comparator (10 and 2 had failed between EOT and TOC). The difference was mainly due to more ceftaroline subjects having persistent or new cSSSI signs and symptoms than comparator-treated subjects (11 vs. 2). Similar results were noted at both time points in the MITT population. Failures not associated with AEs in both groups occurred mainly in subjects with co-morbid conditions and no specific host factor was identified to be associated with failure. There were 3 subjects per treatment group in the CE population who relapsed at late follow-up (21-35 days post-therapy).

Table 7: Clinical response at the test of cure (TOC) visit (CE and MITT population)

Population	*Clinical Response*	*Ceftaroline n (%)*	*Vancomycin plus Aztreonam n (%)*	*Difference[a] (95% CI[b])*	*p-value[c] for Superiority*
CE, N		316	300		
	Clinical cure	288 (91.1)	280 (93.3)	-2.2 (-6.6, 2.1)	p = .367
	Clinical failure	28 (8.9)	20 (6.7)		
MITT, N		351	347		
	Clinical cure	304 (86.6)	297 (85.6)	1.0 (-4.2, 6.2)	p = .743
	Clinical failure	29 (8.3)	21 (6.1)		
	Indeterminate	18 (5.1)	29 (8.4)		

Abbreviations: CE = clinically evaluable; CI = confidence interval; MITT = modified intent-to-treat.

a Difference = ceftaroline group minus vancomycin plus aztreonam group.

b CIs are calculated using the Miettinen and Nurminen method without adjustment.

c p-values are calculated using Fisher's Exact Test.

For subjects with an indeterminate outcome who could be otherwise clinically evaluable the applicant conducted post-hoc sensitivity analyses in which these subjects were classified either as clinical cures or as clinical failures. In both approaches the lower limit of the 95% CI was above -10%.

After exclusion of subjects with abscess the cure rates were 219/248 (88.3%) ceftaroline and 214/246 (87.3%) in the MITT population (95% CI around difference -4.9, 6.9) with rates for the CE population at 92% and 92.8% (95% CI -5.8, 4.4).

The 95% CIs around the treatment differences in the MITT population overlapped and included zero for Eastern Europe and Latin America. The treatment difference in the United States among MITT subjects was 10.2% (95% CI = 0.2, 20.1) with more clinical cures in the ceftaroline group. In Western Europe (2 countries) MITT subjects the pooled treatment difference was -18.7% (95% CI = -36.4, -0.2). This was largely due to Poland where 7/29 (28%) ceftaroline but only 2 (8.3%) comparator subjects failed. The seven failures in the ceftaroline group were enrolled at two sites but a detailed analysis of these cases did not show any obvious trends or reasons accounting for inter-country differences in clinical failure rates.

There was no apparent correlation between clinical response at TOC and severity of illness score, either overall or by treatment group (table 8). This was a planned analysis but the scoring system was of the applicant's derivation.

Table 8: Clinical response at TOC visit by treatment group and risk class based on Severity of Illness Score (MITT population)

Risk Class Quartiles Based on Disease Severity Score	Clinical Response	Ceftaroline (N=351) n (%)	Vancomycin plus Aztreonam (N=347) n (%)	Difference	95% CI for the Difference
Risk class I (<65 points)	N1	120	94		
	Clinical Cure	103 (85.8)	78 (83.0)	2.9	(-6.9, 13.2)
	Clinical Failure	6 (5.0)	5 (5.3)		
	Indeterminate	11 (9.2)	11 (11.7)		
Risk class II (65 to 82 points)	N1	80	83		
	Clinical Cure	70 (87.5)	72 (86.7)	0.8	(-10.0, 11.5)
	Clinical Failure	5 (6.3)	4 (4.8)		
	Indeterminate	5 (6.3)	7 (8.4)		
Risk class III (83 to 100 points)	N1	59	70		
	Clinical Cure	53 (89.8)	61 (87.1)	2.7	(-9.3, 14.2)
	Clinical Failure	5 (8.5)	5 (7.1)		
	Indeterminate	1 (1.7)	4 (5.7)		
Risk class IV (>100 points)	N1	92	100		
	Clinical Cure	78 (84.8)	86 (86.0)	-1.2	(-11.7, 9.0)
	Clinical Failure	13 (14.1)	7 (7.0)		
	Indeterminate	1 (1.1)	7 (7.0)		

The per subject microbiological response rates were generally comparable between treatments.

Table 9: Per-subject microbiological response at the TOC visit (ME and mMITT populations)

Population	*Per-Subject Microbiological Response*	*Ceftaroline n (%)*	*Vancomycin plus Aztreonam n (%)*	*Difference*[a]	*(95% CI)*[b]
ME, N		244	227		
	Favorable[c]	224 (91.8)	210 (92.5)	-0.7	(-5.7, 4.4)
	Unfavorable[d]	20 (8.2)	17 (7.5)		
mMITT, N		271	263		
	Favorable[c]	234 (86.3)	220 (83.7)	2.7	(-3.4, 8.9)
	Unfavorable[d]	22 (8.1)	19 (7.2)		
	Indeterminate	15 (5.5)	24 (9.1)		

Cure rates for infections associated with Gram-positive species, whether or not polymicrobial, were high and comparable between groups. Cure rates were also comparable for those with mixed Gram-positive and Gram-negative pathogens but lower for ceftaroline among the small numbers with single Gram-negative pathogens where the four failures in the ceftaroline group all had *Proteus* species cultured but susceptibility test results were available only for two *P. mirabilis*, one of which showed MIC 16 mg/L. All comparator group subjects with a Gram-negative pathogen received aztreonam.

In the MITT population 21 ceftaroline and 11 comparator group subjects had an organism recovered from blood culture and mostly with only one subject per species. There were 9/11 and 6/6 in respective groups with *S. aureus* in blood who were cured (4/5 and 5/5 of these were MSSA).

The microbiological response rates generally followed the clinical cure rates by pathogen since most outcomes were presumed eradication or persistence based on the clinical outcomes.

Five ceftaroline subjects with only Gram-negative pathogens had an unfavourable microbiological response. Three were failures at EOT with presumed persistence of *P. mirabilis* in one subject [MIC > 16 µg/mL] and *P. vulgaris* group in two subjects [no MIC result] and these subjects had required debridement and/or amputation. Two were clinical cures at EOT, TOC and LFU but had microbiological evidence of persistence of *Serratia marcescens* (MIC 0.5 µg/mL) and *P. aeruginosa* (MIC 8 µg/mL) plus *A. calcoaceticus*. The 15 subjects with only Gram-negative pathogens in the comparator group all received aztreonam to which most isolates were susceptible. There was one instance of an increase in MIC ceftaroline during treatment. One subject had *E. cloacae* at baseline with MIC 1-2 µg/mL but the EOT isolate (identical to the baseline isolate by PFGE and ribotyping) was confirmed to have MIC = 16->16 µg/mL and expressed chromosomal AmpC β-lactamase at higher levels vs. the baseline isolate.

Table 10: Clinical cure rate at the TOC visit by baseline pathogen from the primary infection site or blood (ME population)

Baseline Pathogen	*Ceftaroline* n^b/N^a *(%)*	*Vancomycin plus Aztreonam* n^b/N^a *(%)*
Gram-positive organisms[c]	178/190 (93.7)	162/172 (94.2)
Staphylococcus aureus[d]	170/183 (92.9)	164/173 (94.8)
MRSA	78/82 (95.1)	59/62 (95.2)
MSSA	94/103 (91.3)	106/112 (94.6)
Enterococcus faecalis	13/14 (92.9)	11/12 (91.7)
Staphylococcus lugdunensis	2/2 (100.0)	2/3 (66.7)
Streptococcus agalactiae	15/16 (93.8)	13/13 (100.0)
Streptococcus anginosus	4/5 (80.0)	2/2 (100.0)
Streptococcus anginosus group	3/3 (100.0)	0
Streptococcus dysgalactiae	5/5 (100.0)	8/9 (88.9)
Streptococcus intermedius	0	4/4 (100.0)
Streptococcus pyogenes	24/24 (100.0)	32/32 (100.0)
Monomicrobial gram-positive infection	151/162 (93.2)	125/135 (92.6)
Polymicrobial gram-positive infection	27/28 (96.4)	37/37 (100.0)

Gram-negative organisms[c]	14/18 (77.8)	15/15 (100.0)
Acinetobacter calcoaceticus - *A. baumannii* complex	3/3 (100.0)	7/7 (100.0)
Citrobacter freundii complex	2/2 (100.0)	3/3 (100.0)
Enterobacter cloacae	2/3 (66.7)	4/4 (100.0)
Escherichia coli	9/10 (90.0)	13/15 (86.7)
Klebsiella oxytoca	3/5 (60.0)	3/3 (100.0)
Klebsiella pneumoniae	10/11 (90.9)	10/10 (100.0)
Morganella morganii	6/6 (100.0)	3/3 (100.0)
Proteus mirabilis	7/10 (70.0)	9/10 (90.0)
Proteus vulgaris group	3/5 (60.0)	1/1 (100.0)
Pseudomonas aeruginosa	9/9 (100.0)	9/10 (90.0)
Monomicrobial gram-negative infection	10/14 (71.4)	11/11 (100.0)
Polymicrobial gram-negative infection	4/4 (100.0)	4/4 (100.0)
Mixed gram-positive and gram-negative infection	33/36 (91.7)	38/40 (95.0)

Microbiological responses at TOC were analysed according to two or more signs and symptoms of severe cSSSI at baseline (89.6% ceftaroline vs. 84.4% comparator in the MITT population), fever (90% both groups), leukocytosis > 10,000 WBC/mm3 (78.5% vs. 80.8%), age > 75 years (10/14 vs. 16/20) or < 75 years (87.2% vs. 84%), diabetes (44/53 vs. 47/51), PVD (33/39 vs. 31/41), mono- and polymicrobial infection (also ± MRSA), moderate renal insufficiency (6/8 and 10/13) and abscess > 5 cm (58/68 vs. 57/74). The 95% CIs around the treatment differences were sometimes wide due to small numbers per subgroup but included zero except for monomicrobial MRSA (lower 95% CI above zero, i.e. in favour of ceftaroline).

Study P903-07 in cSSTI: A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in adult subjects with complicated skin and skin structure infection

Methods

Study Participants

The study was conducted between March and December 2007 (dates of first enrolment and last completion) in 56 study centers from 12 countries (Europe, Latin America and the United States).

The mean/median age was 47 - 48 years (range 18-96 years) and 63% overall were male subjects (65.5% ceftaroline and 59.5% comparator). About 18% and 15% in respective groups were diabetic while 14% and 12% had PVD. Baseline features of cSSTI were considered severe for erythema in 55% and 53% per group, swelling in 46%, tenderness in 51% and 53% and discharge was purulent in about 54% overall. The mean lesion areas were 284 and 279 cm^2 in respective groups but the median areas were 151 and 120 cm^2. The distribution of lesion types contrasted with P903-06 in that abscesses predominated over cellulitis.

Inclusion and exclusion criteria

See study P903-06.

Treatments

Ceftaroline fosamil 600 mg was administered intravenously over 60 minutes every 12 hours, followed by placebo administered over 60 minutes every 12 hours. Vancomycin 1 g was administered over 60 minutes every 12 hours followed by aztreonam 1 g administered over 60 minutes every 12 hours. The duration of therapy was from 5-14 days with up to 21 days allowed (sponsor approval for individual subjects.

Objectives

See study P903-06.

Outcomes/endpoints

The coprimary efficacy outcome measures were the per-subject clinical cure rate at the TOC Visit in the CE and MITT populations. Subjects were considered clinically cured at the TOC visit if they had total resolution of all signs and symptoms of the baseline infection, or improvement of the infection such that no further antimicrobial therapy was necessary.

The secondary efficacy outcome measures were:

- Per-subject clinical cure rate at the TOC visit in the clinical MITT (cMITT) population.
- Per-subject clinical cure rate at the EOT visit in the MITT, cMITT, and CE populations
- Per-subject microbiological response at the TOC visit in the microbiological MITT (mMITT) and microbiologically evaluable (ME) populations.
- Per-subject clinical and microbiological response by pathogen at the TOC visit in the mMITT and ME populations
- Per-subject relapse rate at the LFU visit in those subjects who were clinically cured at the TOC visit
- Per-subject reinfection or recurrence rate at the LFU visit in those subjects who had a favorable microbiological outcome (eradication or presumed eradication) at the TOC visit

Sample size

Assuming a point estimate for the clinical cure rate of 85% in the vancomycin plus aztreonam group and 85% in the ceftaroline group in the CE population, a non-inferiority margin of 10%, a power of 90%, and a 20% non-evaluable rate, a total sample size of 690 patients was required (345 patients in each treatment group).

Randomisation

Block randomization using an interactive voice response system (IVRS), stratified by country was used to assign subjects (1:1) to the ceftaroline or vancomycin plus aztreonam groups.

Blinding (masking)

See study P903-06

Statistical methods

See study P903-06

Results

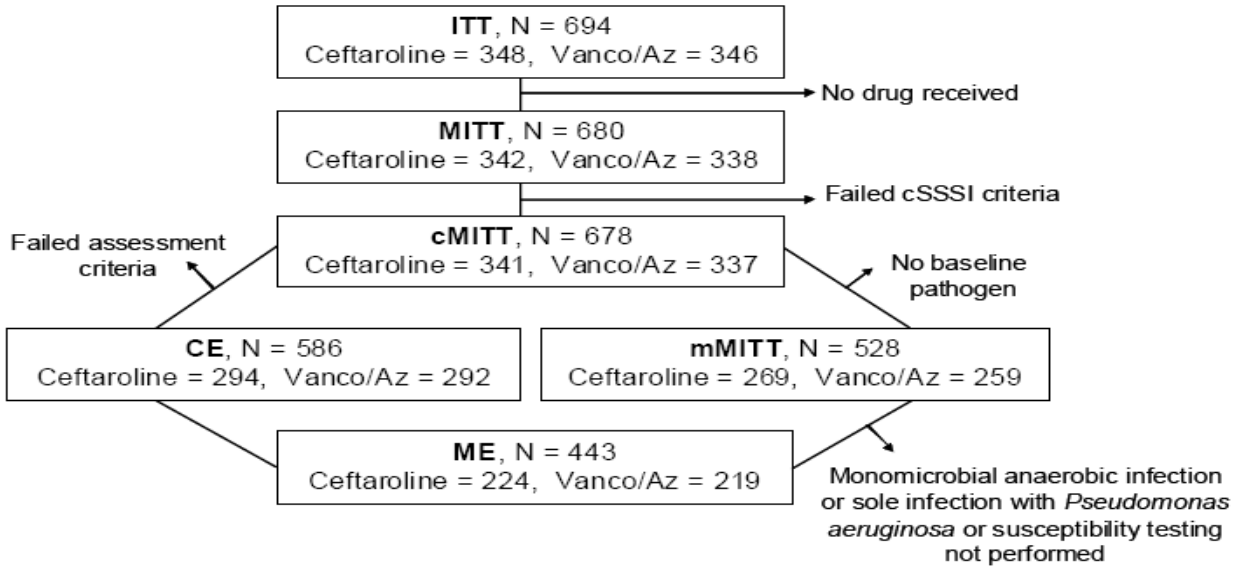
Of 694 patients enrolled, 586 were CE (294 in the ceftaroline group and 292 in the vancomycin plus aztreonam group) and 443 were ME (224 in the ceftaroline group and 219 in the vancomycin plus aztreonam group).

- The primary objective of determining the non-inferiority of ceftaroline compared with vancomycin plus aztreonam was demonstrated for the treatment of cSSTI.
- Clinical cure rates were high and similar between the treatment groups at TOC in the MITT population (85.1% for ceftaroline vs 85.5% for vancomycin plus aztreonam) and CE population (92.2% for ceftaroline vs 92.1% for vancomycin plus aztreonam).
- Clinical cure rates within clinically-relevant subgroups, including patients with PVD, DM, polymicrobial infections, and MRSA infections, were comparable to the overall cures rates in the CE population at TOC.
- Per-subject microbiological responses at TOC were similar between the 2 treatment groups in both the ME and mMITT populations.
- Clinical cure rates for patients in the MITT, cMITT, and CE populations at EOT were similar in the 2 treatment groups and slightly greater than those at the TOC visit.
- Clinical cure rates by baseline pathogen were high and similar between the 2 treatment groups in the ME population at the TOC visit, including patients with infections due to MSSA and MRSA.
- Clinical relapse at LFU in those patients who were clinically cured at TOC was rare in both treatment groups. No microbiological recurrences were observed in this study.

Participant flow

In the ITT population 91% ceftaroline and 88% comparator group subjects completed therapy while 2% and 5% in respective groups discontinued due to AEs.

Figure 3: Participant flow in study P903-07



Recruitment

A total of 694 patients were randomised: 348 to ceftaroline and 346 to vancomycin plus aztreonam in the ITT population; 342 to ceftaroline and 338 to vancomycin plus aztreonam in the MITT and safety populations. Patients were predominately male (63%) and white (74%) with a mean age of 48 years. Treatment groups were well balanced with respect to relevant medical and surgical histories (recent trauma, 30%; DM, 17%; previous skin infection, 10%; and PVD, 13%); infection size (length, width, and area); description and location of the primary infection site (43% occurred in the lower extremity and 31% in an upper extremity); and the pathogens that grew from cSSTI specimens (majority due to monomicrobial Gram-positive pathogens, with S. aureus the most common pathogen isolated). Demographics and baseline characteristics in the cMITT, CE, and ME populations were similar to those in the MITT population.

Conduct of the study

See study P903-06

Baseline data

The mean/median age was 47 - 48 years (range 18-96 years) and 63% overall were male subjects (65.5% ceftaroline and 59.5% comparator). About 18% and 15% in respective groups were diabetic while 14% and 12% had PVD. Baseline features of cSSTI were considered severe for erythema in 55% and 53% per group, swelling in 46%, tenderness in 51% and 53% and discharge was purulent in about 54% overall. The mean lesion areas were 284 and 279 cm^2 in respective groups but the median areas were 151 and 120 cm^2. The distribution of lesion types contrasted with P903-06 in that abscesses predominated over cellulitis.

Table 11: Description and location of primary site of cSSTI at baseline (MITT population)

Description of Infection	*Ceftaroline (N = 342) n (%)*	*Vancomycin plus Aztreonam (N = 338) n (%)*	*Total (N = 680) n (%)*
Type of infection			
Major abscess	139 (40.6)	133 (39.3)	272 (40.0)
Deep/extensive cellulitis	103 (30.1)	123 (36.4)	226 (33.2)
Infected wound	48 (14.0)	39 (11.5)	87 (12.8)
Infected ulcer	31 (9.1)	21 (6.2)	52 (7.6)
Lower extremity cSSSI in subject with diabetes or PVD	9 (2.6)	12 (3.6)	21 (3.1)
Cellulitis	8 (2.3)	11 (3.3)	19 (2.8)
Abscess	1 (0.3)	1 (0.3)	2 (0.3)
Infected bite[a]	6 (1.8)	4 (1.2)	10 (1.5)
Infected burn	1 (0.3)	2(0.6)	3 (0.4)
Other	5 (1.5)	4 (1.2)	9 (1.3)

At least one pathogen was obtained from 76% of subjects and about 82% of all pathogens were *S. aureus* (30% MRSA and 52% MSSA) while 12.5% were *S. pyogenes*. Overall 5% had a pathogen isolated from blood cultures including 9 (3.3%) in the ceftaroline group and 14 (5.4%) in the comparative group.

There were 34.8% ceftaroline and 32.5% comparator group subjects who had received prior antibacterial therapy for the target infection, although mostly for < 24 h and most of those treated for > 48 h had evidence of failure. In addition, 30 subjects (~ 9%) per group received another antibacterial agent between randomisation and TOC, including 17/30 ceftaroline and 15/30 comparator subjects treated for reason of failure. The median duration of study treatment was 6.5 days in each group with means of 7.4 days and 2.5% extended therapy beyond day 14. Aztreonam was given for a median of 3.5 days.

Outcomes and estimation

In the CE and MITT populations non-inferiority of ceftaroline vs. comparative therapy was demonstrated with lower 95% CI within -6. Clinical cure rates in the cMITT population were nearly identical to those in the MITT population. Most of the indeterminate outcomes were due to loss to follow-up or the subject's withdrawal of consent. By TOC, the median infection area was zero in both treatment groups. Similar results applied to the MITT population.

Three ceftaroline and two comparator group subjects experienced a clinical relapse at LFU after having been designated as cured at TOC.

For subjects with an indeterminate outcome who could be otherwise clinically evaluable the applicant conducted post-hoc sensitivity analyses in which these subjects were classified either as clinical cures or as clinical failures. In both approaches the lower limit of the 95% CI was above -10%.

After exclusion of subjects with abscess the cure rates were 164/179 (91.6%) ceftaroline and 165/181 (91.2%) in the CE population (95% CI around difference -5.6, 6.5) with rates for the MITT population at 86.6% and 86.3% (95% CI -6.4, 7.1).

Table 12: Clinical response at the TOC visit (CE and MITT populations)

Population	*Clinical Response*	*Ceftaroline n (%)*	*Vancomycin plus Aztreonam n (%)*	*Difference[a] (95% CI[b])*	*p-value[c] for Superiority*
CE, N		294	292		
	Clinical cure	271 (92.2)	269 (92.1)	0.1 (-4.4, 4.5)	p = 1.000
	Clinical failure	23 (7.8)	23 (7.9)		
MITT, N		342	338		
	Clinical cure	291 (85.1)	289 (85.5)	-0.4 (-5.8, 5.0)	p = .914
	Clinical failure	25 (7.3)	28 (8.3)		
	Indeterminate	26 (7.6)	21 (6.2)		

There was no apparent correlation between clinical response at TOC and severity of illness score.

Table 13: Overall clinical response at TOC visit by risk class based on Severity of Ilness Score (MITT population)

Risk Class Quartiles Based on Disease Severity Score	Clinical Response	Total (N=680) n (%)	95% CI for the Clinical Cure Rate
Risk class I (<65 points)	N1	247	
	Clinical Cure	206 (83.4)	(78.2, 87.8)
	Clinical Failure	20 (8.1)	
	Indeterminate	21 (8.5)	
Risk class II (65 to 82 points)	N1	147	
	Clinical Cure	127 (86.4)	(79.8, 91.5)
	Clinical Failure	7 (4.8)	
	Indeterminate	13 (8.8)	
Risk class III (83 to 100 points)	N1	109	
	Clinical Cure	97 (89.0)	(81.6, 94.2)
	Clinical Failure	9 (8.3)	
	Indeterminate	3 (2.8)	
Risk class IV (>100 points)	N1	177	
	Clinical Cure	150 (84.7)	(78.6, 89.7)
	Clinical Failure	17 (9.6)	
	Indeterminate	10 (5.6)	

Overall per-subject microbiological response at TOC for the ME and mMITT populations gave comparable rates with lower 95% CI above -8.

There were two ceftaroline subjects with only Gram-negative pathogens who had an unfavourable microbiological response. One was a failure at EOT with presumed persistence of *P. aeruginosa* and *M. morganii.* The other was a clinical cure at EOT, TOC and LFU but had microbiological evidence of persistence of *E. cloacae* (MIC 0.12 – 0.25 µg/mL). The 9 subjects with only Gram-negative pathogens in the comparator group all received aztreonam to which most isolates were susceptible. There was no instance of an increase in MIC ceftaroline during treatment in this study.

Table 14: Per-subject microbiological response at the TOC visit (ME and mMITT populations)

Population	*Per-Subject Microbiological Response*	*Ceftaroline n (%)*	*Vancomycin plus Aztreonam n (%)*	*Difference[a]*	*(95% CI)[b]*
ME, N		224	219		
	Favorable[c]	208 (92.9)	208 (95.0)	-2.1	(-6.9, 2.5)
	Unfavorable[d]	16 (7.1)	11 (5.0)		
mMITT, N		269	259		
	Favorable	233 (86.6)	229 (88.4)	-1.8	(-7.5, 3.9)
	Unfavorable	18 (6.7)	13 (5.0)		
	Indeterminate	18 (6.7)	17 (6.6)		

The clinical cure rates at TOC by baseline pathogen gave generally comparable rates, including rates for those with monomicrobial and polymicrobial infections. The clinical response rates for *S. aureus* infections (MRSA and MSSA) and streptococcal infections were high and comparable between treatments. The per pathogen microbiological response rates closely resembled clinical response rates.

Microbiological responses at TOC were analysed according to two or more signs and symptoms of severe cSSSI at baseline (90.3% ceftaroline vs. 92.4% comparator in the MITT population), fever (87% vs. 92%), leukocytosis > 10,000 WBC/mm3 (86.3% vs. 90.6%), age > 75 years (13/16 vs. 12/16) or < 75 years (87% vs. 89%), diabetes (37/46 vs. 33/36), PVD (37/44 vs. 33/35), mono- and polymicrobial infection (also ± MRSA), moderate renal insufficiency (7/7 and 10/12) and abscess > 5 cm (85% vs. 88%). The 95% CIs around the treatment differences were sometimes wide due to small numbers per subgroup but included zero.

Table 15: Clinical cure rates at the TOC visit by baseline pathogen from the primary infection site or blood (ME population)

Baseline Pathogen	*Ceftaroline* n^a/N^b *(%)*	*Vancomycin plus Aztreonam* n^a/N^b *(%)*
Gram-positive organisms[c]	170/181 (93.9)	170/178 (95.5)
Staphylococcus aureus[d]	182/195 (93.3)	172/183 (94.0)
MRSA	64/70 (91.4)	56/60 (93.3)
MSSA	118/125 (94.4)	119/126 (94.4)
Enterococcus faecalis	7/11 (63.6)	11/12 (91.7)
Streptococcus agalactiae	6/6 (100.0)	5/5 (100.0)
Streptococcus anginosus	3/3 (100.0)	5/5 (100.0)
Streptococcus constellatus	1/1 (100.0)	3/3 (100.0)
Streptococcus dysgalactiae	8/8 (100.0)	7/7 (100.0)
Streptococcus intermedius	2/2 (100.0)	0
Streptococcus pyogenes	32/32 (100.0)	24/26 (92.3)
Monomicrobial gram-positive infections	134/142 (94.4)	144/152 (94.7)
Polymicrobial gram-positive infections	36/39 (92.3)	26/26 (100.0)
Gram-negative organisms[c]	14/16 (87.5)	9/9 (100.0)
Enterobacter cloacae	2/2 (100.0)	7/8 (87.5)
Escherichia coli	11/11 (100.0)	6/6 (100.0)
Klebsiella oxytoca	7/7 (100.0)	3/3 (100.0)
Klebsiella pneumoniae	7/7 (100.0)	3/4 (75.0)
Morganella morganii	5/6 (83.3)	2/3 (66.7)
Proteus mirabilis	3/5 (60.0)	11/11 (100.0)
Pseudomonas aeruginosa	5/7 (71.4)	8/8 (100.0)
Serratia marcescens	2/2 (100.0)	3/3 (100.0)
Monomicrobial gram-negative infections	13/14 (92.9)	9/9 (100.0)
Polymicrobial gram-negative infections	1/2 (50.0)	0
Mixed gram-positive and gram-negative infections	24/27 (88.9)	29/32 (90.6)

Ancillary analyses

Clinical response at TOC was examined for a variety of subgroups: infection type, disease severity, co-morbid conditions, demographic and baseline characteristics and by protocol amendment. Subgroup analyses based on demographic and baseline disease characteristics were performed in the CE population only. For the region group and protocol amendments subgroups, the analyses were performed in the MITT and CE populations. Generally, point estimates of the treatment differences for all subgroups of sufficient size were of comparable magnitude to the overall population, demonstrating the robustness of the conclusions. Not surprisingly, observed treatment differences (ceftaroline – vancomycin plus aztreonam) in clinical cure rates among smaller subgroups were more variable.

Study P903-08 in CAP: A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus ceftriaxone, with adjunctive clarithromycin, in the treatment of adult subjects with community-acquired pneumonia

Methods

Study Participants

P903-08 was conducted during 2008 and enrolled subjects in Western and Eastern Europe, Asia, North and South America and in S. Africa.

Important inclusion criteria

Eligible adults considered to be in need of initial IV therapy in an urgent health care setting had CAP that met the following criteria:

I. Radiographically-confirmed pneumonia with new or progressive pulmonary infiltrate(s) on chest radiograph (CXR) or chest computed tomography (CT) scan consistent with bacterial pneumonia

AND

II. Acute illness of ≤ 7 days duration with ≥ 3 of the following: new or increased cough, purulent sputum or change in sputum character, auscultatory findings consistent with pneumonia, at least one of dyspnoea, tachypnoea or hypoxaemia (O2 sat < 90% on room air or pO2 < 60 mm Hg), fever > 38ºC oral or > 38.5ºC rectally or tympanically or hypothermia (< 35ºC), WBC > 10,000 cells/mm3 or < 4,500 cells/mm3, > 15% immature neutrophils (bands) irrespective of WBC count

AND

III. PORT score > 70 and ≤ 130 (i.e. PORT Risk Class III or IV)

Important exclusions included:

- Confirmed or suspected non-bacterial and/or non-community-acquired CAP or atypical CAP (based on *L. pneumophila* urinary antigen plus serology for atypical pathogens)
- Pathogen known or very likely to be resistant to ceftriaxone (e.g. *P. aeruginosa*, MRSA)
- Previous antibacterial treatment of CAP within 96 h pre-randomisation unless this consisted only of a single dose of a short-acting agent or there was unequivocal clinical evidence of treatment failure despite ≥48 h treatment PLUS isolation of an organism resistant to the prior therapy (prior therapy was not to be ceftriaxone or other third-generation cephalosporin)
- Severe underlying lung disease
- The corticosteroid dose equivalent to more than 40 mg prednisone/day
- CrCl ≤ 30 mL/min or < 500 neutrophils/mm3 or platelet count < 60,000 cells/mm3
- HIV positive with CD4 < 200 cells/mm3

Treatments

Ceftaroline fosamil was administered as 2 x 30 min infusions of 300 mg given consecutively every 12 h to maintain the blind vs. ceftriaxone 1 g administered once daily as 30-min infusions. The dose was adjusted to 400 mg in case of moderate renal insufficiency (CrCl >30 and up to 50 ml/min). The

duration of therapy was 5-7 days. Both treatment groups also received two doses of oral clarithromycin (500 mg) q12h (± 2 hours) as adjunctive therapy on Study Day 1 only.

Objectives

Primary:

To determine the noninferiority in the clinical cure rate for ceftaroline compared to that for ceftriaxone at the test of cure (TOC) visit in the clinically evaluable (CE) and modified intent to treat efficacy (MITTE) populations in adult subjects with community-acquired bacterial pneumonia (CABP).

Secondary:

- To evaluate the clinical response at End-of-Therapy (EOT)
- To evaluate the microbiological success rate at TOC
- To evaluate the overall (clinical and radiographic) success rate at TOC
- To evaluate the clinical and microbiological response by pathogen at TOC
- To evaluate clinical relapse at late follow-up (LFU)
- To evaluate microbiological reinfection/recurrence at LFU
- To evaluate safety

Outcomes/endpoints

The clinical cure at the TOC Visit was the primary outcome measure and was to be determined for the co-primary study populations - the CE and MITTE Populations. The analysis of non-inferiority was based on a pre-specified margin of 10%.

Subjects were considered clinically cured at TOC if they had total resolution of all signs and symptoms of the baseline infection or improvement of the infection to such an extent that no further antimicrobial therapy was considered to be necessary. The TOC visit window was 8-15 days after EOT for the CE population but in the final SAP the general windows applied were 7-20 days post-treatment for TOC and 21-45 days for LFU.

Sample size

Assuming a point estimate for the clinical cure rate in the CE Population of 90% in the ceftriaxone treatment group, and 90% in the ceftaroline group, a noninferiority margin of 10%, a power of 90%, and a 25% nonevaluability rate, and that 60 subjects in PORT Risk Class II were enrolled, a total sample size of 610 subjects was required to demonstrate noninferiority of ceftaroline to ceftriaxone based on the CE population. For the same sample size this study was expected to have at least 90% power to show noninferiority based on the MITTE Population (305 subjects in each treatment group).

Randomisation

The study was randomised by using block randomisation using IVRS, stratified by country and severity of disease to assign subjects (1:1) to ceftaroline or ceftriaxone.

Blinding (masking)

The study had a double-blind design. The investigator (including data management and analysis personnel), CROs, study personnel and subjects were all blinded to the study therapy. Maintenance of the study blind at both investigative centers and the sponsor and CROs was implemented according to prospectively written blinding plans.

Statistical methods

There were seven study populations, six of which were statistically analyzed.

- The ITT Population included all randomized subjects and was not analyzed
- The MITT Population included all randomized subjects who received any amount of the study drug
- The MITTE Population consisted of all subjects in the MITT Population in PORT Risk Class III or IV
- The mMITT Population consisted of all subjects in the MITT Population who met the minimal disease criteria for CABP, and who had at least one typical bacterial organism consistent with a CABP pathogen identified from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid). Subjects with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all subjects with *L. pneumophila* infection were excluded from the mMITT population.
- The mMITTE Population consisted of all subjects in the mMITT Population in PORT Risk Class III or IV
- The CE Population consisted of all subjects in the MITTE Population who met minimal disease criteria for CABP and all evaluability criteria, including subjects who received at least the prespecified minimal amount of the intended dose and duration of study drug therapy, for whom sufficient information regarding the infection was available to determine the subject's outcome; subjects with *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* as the sole causative pathogen of infection, and all subjects with *L. pneumophila* infection, were excluded from the CE Population.
- The ME Population was a subset of the CE and mMITTE Populations and included each subject in the CE Population who also had at least one "typical" bacterial pathogen that had been isolated from an appropriate microbiological specimen

A two-sided 95% CI for the observed difference in the primary outcome measure (clinical cure rate) between the ceftaroline group and the ceftriaxone group was calculated based on each of the CE and the MITTE Populations at the TOC visit. Non-inferiority was concluded if the lower limit of the 95% CI was higher than –10% for each of the CE and MITTE Populations.

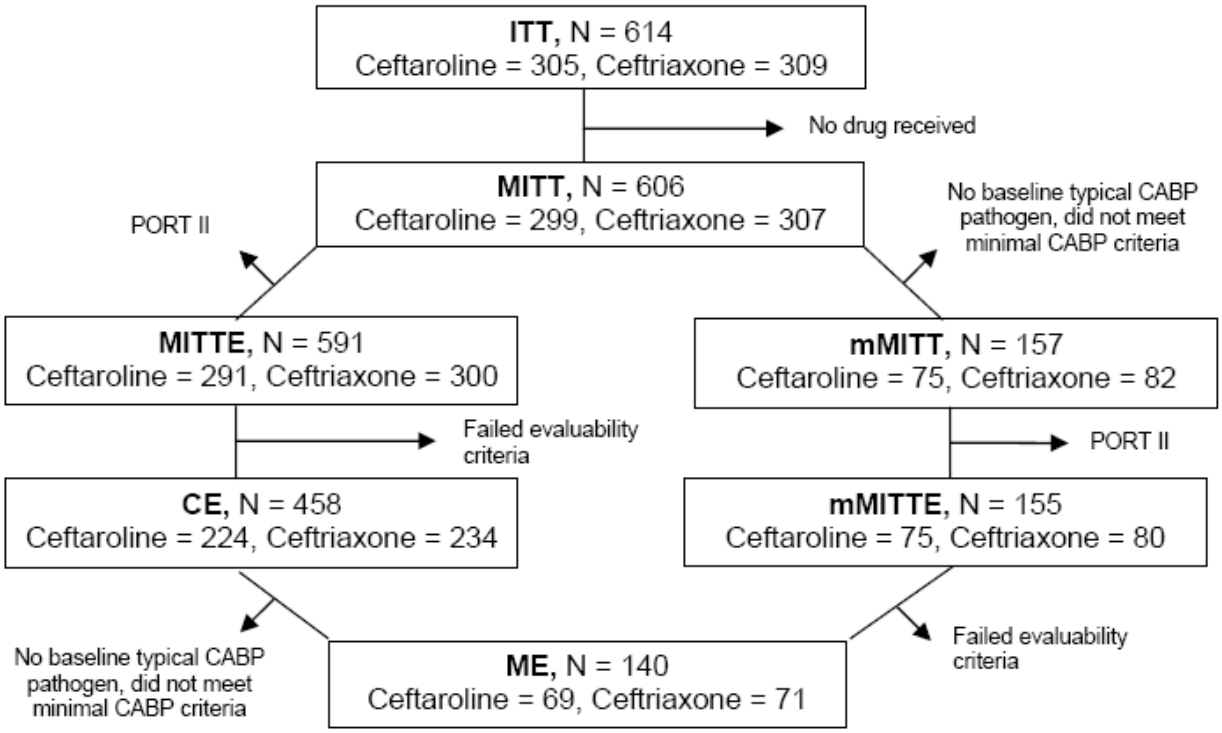
Results

Of 614 patients enrolled, 591 were clinically evaluable (291 in the ceftaroline group and 300 in the ceftriaxone group) and 157 were microbiologically evaluable (75 in the ceftaroline group and 82 in the ceftriaxone group). The primary objective of determining the noninferiority of ceftaroline compared with ceftriaxone was demonstrated for the treatment of CABP. Clinical cure rates were higher in the ceftaroline group than the ceftriaxone group at TOC in the MITTE (83.8% and 77.7%, respectively) and CE Populations (86.6% and 78.2%, respectively). The noninferiority of ceftaroline compared with

ceftriaxone was demonstrated in both of the coprimary populations, as the lower limits of the 95% CIs around the treatment differences (ceftaroline - ceftriaxone) were greater than the prespecified noninferiority boundary of -10% (-0.2% for the MITTE Population and 1.4% for the CE Population). Clinical cure rates at TOC in the ME, mMITTE, and mMITT Populations were higher in the ceftaroline group than the ceftriaxone group. Clinical cure rates at EOT were higher in the ceftaroline group than the ceftriaxone group for both the MITTE and CE Populations, and the noninferiority of ceftaroline compared with ceftriaxone was demonstrated in both populations, as the lower limits of the 95% CIs around the treatment differences ceftaroline - ceftriaxone) were greater than the prespecified noninferiority boundary of -10%;

Participant flow

Figure 4: Participant flow in study P903-08



Recruitment

A total of 614 patients were randomised: 305 to ceftaroline and 309 to ceftriaxone (intent-to-treat [ITT] population); 299 to ceftaroline and 307 to ceftriaxone in the MITT or safety population. Patients in both treatment groups also received 2 doses of oral adjunctive therapy (clarithromycin) starting on Day 1 following randomisation. The demographic and baseline characteristics between treatment groups were similar. Patients were predominately male (64%), non-Hispanic (91%), and white (89%), and had a mean age of 61 years.

Treatment groups were well balanced with respect to relevant medical and surgical histories (structural lung disease [21%], gastro-oesophageal reflux [3%], asthma [9%], chronic sinusitis [1%], alcohol abuse [3%], and prior pneumonia [19%]). In the MITTE population, approximately 63% of patients had PORT risk class III and 37% were in Class IV; there was a higher percentage of ceftriaxone patients in Class IV (39% vs. 35% for ceftaroline). There were similar CAP pathogen recovery rates of approximately 26% in the 2 treatment groups, with comparable pathogens, the majority of which were monomicrobial Gram-positive and Gram-negative pathogens. The most commonly isolated pathogen

was *S. pneumoniae*. Demographics and baseline characteristics in the MITT and CE populations were similar to those in the MITTE population.

Conduct of the study

Protocol amendments

The original protocol was dated January 12, 2007. No subjects were enrolled under the original protocol. During the study, there were four protocol amendments:

Amendment 1 (July 25, 2007)

- Increased the sample size of evaluable subjects from 510 to 550 and the number in each treatment group from 255 to 275.
- The adjunctive macrolide therapy was changed from azithromycin to shorter-acting clarithromycin, and the potential for oral switch to amoxicillin-clavulanate was eliminated.

Amendment 2 (November 13, 2007)

- Excluded subjects with PORT Risk Class II from the study; restricted primary efficacy analyses to subjects with PORT Risk Class III and IV
- Increased the sample size to 610 subjects (305 per treatment arm) as it was assumed that 60 subjects in PORT Risk Class II had been enrolled before implementation of this amendment. Thus, 60 additional subjects were need to ensure 90% power in the CE Population to determine noninferiority.

Amendment 3 (October 20, 2008)

- Administrative amendment only

Amendment 4 (June 9, 2009)

- Changed the primary efficacy parameter from "overall (clinical and radiographic) response at TOC visit" to "clinical response at TOC visit"
- Removed the test of superiority from primary efficacy analyses
- Included all-cause death as clinical failure in analyses

Baseline data

The mean age was 61 years (median 64 years) and 64% of subjects were male while half (49%) were over 65 years and nearly a quarter (23%) were over 75 years. At baseline 35% were hypoxic, 65% were febrile and 22% had both hypoxia and fever. About 70% had a single lobe and 30% multilobar CAP while 20% had an effusion. In the MITTE population two thirds had PORT score III (65% ceftaroline and 61% comparator) and 37% had a score of IV (35% and 39%). Also, 77% per group had CURB-65 scores of 1-2, which approximate to PORT scores of III-IV in terms of predicted mortality rates, while 10% had a score of at least 3.

In the mMITTE population 51% had at least one Gram-positive pathogen (37% had S. pneumoniae) while 57% had at least one Gram-negative pathogen (as designated by the applicant) although these were mostly enterobacterial species. Nearly 80% had only one pathogen. Overall 17 subjects had a pathogen found in blood culture of which 12 were *S. pneumoniae* (7 and 5 per group). About 10% also had evidence of an atypical pathogen (noting that those with evidence of Legionella were excluded from the MITT, mMITTE and ME populations).

Approximately 48% of MITT subjects had received prior antibacterial therapy for CAP in the 96 h prior to randomisation. However, almost all of these subjects had received a single dose of a short acting

agent by the oral or parenteral route, none had received 48 h or more prior therapy and only 2 ceftaroline and 4 comparator subjects were excluded from the CE population due to prior therapy. The median duration of study treatment was 6.5 days, 83% and 87% per group received from 5-8 days and no subject received > 8 days.

Outcomes and estimation

Non-inferiority of ceftaroline vs. ceftriaxone was demonstrated in the co-primary populations with lower limits of the 95% CIs within -1. The comparison in the CE population gave 95% CI around the treatment difference that did not span zero and favoured ceftaroline. Cure rates for all treated subjects (MITT) were 82.9% and 77.6% (95% CI -1.0, 11.8).

Table 16: Clinical response at TOC (CE and MITTE populations)

Population	*Clinical Response*	*Ceftaroline n (%)*	*Ceftriaxone n (%)*	*Difference*[a]	*(95% CI*[b]*)*
MITTE					
	N	291	300		
	Clinical cure	244 (83.8)	233 (77.7)	6.2	(–0.2, 12.6)
	Clinical failure	34 (11.7)	58 (19.3)		
	Indeterminate	13 (4.5)	9 (3.0)		
CE					
	N	224	234		
	Clinical cure	194 (86.6)	183 (78.2)	8.4	(1.4, 15.4)
	Clinical failure	30 (13.4)	51 (21.8)		

For the 15 subjects with an indeterminate outcome who could be otherwise clinically evaluable additional sensitivity analyses (CE population) in which these subjects were classified either as cures or failures gave higher cure rates for ceftaroline and lower limits of the 95% CI around the differences that were within -10% (1.7%, 16.3% and -0.9%, 13.6%).

Among the failures in the MITTE population 31/34 in the ceftaroline group and 53/58 in the ceftriaxone group were due to persistence, incomplete resolution or worsening of CABP. There were 6 deaths in each treatment group, with 4 and 5 per group within 30 days in the MITTE population, of which 1 and 3 were thought to be due to CAP.

In an analysis in which only subjects with complete resolution of signs and symptoms were counted as cures there were much lower cure rates but there was still a numerical advantage for ceftaroline and the lower 95% CI were within -3.

In CE and MITTE populations the cure rates at TOC were higher for ceftaroline in those who did not receive other antibacterial agents within 96 hours of the first dose of study drug (MITTE 90.3% vs. 77.1% for ceftriaxone; CE 91.6% vs. 75%) compared to those who did (MITTE 76.6% vs. 78.3%; CE 81% vs. 82.1%).

Clinical outcomes in the CE population by region showed that in areas where 10 or more subjects were enrolled the pattern of responses was in line with the overall treatment differences in the study with the exception of Germany (9/13 ceftaroline and 12/13 ceftriaxone).

In the CE Population the clinical cure rates in the ceftaroline group were similar to or higher than those in the ceftriaxone group for most subsets examined, including PORT Risk Class III. Rates were comparable between treatments in those aged over 75 years, with a CURB-65 score of 3, in PORT Risk Class IV or with moderate renal impairment.

The analysis of clinical outcomes applied to other pre-defined populations (mMITTE, ME, mMITT) also gave 95% CI around the treatment differences that did not span zero and favoured ceftaroline.

By-pathogen clinical outcomes for the two most common pathogens were as shown below. The same pattern applied regardless of the pneumococcal susceptibility to penicillin and for cases diagnosed only by urinary antigen. Results for the mMITTE population were similar.

Table 17: Clinical response at test of cure by baseline pathogen (ME population)

Baseline Pathogen	*Clinical Response*	*Ceftaroline n (%)*	*Ceftriaxone n (%)*
Gram-positive Organisms (aerobes)			
Staphylococcus aureus	**N**	10	12
	Clinical cure	8 (80.0)	7 (58.3)
	Clinical failure	2(20.0)	5 (41.7)
Streptococcus pneumoniae	**N**	24	27
	Clinical cure	21 (87.5)	18 (66.7)
	Clinical failure	3 (12.5)	9 (33.3)

Clinical cure was observed for 6/8 ceftaroline and 4/7 ceftriaxone ME subjects at TOC with a pathogen isolated from baseline blood culture. Rates were 6/7 and 3/5 for those with pneumococcal bacteraemia.

Since most microbiological responses per subject and by-pathogen were presumed it follows that the rates resembled those for clinical outcomes at TOC. For example, in the mMITT population all those with clinical cure at TOC had a favourable microbiological outcome.

There were no documented cases of re-infection or recurrence at LFU and no evidence of decreasing susceptibility to ceftaroline while on therapy.

Ancillary analyses

Additional analyses across a variety of subgroups including demographic and baseline characteristics, geographical regions, disease severity, comorbid conditions, and the subset of patients who had not received prior systemic antibacterials were conducted and showed consistent treatment effects.

Study P903-09 in CAP: A Phase 3, multicentre, randomised, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus ceftriaxone in the treatment of adult subjects with community-acquired pneumonia

Methods

Study Participants

P903-09 was conducted during 2007-2008 and enrolled subjects in Asia, Western and Eastern Europe and in Latin America.

Important inclusion criteria

Eligible adults considered to be in need of initial IV therapy in an urgent health care setting had CAP that met the following criteria:

I. Radiographically-confirmed pneumonia with new or progressive pulmonary infiltrate(s) on chest radiograph (CXR) or chest computed tomography (CT) scan consistent with bacterial pneumonia

AND

II. Acute illness of ≤ 7 days duration with ≥ 3 of the following: new or increased cough, purulent sputum or change in sputum character, auscultatory findings consistent with pneumonia, at least one of dyspnoea, tachypnoea or hypoxaemia (O2 sat < 90% on room air or pO2 < 60 mm Hg), fever > 38ºC oral or > 38.5ºC rectally or tympanically or hypothermia (< 35ºC), WBC > 10,000 cells/mm3 or < 4,500 cells/mm3, > 15% immature neutrophils (bands) irrespective of WBC count

AND

III. PORT score > 70 and ≤ 130 (i.e. PORT Risk Class III or IV)

Important exclusions included:

- Confirmed or suspected non-bacterial and/or non-community-acquired CAP or atypical CAP (based on *L. pneumophila* urinary antigen plus serology for atypical pathogens)
- Pathogen known or very likely to be resistant to ceftriaxone (e.g. *P. aeruginosa*, MRSA)
- Previous antibacterial treatment of CAP within 96 h pre-randomisation unless this consisted only of a single dose of a short-acting agent or there was unequivocal clinical evidence of treatment failure despite ≥48 h treatment PLUS isolation of an organism resistant to the prior therapy (prior therapy was not to be ceftriaxone or other third-generation cephalosporin)
- Severe underlying lung disease
- The corticosteroid dose equivalent to more than 40 mg prednisone/day
- CrCl ≤ 30 mL/min or < 500 neutrophils/mm3 or platelet count < 60,000 cells/mm3
- HIV positive with CD4 < 200 cells/mm3

Treatments

Ceftaroline fosamil was administered as 2 x 30 min infusions of 300 mg given consecutively every 12 h to maintain the blind vs. ceftriaxone 1 g administered once daily as 30-min infusions. The dose was adjusted to 400 mg in case of moderate renal insufficiency (CrCl >30 and up to 50 ml/min). The duration of therapy was 5-7 days.

Objectives

Primary:

To determine the noninferiority in the clinical cure rate for ceftaroline compared with that for ceftriaxone at the test-of-cure (TOC) visit in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations in adult subjects with community-acquired bacterial pneumonia (CABP).

Secondary:

1. To evaluate the clinical response at End-of-Therapy (EOT)

2. To evaluate the microbiological success rate at TOC

3. To evaluate the overall (clinical and radiographic) success rate at TOC

4. To evaluate the clinical and microbiological response by pathogen at TOC

5. To evaluate clinical relapse at Late Follow-up (LFU)

6. To evaluate microbiological reinfection/recurrence at LFU

7. To evaluate safety

Outcomes/endpoints

The primary efficacy outcome measure was the per-subject clinical cure rate at TOC in the CE and MITTE populations. The analysis of non-inferiority was based on a pre-specified margin of 10%. Subjects were considered clinically cured at TOC if they had total resolution of all signs and symptoms of the baseline infection, or improvement of the infection such that no further antimicrobial therapy was necessary. In addition, the clinical response at TOC was evaluated in the mMITT, mMITTE, and ME Populations.

Sample size

Assuming a point estimate for the clinical cure rate in the CE Population of 90% in the ceftriaxone group, and 90% in the ceftaroline group, a noninferiority margin of 10%, a power of 90% and 25% nonevaluability rate, and 76 subjects in PORT Risk Class II were enrolled, a total sample size of 626 subjects was required to demonstrate noninferiority of ceftaroline to ceftriaxone based on the CE population. For the same sample size this study was expected to have at least 90% power to show noninferiority based on the MITTE Population (313 subjects in each treatment group).

Randomisation

Block randomization using an interactive voice response system (IVRS), stratified bycountry and severity of disease, was used to assign subjects (1:1) to the ceftaroline or ceftriaxone group.

Blinding (masking)

The study had a double-blind design. The investigator (including data management and analysis personnel), CROs, study personnel and subjects were all blinded to the study therapy. Maintenance of the study blind at both investigative centers and the sponsor and CROs was implemented according to prospectively written blinding plans.

Statistical methods

See study P903-08

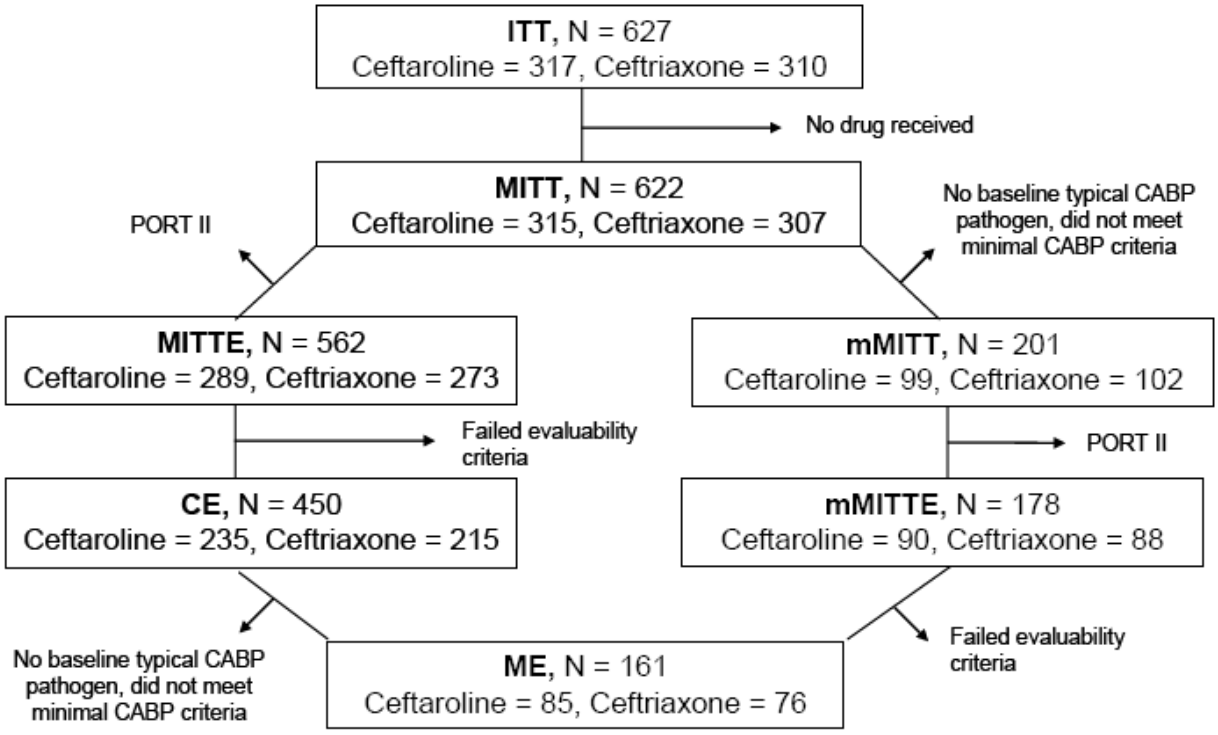
Results

Of 627 patients enrolled, 562 were clinically evaluable (289 in the ceftaroline group and 273 in the ceftriaxone group) and 201 were microbiologically evaluable (99 in the ceftaroline group and 102 in the ceftriaxone group). The primary objective of the non-inferiority of ceftaroline compared with ceftriaxone was confirmed for the treatment of CAP. Clinical cure rates were higher in the ceftaroline group than the ceftriaxone group at TOC in both the MITTE and CE populations. Clinical cure rates at

TOC in the ME, mMITTE, and mMITT populations were similar to those observed for the CE and MITTE populations. Clinical cure rates at EOT were higher in the ceftaroline group than the ceftriaxone group for both the MITTE and CE populations, and the non-inferiority of ceftaroline compared with ceftriaxone was demonstrated in both populations. Per-patient microbiological favourable outcome rates at TOC were similar in the 2 treatment groups in the mMITT population and non-inferiority of ceftaroline was demonstrated compared with ceftriaxone. The by-patient favourable microbiological outcome rates at TOC in both the ME and mMITTE populations supported these conclusions. The overall (clinical and radiographic) success rates for both treatment groups in both the CE and MITTE populations were essentially identical to those observed for clinical cure rate alone in the primary analysis; radiographic success rates and treatment differences were concordant with clinical cure rates and treatment differences for the CE and MITTE populations. Clinical cure rates and favourable microbiological outcome rates by pathogen at TOC in the mMITT, mMITTE and ME populations were higher in the ceftaroline group than in the ceftriaxone group for patients with infections due to Gram-positive pathogens including S. pneumoniae. The clinical cure rates and favourable microbiological rates in patients with infections due to respiratory Gram-negative bacilli (including H. influenzae, H. parainfluenzae, and K. pneumoniae) were similar in the 2 treatment groups.

Participant flow

Figure 5: Participant flow in study P903-09



Recruitment

Conduct of the study

Baseline data

The mean age was 61 years (median 63 years) and 62% of subjects were male while 47% were over 65 years and 21% were over 75 years. At baseline 37% were hypoxic, 48% were febrile and 17% had both hypoxia and fever. About 74% had a single lobe involved and 26% had multilobar CAP while 17% had an effusion. In the MITTE population 61% had PORT score III (59% ceftaroline and 63% comparator) and 39% had a score of IV (41% and 37%). Also, 76% per group had CURB-65 scores of 1-2, which approximate to PORT scores of III-IV in terms of predicted mortality rates, while 10% had a score of at least 3.

In the mMITTE population 62% had at least one Gram-positive pathogen (46% had *S. pneumoniae*) and 39% had at least one Gram-negative pathogen (26% had *Haemophilus spp*.). Almost all mMITTE subjects had a single pathogen. Overall 26 mMITTE subjects had a pathogen found in blood culture (15 ceftaroline and 11 comparator) of which 19 were *S. pneumoniae* (12 and 7 per group). About 14% also had evidence of an atypical pathogen (noting that those with evidence of Legionella were excluded from the MITT, mMITTE and ME populations).

Approximately 36% ceftaroline and 42% ceftriaxone MITT subjects had received prior antibacterial therapy for CAP in the 96 h prior to randomisation. All of these subjects (3 exceptions) had received a single dose of a short acting agent by the oral or parenteral route, none had received ≥48 h therapy and only 3 were excluded from the CE population due to prior therapy. The median duration of study treatment was 6.0 days with means of 5.9 days, 89% and 86% per group received from 5-8 days and no subject received > 8 days.

Outcomes and estimation

Non-inferiority of ceftaroline vs. ceftriaxone was demonstrated in the co-primary populations with lower limits of the 95% CIs within -3. Cure rates in the MITT (all treated) population were 81.9% and 76.5% (95% CI -1.0, 11.8).

Table 18: Clinical response at TOC (CE and MITTE populations)

Population	*Clinical Response*	*Ceftaroline n (%)*	*Ceftriaxone n (%)*	*Difference*[a]	*(95% CI*[b]*)*
MITTE					
	N	289	273		
	Clinical cure	235 (81.3)	206 (75.5)	5.9	(-1.0, 12.7)
	Clinical failure	47 (16.3)	56 (20.5)		
	Indeterminate	7 (2.4)	11 (4.0)		
CE					
	N	235	215		
	Clinical cure	193 (82.1)	166 (77.2)	4.9	(-2.5, 12.5)
	Clinical failure	42 (17.9)	49 (22.8)		

For the 13 subjects with an indeterminate outcome who could be otherwise clinically evaluable additional sensitivity analyses (CE population) in which these subjects were classified either as cures or failures gave higher cure rates for ceftaroline (82% vs. 78% and 81% vs. 74% in respective classification approaches) and lower limits of the 95% CI around the differences that were within -10% (-3.1, 11.6 and -0.3, 16, respectively).

Among the failures in the MITTE population 37/47 in the ceftaroline group and 51/56 in the ceftriaxone group were due to persistence, incomplete resolution or worsening of CABP. There were 8 deaths in the ceftaroline group and 5 in the ceftriaxone group within 30 days of end of treatment or LFU in the MITTE population, of which one in the ceftaroline group was thought to be due to CAP by the investigator.

In an analysis in which only subjects with complete resolution of signs and symptoms were counted as cures there were much lower cure rates but there was still a numerical advantage (MITTE) for ceftaroline or comparability between treatments (CE) and the lower 95% CI were within -9.

Table 19: Clinical response at TOC (clinical cure defined as total resolution of all symptoms and signs of CAP)-CE and MITTE populations

Population	Clinical Response	Ceftaroline n (%)	Ceftriaxone n (%)	Difference	95% CI for the difference
MITTE	N	289	273		
	Clinical Cure	150 (51.9)	126 (46.2)	5.7	(-2.5, 13.9)
	Clinical Failure	132 (45.7)	136 (49.8)		
	Indeterminate	7 (2.4)	11 (4.0)		
CE	N	235	215		
	Clinical Cure	123 (52.3)	110 (51.2)	1.2	(-8.1, 10.4)
	Clinical Failure	112 (47.7)	105 (48.8)		

In CE and MITTE populations the cure rates at TOC for ceftaroline were slightly higher for those who received other antibacterial agents within 96 hours of the first dose of study drug compared to those who did not (MITTE 84% with and 80% without; CE 84% and 81%, respectively). In the ceftriaxone group the pattern was the same but the difference was greater (MITTE 80% with and 72% without; CE 81% and 75%).

In the CE Population the clinical cure rates in the ceftaroline group were similar to or slightly higher than those in the ceftriaxone group for most subsets examined, including PORT Risk Class III or IV, age over 75 years and CURB-65 scores 1-3.

The analyses of clinical outcomes applied to other three pre-defined populations gave lower bounds of the 95% CI around the treatment differences that all fell within -9%.

By-pathogen clinical outcomes for the two most common pathogens were as shown below. The same pattern applied regardless of the pneumococcal susceptibility to penicillin and for cases diagnosed only by urinary antigen. Results for the mMITTE population were similar.

Clinical cure was observed for 9/13 ceftaroline (10 microbiological success) and 6/10 ceftriaxone (7 microbiological success) ME subjects at TOC with a pathogen isolated from baseline blood culture. Microbiological response rates were 8/10 and 4/6 for those with pneumococcal bacteraemia. Two ceftaroline subjects had *S. aureus* bacteraemia (MSSA) along with positive respiratory specimens and failed therapy. In addition, it seems that for all subjects with *S. pneumoniae* bacteraemia and an outcome recorded in this study the clinical cure rates were 14/17 ceftaroline and 7/11 ceftriaxone.

Table 20: Clinical response at the TOC visit by baseline pathogen (ME population)

Baseline Pathogen	*Clinical Response*	*Ceftaroline n (%)*	*Ceftriaxone n (%)*
Gram-positive Organisms (aerobes)			
Staphylococcus aureus	**N**	15	15
	Clinical cure	10 (66.7)	8 (53.3)
	Clinical failure	5 (33.3)	7 (46.7)
Streptococcus pneumoniae	**N**	39	32
	Clinical cure	33 (84.6)	23 (71.9)
	Clinical failure	6 (15.4)	9 (28.1)

Since most microbiological responses per subject and by-pathogen were presumed it follows that the rates closely resembled those for clinical outcomes at TOC. For example, in the mMITT population 99% with clinical cure at TOC had a favourable microbiological outcome. Two subjects per treatment group had an unfavourable microbiological outcome despite being classified as clinical cures. There were also 3 ceftaroline and 6 ceftriaxone subjects who failed clinically but had a favourable microbiological response.

Table 21: Per-subject microbiological response at the TOC visit overall (mMITT, mMITTE and ME populations)

Per-Subject Microbiological Response		*Ceftaroline n (%)*	*Ceftriaxone n (%)*	*Difference*[a]	*(95% CI)*[b]
mMITT					
	N	99	102		
	Favorable	81 (81.8)	83 (81.4)	0.4	(-10.5, 11.3)
	Unfavorable	16 (16.2)	15 (14.7)		
	Indeterminate	2 (2.0)	4 (3.9)		
mMITTE					
	N	90	88		
	Favorable	74 (82.2)	72 (81.8)	0.4	(-11.1, 11.9)
	Unfavorable	14 (15.6)	13 (14.8)		
	Indeterminate	2 (2.2)	3 (3.4)		
ME					
	N	85	76		
	Favorable	72 (84.7)	63 (82.9)	1.8	(-9.7, 13.7)
	Unfavorable	13 (15.3)	13 (17.1)		

Rates for favourable microbiological outcomes were the same for *S. aureus* (11/15 and 73% per treatment group). However, the rates of favourable microbiological outcomes for *S. pneumoniae* were 34/39 (87%) for ceftaroline and 25/32 (78%) for ceftriaxone, which closely resembled the clinical cure rates.

In both treatment groups and both co-primary populations, the relapse rate at LFU following designation of cure at TOC was less than 3%. In the MITTE population there were 5 relapses following ceftaroline and 2 following ceftriaxone. There were no documented cases of re-infection or recurrence at LFU and no evidence of decreasing susceptibility to ceftaroline while on therapy.

Ancillary analyses

See study P903-08

Summary of main efficacy results

Table 22. Summary of Efficacy for trial P903-06

Title: A Phase 3, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of Ceftaroline Versus Vancomycin plus Aztreonam in Adult Subjects With Complicated Skin and Skin Structure Infection			
Study identifier	P903-06		
Design	This was a Phase 3, multicenter, randomized, double-blind, comparative safety and efficacy study of intravenous (IV) ceftaroline fosamil versus IV vancomycin plus IV aztreonam for 5 to 14 days in adults with cSSSI.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 to 56 days Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Ceftaroline		Ceftaroline fosamil 600mg q12, 5 to 14 days, 353 patients
	Vancomycin plus Aztreonam		Vancomycin 1g q12 plus Aztreonam 1g q12, 5 to 14 days, 349 patients
Endpoints and definitions	Primary endpoint	Clinical response at TOC	Noninferiority in clinical cure rate of ceftaroline treatment compared with that of vancomycin plus aztreonam treatment at the Test-of-Cure (TOC) Visit in co-primary Clinically Evaluable (CE) and Modified Intent-to-Treat (MITT) analysis populations
	Secondary	By-subject micro response at TOC	To evaluate the microbiological success rate at the TOC Visit
	Secondary	Clinical response at EOT	To evaluate the clinical response at the End-of-Therapy (EOT) Visit
Database lock	5/6/08		

Results and Analysis			
Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Modified Intent-to-Treat (MITT) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	351	347
	Clinical cure at TOC (%)	304 (86.6%)	297 (85.6%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate in MITT population	1.0
		95% confidence interval	(-4.2, 6.2)
Analysis description	**Co-primary Analysis**		
Analysis population and time point description	Clinically Evaluable (CE) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	316	300
	Clinical cure at TOC (%)	288 (91.1%)	280 (93.3%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate in CE population	-2.2
		95% confidence interval	(-6.6, 2.1)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Microbiologically Evaluable (ME) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	244	227
	Per-subject microbiologically favourable response at TOC (%)	224 (91.8%)	210 (92.5%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in microbiologically favourable response rate	-0.7
		95% confidence interval	(-5.7, 4.4)

Analysis description	**Secondary analysis**		
Analysis population and time point description	Modified microbiologically intent-to-treat (mMITT) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	271	263
	Per-subject microbiologically favourable response at TOC (%)	234 (86.3%)	220 (83.7%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in microbiologically favourable response rate	2.7
		95% confidence interval	(-3.4, 8.9)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Clinically Evaluable (CE) at end of treatment (EOT) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	316	300
	Clinical cure rate at EOT (%)	298 (94.3%)	282 (94.0%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate	0.3
		95% confidence interval	(-3.5, 4.2)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Modified Intent-to-Treat (MITT) at end of treatment (EOT) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	351	347
	Clinical cure rate at EOT (%)	322 (91.7%)	313 (90.2%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate	1.5
		95% confidence interval	(-2.8, 5.9)

Table 23. Summary of Efficacy for trial P903-07

Title: A Phase 3, Multicenter, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of Ceftaroline Versus Vancomycin plus Aztreonam in Adult Subjects With Complicated Skin and Skin Structure Infection			
Study identifier	P903-07		
Design	This was a Phase 3, multicenter, randomized (1:1), double-blind, comparative safety and efficacy study of intravenous (IV) ceftaroline fosamil versus IV vancomycin plus IV aztreonam for 5 to 14 days in adults with cSSSI.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 to 56 days Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Ceftaroline		Ceftaroline fosamil 600mg q12, 5 to 14 days, 348 patients
	Vancomycin plus Aztreonam		Vancomycin 1g q12 plus Aztreonam 1g q12, 5 to 14 days, 346 patients
Endpoints and definitions	Primary endpoint	Clinical response at TOC	Noninferiority in clinical cure rate of ceftaroline treatment compared with that of vancomycin plus aztreonam treatment at the Test-of-Cure (TOC) Visit in co-primary Clinically Evaluable (CE) and Modified Intent-to-Treat (MITT) analysis populations
	Secondary	By-subject micro response at TOC	To evaluate the microbiological success rate at the TOC Visit
	Secondary	Clinical response at EOT	To evaluate the clinical response at the End-of-Therapy (EOT) Visit
Database lock	5/6/08		

Results and Analysis

Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Modified Intent-to-Treat (MITT) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	342	338
	Clinical cure at TOC (%)	291 (85.1%)	289 (85.5%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate in MITT population	-0.4
		95% confidence interval	(-5.8, 5.0)

Analysis description	**Co-primary Analysis**		
Analysis population and time point description	Clinically Evaluable (CE) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	294	292
	Clinical cure at TOC (%)	271 (92.2%)	269 (92.1%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate in CE population	0.1
		95% confidence interval	(-4.4, 4.5)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Microbiologically Evaluable (ME) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	224	219
	Per-subject microbiologically favourable response at TOC (%)	208 (92.9%)	208 (95.0%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in microbiologically favourable response rate	-2.1
		95% confidence interval	(-6.9, 2.5)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Modified microbiologically intent-to-treat (mMITT) at test of cure (TOC) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	269	259
	Per-subject microbiologically favourable response at TOC (%)	233 (86.6%)	229 (88.4%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in microbiologically favourable response rate	-1.8
		95% confidence interval	(-7.5, 3.9)

Analysis description	**Secondary analysis**		
Analysis population and time point description	Clinically Evaluable (CE) at end of treatment (EOT) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	294	292
	Clinical cure rate at EOT (%)	274 (93.2%)	271 (92.8%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate	0.4
		95% confidence interval	(-3.9, 4.7)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Modified Intent-to-Treat (MITT) at end of treatment (EOT) visit		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Vancomycin plus Aztreonam
	Number of subject	342	338
	Clinical cure rate at EOT (%)	304 (88.9%)	302 (89.3%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Vancomycin plus Aztreonam
		Difference in clinical cure rate	-0.5
		95% confidence interval	(-5.2, 4.3)

Table 24. Summary of Efficacy for trial P903-08

Title: A Phase 3, multi-centre, randomized, double blind comparative study to evaluate the safety and efficacy of ceftaroline versus ceftriaxone, with adjunctive clarithromycin, in the treatment of adult subjects with community acquired pneumonia		
Study identifier	P903-08	
Design	This was a Phase 3, multi-centre, randomized (1:1), double-blind comparative study of intravenous (IV) ceftaroline fosamil versus IV ceftriaxone for 5 to 7 days in adults with CAP	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 to 42 days Not applicable Not applicable
Hypothesis	Non-inferiority	
Treatments groups	Ceftaroline fosamil (Ceftaroline in tables below)	600mg q12h for 5-7 days. 305 randomized. Adjunctive therapy of 2 doses of clarithromycin on day 1
	Ceftriaxone	1g q24h for 5-7 days . 309 randomized. Adjunctive therapy of 2 doses of clarithromycin on day 1.

Endpoints and definitions	Primary endpoint	Clinical response at TOC	Noninferiority in clinical cure rate of ceftaroline treatment compared with ceftriaxone at test of cure (8 to 15 days after last dose of study drug) in co-primary Clinically Evaluable (CE) and Modified Intent-to-Treat (MITT) analysis populations
	Secondary endpoint	Clinical response at EOT	To evaluate clinical response at end of therapy (EOT)
	Secondary Endpoint	By-subject micro response at TOC	To evaluate microbiological success rate at TOC
	Secondary Endpoint	TOC (overall success)	To evaluate overall (clinical and radiographic) success rate at TOC
Database lock	24/7/09		

Results and Analysis

Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Modified Intent to Treat Efficacy – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	291	300
	Clinical cure at TOC (%)	244/291 (83.8%)	233/300 (77.7%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in MITTE population	6.2
		Confidence Interval	(-0.2, 12.6)
Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Clinically Evaluable - TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	224	234
	Clinical cure at TOC (%)	194/224 (86.6%)	183/234 (78.2)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in CE population	8.4
		Confidence Interval	(1.4, 15.4)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Modified Intent to Treat Efficacy - EOT		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	291	300
	Clinical cure at EOT (%)	253 / 291 (86.9)	242/300 (80.7)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in MITTE population	6.3
		Confidence Interval	(0.3, 12.3)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Clinically evaluable - EOT		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	224	234
	Clinical cure at EOT (%)	197 / 224 (87.9)	188 / 234 (80.3)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in CE population	7.6
		Confidence Interval	(0.9, 14.3)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Microbiological Modified Intent to Treat –Efficacy – Micro Response at TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	75	80
	Per-subject microbiologically favourable response at TOC (%)	66 / 75 (88.0)	63 / 80 (78.8)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in microbiologically favourable response rate	9.3
		Confidence Interval	(-2.7, 21.1)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Microbiological Evaluable – Micro Response at TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	69	71
	Per-subject microbiologically favourable response at TOC (%)	62 / 69 (89.9)	56 / 71 (78.9)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in microbiologically favourable response rate	11.0
		Confidence Interval	(-1.2, 23.3)
Analysis description	**Secondary Analysis**		

Analysis population and time point description	Modified Intent to Treat – Efficacy Overall Success Rate – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	291	300
	Overall success Rate at TOC (%)	243 / 291 (83.5)	233 / 300 (77.7)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in overall success rate	5.8
		Confidence Interval	(-0.6, 12.2)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Clinically Evaluable Overall Success Rate – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	224	234
	Overall success Rate at TOC (%)	194 / 224 (86.6)	183 / 234 (78.2)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in overall success rate	8.4
		Confidence Interval	(1.4, 15.4)

Table 25. Summary of Efficacy for trial P903-09

Title: A Phase 3, multi-centre, randomized, double blind comparative study to evaluate the safety and efficacy of ceftaroline versus ceftriaxone, in the treatment of adult subjects with community acquired pneumonia			
Study identifier	P903-09		
Design	This was a Phase 3, multi-centre, randomized (1:1), double-blind comparative study of intravenous (IV) ceftaroline fosamil versus IV ceftriaxone for 5 to 7 days in adults with CAP		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 to 42 days Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Ceftaroline fosamil (Ceftaroline in tables below)		600mg q12h for 5-7 days. 317 randomized.
	Ceftriaxone		1g q24h for 5-7 days . 310 randomized.
Endpoints and definitions	Primary endpoint	Clinical response at TOC	Noninferiority in clinical cure rate of ceftaroline treatment compared with ceftriaxone at test of cure (8 to 15 days after last dose of study drug) in co-primary Clinically Evaluable (CE) and Modified Intent-to-Treat (MITT) analysis populations
	Secondary endpoint	Clinical response at EOT	To evaluate clinical response at End of Therapy

	Secondary Endpoint	By-subject micro response at TOC	To evaluate microbiological success rate at TOC
	Secondary Endpoint	TOC (overall success)	To evaluate overall (clinical and radiographic) success rate at TOC
Database lock	01/06/09		

Results and Analysis

Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Modified Intent to Treat Efficacy – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	289	273
	Clinical cure at TOC (%)	235 / 289 (81.3%)	206 / 273 (75.5%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in MITTE population	5.9
		Confidence Interval	(-1.0, 12.7)
Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Clinically Evaluable – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	235	215
	Clinical cure at TOC (%)	193 / 235 (82.1%)	166 / 215 (77.2)
Effect estimate per comparison	Primary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in CE population	4.9
		Confidence Interval	(-2.5, 12.5)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Modified Intent to Treat Efficacy – EOT		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	289	273
	Clinical cure at EOT (%)	249 / 289 (86.2)	215 / 273 (78.8)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in MITTE population	7.4
		Confidence Interval	(1.1, 13.8)
Analysis description	**Secondary Analysis**		

Analysis population and time point description	Clinically evaluable – EOT		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	235	215
	Clinical cure at EOT (%)	202 / 235 (86.0)	172 / 215 (80.0)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in clinical cure rate in CE population	6.0
		Confidence Interval	(-1.0, 13.0)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Microbiological Modified Intent to Treat –Efficacy – Micro Response at TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	90	88
	Per-subject microbiologically favourable response at TOC (%)	74 /90 (82.2)	72 / 88 (81.8)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in microbiologically favourable response rate	0.4
		Confidence Interval	(-11.1, 11.9)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Microbiological Evaluable – Micro Response at TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	85	76
	Per-subject microbiologically favourable response at TOC (%)	72 / 85 (84.7)	63 /76 (82.9)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in microbiologically favourable response rate	1.8
		Confidence Interval	(-9.7, 13.7)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Modified Intent to Treat – Efficacy Overall Success Rate – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	289	273

	Overall success Rate at TOC (%)	234 / 289 (81.0)	206 / 273 (75.5)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline vs Ceftriaxone
		Difference in overall success rate	5.5
		Confidence Interval	(-1.3, 12.4)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Clinically Evaluable Overall Success Rate – TOC		
Descriptive statistics and estimate variability	Treatment group	Ceftaroline	Ceftriaxone
	Number of subject	235	215
	Overall success Rate at TOC (%)	192 / 235 (81.7)	166 / 215 (77.2)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Ceftaroline - Ceftriaxone
		Difference in overall success rate	4.5
		Confidence Interval	(-3.0, 12.1)

Analysis performed across trials (pooled analyses and meta-analysis)

Analysis performed across *the two Phase 3 cSSTI studies*

There were some differences noted for rates of surgical interventions although the pooled data gave comparable findings between treatments. The majority of patients who underwent relevant incision and drainage were enrolled with abscesses (64.2%). The clinical cure rates amongst patients randomised to ceftaroline and vancomycin plus aztreonam in P903-06 and P903-07 combined were comparable within the subset that had relevant incision and drainage (92.3% [203/220] and 94.0% [202/215]), respectively; CE population) and the subset with no relevant incision and drainage (91.3% [356/390] and 92.0% [347/377], respectively; CE population).

For most demographic, medical history and current disease variables the treatment groups were generally comparable across the two studies. In particular, approximatively 30% had a fever and about one third had an elevated WBC at baseline while just < 25% had SIRS. A review of the literature showed that in fact these rates were not so very different from those reported from some other studies in cSSTI within the last decade.

Further exploration of the incidence of fever, elevated WBC and SIRS according to those who did and did not receive prior antibacterial therapy within 2 days of randomisation showed that among the 528 total patients who received prior antibacterial agents 22.3% met the fever criteria vs. 34.7% of those without. In contrast 25.4% who had received prior agents met the SIRS criteria at baseline vs. 21.6% without and raised WBC (cut-off 10,000 cells/mm3) was present in 40.7% vs. 33.5%, respectively.

In each study and treatment group the rates of fever at baseline were lower (by 20-30 percentage points) in those had received prior antibacterial therapy vs. those with no prior therapy within 2 days. However, those who had received prior therapy did not have lower rates of SIRS or raised WBC and, if anything, rates were slightly higher.

The rates of pathogen isolation suggested relatively more MSSA in 07 and MRSA in 06. The available data on PVL status of *S. aureus* isolates in the ME population revealed that 44.6% (161/361) were PVL

positive, of which 101 were MRSA and 60 were MSSA in the ceftaroline-treated group. In the comparator group 43.1% (144/334) were PVL-positive, including 77 MRSA and 68 MSSA. Most MRSA (77%) isolates were from US subjects where 91% were of the USA300 clone (rarely seen otherwise). It followed that 83% of the US MRSA were of SCCmec type IV but MRSA from other regions were distributed among SCCmec types 1-IV. Major abscess was the predominant type of infection among US subjects.

The pooled analyses showed that clinical and microbiological response rates were over 90% for MSSA and MRSA and regardless of the presence of PVL-encoding genes in both treatment groups. When the data were additionally analysed by type of infection there was some indication that cure rates for MRSA were slightly lower than for MSSA at some locations but the same pattern usually applied to both treatments.

MICs of ceftaroline were 0.06 to 0.5 mg/L for MSSA and 0.25 to 2 mg/L for MRSA. The MICs of ceftaroline for haemolytic streptococci were very low. There was no relationship detected between MIC and outcomes. The cure rates in the co-primary populations were comparable across studies as well as treatment groups with approx. 86% MITT and approx. 92% CE subjects cured at TOC. At this visit more than 40% had complete resolution of signs and symptoms (with closely comparable rates between treatments) while the rest had improved such that no further antibacterial therapy was deemed necessary. Cure rates showed relatively small differences according to lesion type and location. An analysis of outcomes according to co-morbid conditions showed some small numerical differences but these variably favoured ceftaroline or comparative therapy.

The pooled data underlined that the highest cure rates were reported from Russia and Ukraine and the lowest in Latin America. The effect of results from Poland was seen for the pooled comparison of EU data between treatments with cure rates of 89% for ceftaroline and 94.7% for comparator. Nevertheless, EU cure rates after removing data from the Polish site gave rates of 92.9% and 95.1% in respective treatment groups. In the US, where most subjects were enrolled, the cure rates were 80.5% vs. 76.3% (MITT) and 89.6% vs. 88.3% (CE).

Outcomes according to subject characteristics showed a small numerical difference in the ceftaroline group only with lower cure rates for those aged over 65 years and of female gender but there did not seem to be any negative effect of prior failure or prior systemic use on responses to ceftaroline.

Pooled rates (CE) according to baseline indicators of severity (see below) showed some small numerical differences that were almost consistently in favour of comparative treatment. There could be many possible factors involved and further exploratory analyses did not lead to any definitive conclusions since the numbers in the subgroups were often small.

The CART analysis suggested that a PK/PD target of 55% T>MIC (free-drug) was significantly associated with per-subject microbiological response of monomicrobial or polymicrobial *S. aureus* infections. However, only 7/431 subjects with *S. aureus* infections had free-drug %T>MIC values less than the CART-derived threshold of 55% so there is high model uncertainty.

Analysis performed across the two *Phase 3 CAP studies*

Due to the treatment regimen imposed there were less than 30 US subjects enrolled at a single study site in the entire CAP development programme. The majority of subjects were enrolled in EU countries (42-47% per study/treatment group) or in other European countries, among which the applicant counts Russia and Ukraine (36-38% per study/treatment group). The summary of severity at enrolment based on various parameters, some of which were calculated retrospectively suggests that generally comparable populations were enrolled into the two studies. The actual cure rates were very

comparable for each treatment across the two studies, suggesting that giving clarithromycin on day 1 in study 08 did not have a major effect on outcomes for either treatment. The analyses of outcomes for those who did and did not have evidence of additional atypical pathogens supported this conclusion. However, the clinical failure rates for ceftaroline were lower in study 08 in both co-primary populations whereas this pattern was not observed for ceftriaxone. Pooled outcomes by demographics and risk classes reflected the individual study data already shown.

Classifying subjects according to the ATS severe CAP criteria showed CE population cure rates of 82% vs. 71% for who did and 85% vs. 81% for those who did not meet the criteria. Rates were 84% vs. 76% for those meeting the SIRS criteria and 86% vs. 83% for those who did not. In contrast, cure rates were not notably different between treatments for those with hypoxia at baseline (78% vs. 75%), structural lung disease (78% vs. 76%), pleural effusion (68% vs. 66%; note rates for those without effusion were 88% vs. 81%) or multilobar pneumonia (78% vs. 76%).

For current smokers cure rates were 87% for ceftaroline (n=119) and 66% for ceftriaxone (n=105) with rates of 89% vs. 81% for those who had never smoked (>200 per group) but for those who were not current smokers rates the cure were 74% [n=128] and 82% [n=126].

Particularly pertinent are the cure rates according to receipt of systemic antibacterial therapy within the 96 h prior to randomisation. In each study the cure rates in the two primary populations at TOC were comparable (small or no numerical difference) between treatments within the subsets who had received prior treatment. In contrast, cure rates were higher for ceftaroline vs. ceftriaxone in each study and each analysis population among subjects with no prior treatment.

The magnitude of the difference between treatments was greater in study 08 than 09. This reflected the fact that cure rates were lower for subjects with no prior therapy in each study/treatment group with the exception of the ceftaroline group in 08, where cure rates were actually higher in those with no prior therapy in the MITTE and CE populations. While 43-47% per treatment/study had a pathogen there were 26-31% included in the mMITTE populations. Overall S. pneumoniae accounted for 41.7% of patients with a pathogen (24% culture and 18% UAT) while 13/80 cultured were MDRSP (4 ceftaroline and 9 ceftriaxone group). However, all were susceptible to penicillin except for one in a ceftriaxone subject (intermediate). Of the 27 serotypes the most common was serotype 3 (n=8). S. pneumoniae also accounted for 31/43 mMITTE subjects with bacteraemia. The highest MIC observed with ceftaroline was 1 mg/L.

Not surprisingly then no relationship could be detected between MIC and outcomes. The PK/PD target could not be estimated using CART analysis since 91.1% of CAP subjects had estimated %T>MIC ranging from 91.7% to 100% based on unbound drug plasma concentrations. Using the median %T >MIC that resulted in stasis, 1-$\log_{10}$ kill, and 2-$\log_{10}$ kill for the various pathogens examined Monte Carlo simulation was used to determine PTA. The PTA for *S. pneumoniae* (MIC_{90} 0.25 mg/L) was ≥ 99.5% for all PD targets while PTA for MSSA (MIC_{90} 0.25 mg/L) was ≥ 99.9% for all PD targets.

Clinical studies in special populations

There were no clinical studies conducted in special populations. The CHMP asked the applicant during this procedure to further justify the use of 600 mg q12h in obese subjects. The applicant explained that the basic PK properties of ceftaroline suggest that obesity is not likely to alter the disposition of the drug in the body. Clearance of ceftaroline approximates to the GFR and, since renal excretion is the major route of elimination, changes in CrCl may influence the PK of the drug. Ceftaroline has low plasma protein binding (20%) and a relatively small volume of distribution at steady state (Vd,ss) of approximately 16 to 21 L in healthy volunteers, which approximates to the volume of extracellular fluid. On this basis obesity would not be expected to alter the ceftaroline PK, since limited distribution

into adipose tissue can be predicted. In the conducted phase 2/3 studies body weight was not found to be a statistically significant covariate in the population PK analysis. The final population PK model was used to predict the Cmax and AUC of ceftaroline in the phase 3 study patients grouped by BMI.

Most patients did however not have plasma samples, so exposures were based on population mean PK parameters and individual covariates for those patients. The mean steady-state AUC and Cmax values within each of the cSSTI and CAP study populations were comparable between patients of normal weight compared to those that were morbidly obese. Thus, available data suggest that the 600 mg q12h is appropriate for obese patients. There were low numbers of morbidly obese patients (BMI ≥40 kg/m2) in both the CAP and cSSTI studies. There was a suggestion of a lower clinical response to ceftaroline in morbidly obese patients with cSSTI with 10/39 failing vs. 5/38 such patients treated with vancomycin. The clinical response rate was slightly lower in morbidly obese patients with cSSTI in both treatment groups. Since the population PK analysis did not indicate an effect of obesity on exposure to ceftaroline the applicant considered and CHMP agreed that the finding could reflect variability of the response in small subgroups.

Supportive studies

There were no supportive studies conducted.

2.5.3. Discussion on clinical efficacy

cSSTI Studies

The comparator regimen chosen for the cSSTI studies could be accepted by CHMP since the studies aimed (and succeeded) in enrolling a high proportion of subjects with MRSA. Justification for the choice of this comparator was requested by CHMP in the D120 list of questions and the submitted response was deemed acceptable. The routine dose of vancomycin was sufficient although vancomycin levels were not routinely collected, apparently because this would have been inconsistent with local practice in many areas.

The aztreonam dose (1g q12h) is that recommended in the US and is lower than that used in the EU (1g q8h or 2g q12h). Overall, ~6% of comparator subjects did not receive aztreonam and another 53% discontinued aztreonam before completing vancomycin therapy. The evaluation of outcomes according to mono-, poly and mixed Gram-negative pathogens did not reveal any disadvantage for the comparator group and cure rates were very high. Therefore, if the Gram-negative bacteria cultured were contributing to the infection there was no evidence that the aztreonam dose or total regimen was inadequate.

The study population was in keeping with that commonly observed in cSSTI studies, noting that some types of infections (e.g. diabetic foot infections) were not included. About 30% in study 06 and 40% in 07 had a major abscess. An analysis of outcomes after excluding all subjects with abscess demonstrated comparability between treatments. In 06 the cure rates for those with abscess > 5 cm were 65/74 (88%) for ceftaroline and 64/67 (96%) for vancomycin. In 07 the corresponding cure rates were 96/103 (93%) vs. 94/100 (94%). The tabulations of surgical interventions showed that 30-40% of all subjects per group underwent incision and drainage and it was clarified that ~two-thirds of these had an abscess.

The primary analyses indicated non-inferiority for ceftaroline vs. comparative treatment. While there were some imbalances between treatments in terms of numbers of subjects who failed and had indeterminate outcomes the analyses in which all such subjects were counted as failures supported comparability between treatments.

Analyses included a comparison of outcomes in all treated subjects with any pathogen, which demonstrated comparability between treatments. For some individual pathogens the numbers are rather small for interpretation. However, there was no instance of a marked difference between treatments.

The analysis of outcomes according to severity of illness scores (derived by the applicant and based on that of Wilson, 2003) showed that there was a spread of subject numbers across the four categories although the highest numbers were in the lowest score category. Cure rates were broadly comparable across the four categories of subjects and also between treatments within each category.

In this regard, about 30% of subjects had a fever and about one third had an elevated WBC at baseline while < 25% had SIRS. These rates may be lower then reported in some other cSSTI studies conducted in recent years. Further analyses showed that the rate of fever may have been influenced by prior therapy but there was no effect apparent for rates of raised WBC and SIRS.

The analyses of outcomes according to baseline features such as fever, WBC and both of these with or without at least one clinical sign judged to be severe showed some numerical inferiority of cure rates for ceftaroline. It remains possible that a higher dose and/or longer infusion time of ceftaroline may be needed in patients with very severe systemic upset due to differences in PK (e.g. greater Vd).

The retrospective analysis in a FDA-defined sub-population of subject status on study day 3 pointed to some possible advantage for ceftaroline at this early time point but this was not evident based on cure rates at the TOC visit, which were closely comparable between treatments. In particular, the Day 3 response did not seem to be a good predictor of an outcome of failure in either treatment group.

CAP Studies

The study population was appropriate for an intravenous antibacterial agent with the spectrum limitations of ceftaroline. PORT class III-IV subjects would fall into the categories for which initial intravenous treatment would usually be considered but would not require ICU admission. There were some regional differences in cure rates that suggest there was not uniformity of the population enrolled. However, further explorations of the data did not detect a consistent relationship between outcome and proportion of patients meeting the criteria for SIRS, ATS severe pneumonia or PORT risk class. Hence the variations in cure rates that were seen between regions and between countries within each region did not consistently correspond to percentages meeting these sets of criteria.

The two studies employed ceftriaxone 1 g daily as the comparator. No concomitant macrolide was administered in study 09 and only two doses of oral clarithromycin were given in study 08. The two studies demonstrated non-inferiority for ceftaroline vs. ceftriaxone 1 g daily. Cure rates in the co-primary analysis populations were only slightly numerically higher for each treatment in study 08 vs. study 09.

There were several features of the analyses that suggested the possibility that the comparative regimen of 1 g q24h ceftriaxone was inadequate, which would have threatened the validity of the demonstration of non-inferiority. In particular:

- The very consistent lower numerical response rates in the ceftriaxone group could not be explained by the presence of non-susceptible pathogens since subjects with MRSA were not enrolled or were excluded from the analyses and there were very few penicillin-insusceptible strains in the MITTE population. In addition, the information on failures in the ceftriaxone group and the supplementary tabulations of outcomes according to MICs of baseline pathogens did not suggest a relationship between failure and higher MICs.

- There were several instances where the difference in cure rates between treatments was particularly marked for subsets with features suggesting more severe illness compared to subsets without these features (e.g. those who met the ATS severe criteria, those with SIRS) that added to the concern that the ceftriaxone dose was not adequate for the entire study populations.
- The analyses of outcomes according to prior therapy suggested that cure rates were comparable between treatments only when there had been pre-study antibacterial therapy.
- Although the applicant provided PK/PD analyses in support of ceftriaxone 1 g q24h and pointed out the lack of clear evidence for an advantage of 2 g vs. 1 g daily, the results still indicated that the adequacy of the selected comparative regimen for PORT III-IV subjects was questionable.

The current European Respiratory Society (ERS), Infectious Diseases Society of America (IDSA) and ATS guidelines recommend a β-lactam plus a macrolide or fluoroquinolone monotherapy to treat CAP requiring hospitalisation. Ceftriaxone is widely accepted as an appropriate treatment for CAP. The 1 g q24h regimen appears in the prescribing information for ceftriaxone with options to give up to 2-4 g daily in severe infections. In some guidelines the recommended dose for CAP requiring hospitalisation is 2 g q24h or 1 g q24h but with mandated accompanying macrolide.

The lack of concomitant cover for atypical pathogens *per se* might not be so important. Several studies have suggested that cure rates are very high even when specific cover for *C. pneumoniae* or *M. pneumoniae* (based on serological evidence of infection) has not been given. In studies 08 and 09 those thought to have *Legionella* (based on urinary antigen) were to be excluded. However, while the addition of a macrolide is intended to cover atypical pathogens it can also contribute to overall treatment effect of the beta-lactam agent for standard pathogens since resistance rates to this class (e.g. in pneumococci) remain fairly low in many countries.

The most important consideration was whether the non-inferiority conclusion made from the two CAP studies could be considered robust. The applicant pointed out that to not achieve the pre-specified criterion for non-inferiority (LL 95% CI > -10%) based on the ceftaroline cure rates, the ceftriaxone arm cure rates would have needed to be 88% to 90% in study 08 in the MITTE and CE populations, respectively, and 85% in study 09 (both populations). Ceftaroline would have still shown non-inferiority even if the comparator response rate had been 8% to 12% higher than that actually observed. Such response rates would be in the same range as the highest response rates observed with ceftriaxone in published studies and would be higher than expected for PORT risk class III or IV. Thus, the applicant proposed that even a very positive view on the cure rate of ceftriaxone still supported the conclusion of non-inferiority for ceftaroline vs. ceftriaxone for the treatment of CAP in patients with PORT risk class III or IV. On this basis, the demonstration of non-inferiority was accepted by the CHMP.

2.5.4. Conclusions on the clinical efficacy

cSSTI Studies

The primary analyses indicated non-inferiority for ceftaroline vs. comparator in the treatment of cSSTI. While there were some imbalances between treatments in terms of numbers of subjects who failed and had indeterminate outcomes the analyses in which all such subjects were counted as failures supported comparability between treatments. It remains possible that a higher dose and/or longer infusion time of ceftaroline may be needed in patients with very severe systemic upset due to differences in PK (e.g. greater volume of distribution).

CAP Studies

The two studies demonstrated non-inferiority for ceftaroline vs. ceftriaxone 1 g daily. Cure rates in the co-primary analysis populations were only slightly numerically higher for each treatment in study 08 vs. study 09. Although the comparative regimen of 1 g q24h ceftriaxone may not have been the most appropriate, the applicant's argument that even a very positive view on the cure rate of ceftriaxone would still supports the conclusion of non-inferiority for ceftaroline vs. ceftriaxone for the treatment of CAP and on that basis the demonstration of non-inferiority of ceftaroline to ceftriaxone was accepted by the CHMP.

2.6. Clinical safety

The safety population consists of more than 1700 subjects exposed to at least one dose of ceftaroline of which 1470 were treated with ceftaroline for cSSTI or CAP. In the Phase 3 studies 1305 subjects received ceftaroline, including 879 dosed for 5-7 days and 236 for 8-10 days. The mean number of days dosed was 8.4 in cSSTI studies (92.5% completed) and 6.5 in CAP studies (94.1% completed treatment).

Patient exposure

The safety population consists of > 1700 subjects exposed to at least one dose of ceftaroline of which 1470 were treated with ceftaroline for cSSTI or CAP in the 6 Phase 2/3 studies.

- In Phase 1 studies 236 subjects were exposed to ceftaroline across 10 studies. The highest single dose was 2000 mg while the intended therapeutic dose of 600 mg q12h was given for up to 14 days. Most subjects (192/236) received one day of dosing, six ESRD subjects received two doses while 38 received 5-14 days.
- Another 69 subjects were dosed in the NXL104 interaction study and the adolescent PK study.
- In the Phase 2 cSSTI studies 165 subjects received ceftaroline of which 98 were dosed IM and 67 IV. The majority of subjects (120/165) received 5-10 days ceftaroline either IV (45) or IM (75).
- In the Phase 3 studies 1305 subjects received ceftaroline, including 879 dosed for 5-7 days and 236 for 8-10 days. The mean number of days dosed was 8.4 in cSSTI studies (92.5% completed treatment) and 6.5 in CAP studies (94.1% completed treatment).

Adverse events

In Phase 3 studies 46% ceftaroline and 47% pooled comparator subjects reported at least one TEAE with respective treatment group rates of 45% vs. 48% in cSSTI and 47% vs. 46% in CAP studies.

- In the cSSTI pool the most common TEAEs in the ceftaroline group were nausea, headache and diarrhoea. Pruritus was the only TEAE for which rates differed by 2% and this occurred more frequently in the vancomycin group. About 25% subjects per group reported TEAEs of mild intensity while ~4% reported severe TEAEs but no single event predominated in this category.
- In the CAP pool the most common TEAEs in the ceftaroline group were diarrhoea, headache and insomnia and each of these AEs occurred with greater frequency in the ceftaroline group. There were no TEAEs for which rates differed by > 2% between treatment groups. About 25% ceftaroline and 20% vancomycin subjects reported TEAEs of mild intensity while ~7% per group reported severe TEAEs but no single event predominated in this category.

Rates of subjects with at least one TEAEs assessed as related to study drug in the cSSTI pool were 24% for ceftaroline and 26% for vancomycin. The most common TEAEs related to study drug were nausea (3.5% of subjects vs. 3.1%), diarrhoea (3.3% vs. 2.6%), headache (2.5% vs. 2.6%), pruritus (2.3% vs. 6.6%) and generalised pruritus (1.7% vs. 2.8%). In the CAP pool the rates of subjects with at least one TEAE assessed as related to study drug were comparable between ceftaroline and ceftriaxone groups (14.7% vs. 13.2%). The most common TEAEs in both treatment groups were diarrhoea (3.1% vs. 1.5%), phlebitis (2.1% vs. 1.1%) and nausea (1% per group).

In the pooled cSSTI studies the highest subject reporting rates for TEAEs were observed in the US (62% ceftaroline and 69% vancomycin) and the lowest in Europe (EU and non-EU; ~ 28% per treatment group). In the pooled CAP studies the overall TEAE reporting rates were higher than for cSSTI studies. The highest rates were seen for subjects enrolled in Latin America (72% and 68%) and the US (62% vs. 85%; but only 13 were enrolled per treatment group) with lower and generally comparable rates for Europe (EU and non-EU in the range 39-45%) and rates in Asia of ~57% (only 18 and 19 subjects per treatment group).

Table 26: TEAEs occurring in ≥1% of subjects in any treatment group of the phase 3 pool, phase 3 studies for cSSTI and CAP (safety population)

	cSSTI pool (Studies 06, 07)		CAP pool (Studies 08, 09)		Phase 3 pool (Studies 06, 07, 08, 09)	
System organ class/ Preferred term	Ceftaroline (N=692) n (%)	Vancomycin[a] (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n (%)	Ceftaroline (N=1305) n (%)	Pooled comparators (N=1301) n (%)
Subjects with at least 1 TEAE	309 (44.7)	326 (47.5)	288 (47.0)	281 (45.7)	597 (45.7)	607 (46.7)
Gastrointestinal disorders	99 (14.3)	88 (12.8)	74 (12.1)	57 (9.3)	173 (13.3)	145 (11.1)
Diarrhoea	34 (4.9)	26 (3.8)	26 (4.2)	16 (2.6)	60 (4.6)	42 (3.2)
Nausea	41 (5.9)	35 (5.1)	14 (2.3)	14 (2.3)	55 (4.2)	49 (3.8)
Constipation	18 (2.6)	18 (2.6)	9 (1.5)	6 (1.0)	27 (2.1)	24 (1.8)
Vomiting	20 (2.9)	18 (2.6)	7 (1.1)	2 (0.3)	27 (2.1)	20 (1.5)
Abdominal pain	9 (1.3)	7 (1.0)	5 (0.8)	3 (0.5)	14 (1.1)	10 (0.8)
General disorders and administration site conditions	66 (9.5)	69 (10.1)	25 (4.1)	24 (3.9)	91 (7.0)	93 (7.1)
Pyrexia	9 (1.3)	16 (2.3)	4 (0.7)	5 (0.8)	13 (1.0)	21 (1.6)
Investigations	62 (9.0)	60 (8.7)	34 (5.5)	35 (5.7)	96 (7.4)	95 (7.3)
Blood pressure increased	9 (1.3)	9 (1.3)	5 (0.8)	4 (0.7)	14 (1.1)	13 (1.0)
Alanine aminotransferase increased	8 (1.2)	12 (1.7)	5 (0.8)	6 (1.0)	13 (1.0)	18 (1.4)
Metabolism and nutrition disorders	40 (5.8)	43 (6.3)	33 (5.4)	39 (6.3)	73 (5.6)	82 (6.3)
Hypokalaemia	10 (1.4)	15 (2.2)	14 (2.3)	15 (2.4)	24 (1.8)	30 (2.3)
Nervous system disorders	64 (9.2)	56 (8.2)	31 (5.1)	24 (3.9)	95 (7.3)	80 (6.1)
Headache	36 (5.2)	31 (4.5)	21 (3.4)	9 (1.5)	57 (4.4)	40 (3.1)
Dizziness	14 (2.0)	8 (1.2)	3 (0.5)	2 (0.3)	17 (1.3)	10 (0.8)
Psychiatric disorders	32 (4.6)	31 (4.5)	26 (4.2)	26 (4.2)	58 (4.4)	57 (4.4)
Insomnia	17 (2.5)	17 (2.5)	19 (3.1)	14 (2.3)	36 (2.8)	31 (2.4)
Skin and subcutaneous tissue disorders	75 (10.8)	110 (16.0)	13 (2.1)	13 (2.1)	88 (6.7)	123 (9.5)
Pruritus	24 (3.5)	56 (8.2)	1 (0.2)	3 (0.5)	25 (1.9)	59 (4.5)
Rash	22 (3.2)	17 (2.5)	2 (0.3)	2 (0.3)	24 (1.8)	19 (1.5)
Pruritus generalised	15 (2.2)	19 (2.8)	0	0	15 (1.1)	19 (1.5)
Vascular disorders	28 (4.0)	30 (4.4)	43 (7.0)	37 (6.0)	71 (5.4)	67 (5.1)
Hypertension	9 (1.3)	10 (1.5)	14 (2.3)	16 (2.6)	23 (1.8)	26 (2.0)
Phlebitis	3 (0.4)	5 (0.7)	17 (2.8)	13 (2.1)	20 (1.5)	18 (1.4)

[a] Plus aztreonam.

Note: Table presents events occurring ≥1% in any treatment group for the Phase 3 pool, organized by SOC.

Serious adverse event/deaths/other significant events

There were more deaths in Phase 3 CAP studies (15 [2.4%] ceftaroline and 12 [2%] ceftriaxone) than in cSSTI studies (3 and 0) and a small numerical excess in the ceftaroline group within each pooling, leading to an overall comparison of 18 (1.4%) vs. 12 (0.9%) for the pooled comparators.

The types of SAEs with fatal outcomes were very scattered in nature and no association between type of preceding SAE and treatment group can be discerned from these small numbers.

In the IV ceftaroline Phase 2 study percentages of subjects with at least one SAE were 4.5% ceftaroline and 6.3% vancomycin. SAEs in the ceftaroline group were skin infection, pulmonary oedema and gangrene (assessed as unrelated to study drug).

In the Phase 3 studies, the incidence of SAEs was lower in subjects with cSSTI (4.3% ceftaroline [30] and 4.1% vancomycin [28]) compared to subjects with CAP (11.3% ceftaroline [69] and 11.7% ceftriaxone [72]). The two studies within each indication showed broadly comparable rates for SAEs overall and for individual types of event as far as can be judged given the very scattered nature and hence low numbers of subjects per event. The most common SAEs were related to the illnesses observed in the study population and most were assessed as not related to study drug.

In the cSSTI pool, seven subjects (4 ceftaroline) had SAEs assessed by an Investigator to be related to study drug and in six cases there was premature discontinuation of study drug or study. In the ceftaroline group these cases involved anaphylactic shock, anaphylactoid reaction, hypersensitivity and *Clostridium difficile* colitis. The two cases in the vancomycin group involved hypersensitivity and acute renal failure.

In the CAP pool the most common SAE was pneumonia, which occurred in 9 subjects in each group and all represented worsening or relapse of CAP or onset of nosocomial pneumonia while none was assessed by an investigator as related to study drug. However, there were 9 subjects (3 ceftaroline) who had SAEs assessed by an Investigator to be related to study drug of which 4 (1 ceftaroline) that led to premature discontinuation of study drug or withdrawal from study. The ceftaroline case involved sudden death in a 73-year-old on day 3 with no notable medical history or baseline laboratory or ECG findings. While the investigator considered this was a treatment failure a cardiologist considered that myocardial infarction was a possible explanation.

Laboratory findings

One Phase 1 subject had neutropenia (1.1 x 109/L) on day 11 with ceftaroline 900 mg q12h and NXL104, which recovered by day 12-17. In Phase 2 studies DAGT seroconversion occurred at higher rates in ceftaroline groups (22% vs. 5% and 15% vs. 5% in the two studies). Subjects with on-study conversion to positive DAGT results did not have evidence of haemolytic anaemia.

In each of the Phase 3 cSSTI and CAP pools shifts in haematology parameters up to EOT were generally comparable between treatments. The number of WBC count shifts from normal to low was slightly higher for ceftaroline (4.8% vs. 2.3% in cSSTI; 5.3% vs. 1.6% in CAP) while numbers of subjects with low absolute neutrophil count were 3.1% vs. 3.5% in cSSTI and 4.4% vs. 2.4% in CAP). Rates for shifts from normal to high absolute eosinophil counts occurred in 2.6% and 1.5% in cSSTI studies but there was no difference between treatments in CAP studies (2.6% both groups).

A further exploration of shifts from normal to low WBC in cSSTI studies showed that:

- The lowest WBC count at EOT was 2.44 x 10^3/µL for ceftaroline vs. 2.8 x 10^3/µL for comparators
- Most low WBC counts were just below the lower normal reference range in both treatment groups
- In 4/17 ceftaroline and 3/8 comparative patients a low WBC count was documented prior to EOT. Two of the 4 in the ceftaroline group had a normal WBC count between D0 and EOT.

One ceftaroline and two comparator patients with cSSTI had a first low WBC count on Day 3. The largest difference was seen at Day 7 with more low WBC counts in the ceftaroline group. The WBC

count data were also analysed by each measurement day (i.e. not taking into account the time window around each scheduled visit), which confirmed that the earliest low WBC count occurred on D3 and the initial low WBC count observation ranged from D3-14 for ceftaroline and from D3-11 for vancomycin plus aztreonam.

Review of the differential WBC counts showed that at EOT there were 10 ceftaroline patients with a low neutrophil count (the lowest value was 1270/µL [LLN 1960/µL]). One of the 10 patients also had a low lymphocyte count [580/µL; LLN 800/µL] and one other patient had a low lymphocyte count (750/µL). In the comparative group five patients had a low neutrophil count (the lowest value was 1570/µL) and two had a low lymphocyte count (the lowest value was 460/µL).

A comparable analysis in CAP studies showed that:

- The lowest WBC count at EOT was 2.8 x 10^3/µL for ceftaroline vs. 1.58 x 10^3/µL for ceftriaxone
- The number of ceftaroline patients with WBC counts at EOT < 3.0 x 10^3/µL was slightly higher in the CAP vs. cSSTI population but no clinically relevant low WBC counts occurred
- In 4/13 ceftaroline and 1/4 ceftriaxone patients a prior low WBC count was documented

Among all those with post-baseline shift from normal to low, 4 ceftaroline and one ceftriaxone patients had a first low WBC count on Day 3. The largest difference across treatment groups was seen at Day 7, with more low WBC counts in the ceftaroline group. Analysis of the WBC count data by each measurement day confirmed that the earliest low WBC count in these subjects was on D3 in both treatment groups and the initial low WBC ranged from D3-8 for both treatment groups.

At EOT a low neutrophil count was noted in 8 ceftaroline patients (the lowest value was 1050/µL). One of these also had a low lymphocyte count [740/µL] and a low monocyte count [100/µL; LLN 120/µL]. Another four patients had a low lymphocyte count (the lowest value was 510/µL). Four ceftriaxone patients had a low neutrophil count (the lowest value was 1050/µL) and one also had a low lymphocyte count [270/µL].

In Phase 3 studies a DAGT was to be performed at baseline, EOT and TOC visits. The post-baseline DAGT positivity rates by subject were 11.6% ceftaroline vs. 4.3% vancomycin in the cSSTI studies and 9.8% vs. 4.5% in the CAP studies. There were slightly higher baseline DAGT positivity rates in the ceftaroline groups (4.6% vs. 3.2% cSSTI and 5% vs. 2.7% in CAP). However, in the CAP studies the DAGT conversion rates were 9.4% for ceftaroline vs. 4.3% for ceftriaxone.

Table 27: Potentially clinically significant post-baseline haematology values in phase 2 and 3 for cSSTI and pahse 3 studies for CAP (safety population)

Potentially Clinically Significant Post-Baseline Hematology Values
Phase 2 and Phase 3 Studies for cSSSI
Safety Population

	Phase 2 IM Study (P903-19)		Phase 2 IV Study (P903-03)		Pooled Phase 3 Studies (06, 07)		Pooled IV Studies (03, 06, 07)	
Clinical Laboratory Parameter (Unit) PCS Criterion	Ceftaroline (N=98) n/N1 (%)	Linezolid plus Aztreonam (N=45) n/N1 (%)	Ceftaroline (N=67) n/N1 (%)	Vancomycin plus Aztreonam (N=32) n/N1 (%)	Ceftaroline (N=692) n/N1 (%)	Vancomycin plus Aztreonam (N=686) n/N1 (%)	Ceftaroline (N=759) n/N1 (%)	Vancomycin plus Aztreonam (N=718) n/N1 (%)
Direct Antiglobulin (Coombs)								
Positive	19/ 88 (21.6)	2/ 42 (4.8)	6/ 40 (15.0)	1/ 20 (5.0)	69/ 594 (11.6)	25/ 582 (4.3)	75/ 634 (11.8)	26/ 602 (4.3)

Potentially Clinically Significant Post-Baseline Hematology Values
Phase 3 Studies for CAP
Safety Population

	P903-08		P903-09		Pooled Phase 3 Studies (08, 09)	
Clinical Laboratory Parameter (Unit) PCS Criterion	Ceftaroline (N=298) n/N1 (%)	Ceftriaxone (N=308) n/N1 (%)	Ceftaroline (N=315) n/N1 (%)	Ceftriaxone (N=307) n/N1 (%)	Ceftaroline (N=613) n/N1 (%)	Ceftriaxone (N=615) n/N1 (%)
Direct Antiglobulin (Coombs)						
Positive	28/ 239 (11.7)	14/ 271 (5.2)	23/ 284 (8.1)	10/ 266 (3.8)	51/ 523 (9.8)	24/ 537 (4.5)

The applicant explored the baseline characteristics for those who did and did not show DAGT seroconversion. There were some numerical differences for age, gender, race, BMI and pre-existing renal impairment but due to the relatively low numbers with seroconversion these numerical differences need to be interpreted with caution.

Additional analyses conducted on concomitant drugs and pre-existing medical conditions that could have contributed to DAGT seroconversion did not detect any clustering in the group that seroconverted. A review of subjects who did and did not convert to a positive DAGT did not reveal clinical or laboratory evidence of haemolytic anaemia.

In the Phase 3 cSSTI pool, numbers with shifts from normal at baseline to high at EOT were comparable across treatment group for aPTT, PT and INR. In the Phase 3 CAP a greater number in the ceftaroline group developed a prolonged aPTT (9.3% vs. 4.8%). The percent of subjects who shifted from normal to high prothrombin time (PT) and international normalized ratio (INR) values was also somewhat higher in the ceftaroline group (5.6% vs. 4.2% for INR, 8.9% vs. 7.5% for PT) but the differences were small. Six CAP patients had a shift in aPTT to reach > 1.5 x ULN and all were treated with ceftaroline. One of the six had a prolonged aPTT on more than one evaluation. However, 4 had aPTT values > 150 seconds and two of these patients also had a markedly increased PT (>120 seconds) while one had PT=15.7 sec and the other had a normal PT. In the absence of testing for coagulation deficiencies or inhibitors it is not possible to determine the cause of the prolongations. However, none of the patients had AEs of excessive bleeding.

In both Phase 2 studies four ceftaroline subjects experienced increases of ALT >3×ULN (1 subject) or AST >3×ULN (2 subjects) vs. none for the comparator. The fourth subject experienced AST/ALT >3×ULN to reach 197 U/L and 157 U/L, respectively.

In the Phase 3 cSSTI pool, the number of subjects with liver enzyme shifts from normal at baseline to high at EOT was higher in the comparator group. Similarly, in the Phase 3 CAP pool, the number of subjects with AST, ALT and GGT shifts from normal at baseline to high at EOT was higher in the ceftriaxone group. No subject experienced a SAE or AE representing potential liver injury.

In the Phase 3 cSSTI pool, the percentages with serum creatinine shifts from normal at baseline to high at EOT were 2.3% ceftaroline vs. 1.8% vancomycin) whereas the rates for such shifts was higher for BUN in the vancomycin group (0.5% vs. 2.4%). In the Phase 3 CAP pool the percentage with BUN shifts from normal at baseline to high at EOT was comparable across treatment groups (3.9% and 3.7%) while rates for such shifts in serum creatinine were 3.1% vs. 1.8%. Three in the ceftaroline

group had maximum creatinine values > 3 mg/dL but none had SAEs reported that represent potential renal impairment and two had pre-existing renal impairment.

The patients with elevated creatinine were reviewed in detail. Elevations observed in ceftaroline patients were mostly of a modest degree and most had slightly declined by the time the last sample was obtained. There were no major or consistent differences between the treatment groups.

Safety in special populations

Renal impairment

In Phase 3 the incidence of potential renal impairment TEAEs was 1.5% for ceftaroline and 0.8% for comparators. The most frequently observed TEAEs were blood creatinine increased and renal failure. SAEs occurred in 4 subjects, including 3 in the ceftaroline group with an SAE of renal failure. One of these had considerable renal impairment at baseline, one had onset one week after EOT and the third had multiple underlying conditions and an increase in creatinine on therapy (1.3 mg/dL to 2.4 mg/dL).

Analysis of all non-serious TEAEs of renal failure and/or acute renal failure showed that all subjects had significant co-morbid disease and/or were otherwise at high risk for renal failure. An assessment of the 19 ceftaroline subjects with TEAEs representing potential renal impairment (including the Renal and urinary SOC and Investigations SOC) found that 12 did not have post-baseline renal chemistry findings that met PCS criteria and one had PCS changes only for BUN.

Table 28: Incidence of TEAEs indicating potential renal impairment, phase 3 studies for cSSTI and CAP (safety population)

	cSSTI pool (Studies 06, 07)		CAP pool (Studies 08, 09)		Phase 3 pool (Studies 06, 07, 08, 09)	
System organ class/ Preferred term	Ceftaroline (N=692) n (%)	Vancomycin[a] (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n (%)	Ceftaroline (N=1305) n (%)	Pooled comparators (N=1301) n (%)
Subjects with at least 1 TEAE indicating potential renal impairment	9 (1.3)	5 (0.7)	10 (1.6)	5 (0.8)	19 (1.5)	10 (0.8)
Investigations	7 (1.0)	2 (0.3)	4 (0.7)	3 (0.5)	11 (0.8)	5 (0.4)
Blood creatinine increased	5 (0.7)	2 (0.3)	3 (0.5)	0	8 (0.6)	2 (0.2)
Creatinine renal clearance decreased	3 (0.4)	0	1 (0.2)	3 (0.5)	4 (0.3)	3 (0.2)
Glomerular filtration rate decreased	0	0	1 (0.2)	0	1 (0.1)	0
Renal and urinary disorders	3 (0.4)	3 (0.4)	7 (1.1)	2 (0.3)	10 (0.8)	5 (0.4)
Renal failure	1 (0.1)	0	6 (1.0)	0	7 (0.5)	0
Renal impairment	2 (0.3)	0	0	0	2 (0.2)	0
Renal failure acute	1 (0.1)	3 (0.4)	0	2 (0.3)	1 (0.1)	5 (0.4)
Renal failure chronic	0	0	1 (0.2)	0	1 (0.1)	0

[a] Plus aztreonam.

Hepatic impairment

In Phase 3 studies the overall incidence of any potential liver injury TEAE was low and comparable between treatments (2.5% ceftaroline vs. 3.6%) and between cSSTI and CAP populations. Six of the

potential liver-injury TEAEs were considered SAEs (2 ceftaroline, of which one died). A separate analysis of all non-serious TEAEs found 5 subjects in the ceftaroline group with hepatitis, hepatomegaly or toxic hepatitis. There were no subjects on ceftaroline with data that met potential Hy's law chemistry criteria. Nevertheless, drug-induced liver injury was identified as a potential safety concern and shall be monitored by the applicant as per the agreed pharmacovigilance activities.

Diarrhoea

In the Phase 1 pool, the incidence of diarrhoea in the ceftaroline group was 2.5% (n=6) vs. 2.6% (n=2) for placebo. In Phase 2 studies the rates were 6.1% (n=6) vs. 8.9% (n=4; linezolid) and 4.5% (n=3) vs. 3.1% (n=1; vancomycin). In Phase 3 studies the incidence of diarrhoea was slightly higher in the ceftaroline group (4.5% vs. 3.2%; similar pattern within each indication). One ceftaroline and one ceftriaxone subject had potential treatment-related AAD that resulted in discontinuation. There was no requirement for culture or toxin detection tests. *C. difficile* was identified in a few subjects and reported as colitis for 2 ceftaroline and one vancomycin group subject in cSSTI studies with no cases in CAP studies. One TEAE of *C. difficile* colitis in the ceftaroline group was reported as an SAE and resulted in premature discontinuation.

Subject factors

The overall incidence of TEAEs was higher in female vs. male subjects (by up to 8 percentage points) in both Phase 3 cSSTI and CAP pools with apparent difference within the gastro-intestinal and nervous system disorders SOCs. In the Phase 3 CAP pool, the overall TEAE incidence was comparable across treatment groups for male subjects (44% and 45%) but female subjects showed a higher TEAE incidence in the ceftaroline group (52% and 47%). In the Phase 3 cSSTI pool, the overall TEAE incidence was slightly lower in the ceftaroline vs. vancomycin group for both genders.

The differences between genders were most pronounced among females in the ceftaroline group in the cSSTI pool (22.9% with a TEAE in Gastrointestinal disorders SOC vs. 9.5% male subjects; 14.5% with a TEAE in Nervous system disorders SOC versus 11.7% male subjects). In these SOCs, nausea and headache were the most common TEAEs in women and each occurred at a higher incidence in the ceftaroline vs. comparator group.

In the Phase 3 cSSTI pool the incidence of subjects with at least one TEAE in the ceftaroline group was only slightly higher for those aged ≥ 65 years vs. < 65 years (47.5% vs. 44.1%, respectively) but the older subjects had a lower reporting rate in the vancomycin group (40.8% vs. 49.1%). In the Phase 3 CAP pool the reporting rates were higher for older subjects in both treatment groups.

Differences in rates of TEAEs for SOCs by age ≥ and < 65 years varied. Rates were higher in the older cohort in both treatment groups for the SOCs cardiac disorders (8.6% ceftaroline and 9.7% comparators in subjects ≥ 65 years vs. 3.6% and 2.9% in <65 years), metabolism and nutrition (8.8% and 8.0% vs. 4.2% and 5.5%), respiratory (7.1% and 9.7% vs. 3.9% and 5.7%) and vascular (7.8% and 7.2% vs. 4.4% and 4.2%). However, no clinically important differences in the incidence of individual TEAEs were observed.

In the Phase 3 cSSTI pool, the incidence of TEAEs was higher among the 18% of total subjects with diabetes mellitus (63.1% ceftaroline and 55.8% vancomycin in DM vs. 40.7% and 45.8%, respectively). There were five SOCs where the incidence of TEAEs was higher for ceftaroline vs. comparator among DM subjects but the small denominators limit these comparisons.

Immunological events

For the Phase 1 study pool 10 subjects exposed to ceftaroline and none exposed to placebo had a potential allergic reaction. These included rash (3), pruritus (3), rash maculopapular (2), dermatitis allergic (1), pruritus allergic (1), skin disorder (1), and urticaria (1) and three TEAEs led to discontinuation. Co-administration of ceftaroline with NXL104 was associated with several rash events and two subjects discontinued.

In the Phase 2 IM study, 8 (8.2%) ceftaroline subjects had at least one potential allergic TEAE compared to none in the linezolid group. In the IV study potential allergic reactions occurred in 3 ceftaroline and 4 vancomycin subjects. Most common in the ceftaroline group were pruritus and rash and two of these subjects discontinued.

The incidence of potential allergic reactions was higher in the cSSTI (8.8% ceftaroline and 14.7% comparator) vs. CAP (1.5% and 1.6%) populations but lower overall for ceftaroline vs. vancomycin (5.4% vs. 8.5%) mostly due to pruritus in the vancomycin group. In the cSSTI studies the total rash rates were 4.5% for ceftaroline and 5.4% for vancomycin plus aztreonam. However, the potential allergic reactions to ceftaroline were quite distinct since they were mostly rashes. Overall, the data suggest that there may be an increasing risk of rash the longer ceftaroline is given, which has been observed with other antibacterial agents. However, the total rash rates are still quite low and cannot be regarded as a major concern provided that the full picture of hypersensitivity reactions to ceftaroline is adequately reflected in the SmPC.

Three SAEs in the ceftaroline group (all in cSSTI studies) included hypersensitivity, anaphylactoid reaction and anaphylactic shock, which resulted in discontinuation of drug therapy. Three ceftaroline subjects had potential TEAEs of anaphylaxis. One had onset 15 minutes after the start of the first infusion with systemic signs and symptoms such as facial swelling, bronchospasm and cyanosis. Another had angioedema, a maculopapular pruritic rash that became generalised and a sensation of throat closure. The third had a non-serious TEAE of anaphylactic reaction starting 15 minutes after the start of the third dose but symptoms were atypical and included acute pain, burning, dizziness, pain in chest and facial hyperaemia

Safety related to drug-drug interactions and other interactions

The applicant explored the safety database for TEAEs in Phase 3 study in subjects who took concomitant warfarin, furosemide or one of the three most commonly used concomitant medications (acetylsalicylic acid, paracetamol and metamizole [dipyrone; banned in much of the EU due to risk of agranulocytosis]). In all instances except for metamizole the total AE reporting rates were higher in users vs. non-users but mostly comparable between treatment groups (noting 73% ceftaroline vs. 64% comparators in those who did and 42% vs. 44% in those who did not take furosemide).

Metamizole was taken by 14.6% (381) and TEAE rates were lower in users vs. non-users in both treatment groups (39.8% and 39.0% vs. 46.7% and 48.0%). Further analysis showed that the difference was wholly accounted for by the lower TEAE rate in cSSTI studies that was observed in both treatment groups. In contrast, in the CAP studies the TEAE rates were higher in metamizole users than non-users in both groups. Since the decrease in TEAE rates was noted in only cSSTI studies and it occurred in both treatment groups, it seemed likely that the finding does not represent a drug interaction between ceftaroline and metamizole. There is no plausible explanation for a real effect to occur in only one of cSSTI or CAP studies and the lower rate of TEAEs in subjects treated concomitantly with metamizole was thought likely to be a chance finding.

Discontinuation due to adverse events

In Phase 1 studies 4 subjects exposed to ceftaroline (pruritus, maculopapular rash, urticaria and phlebitis) discontinued due to treatment-related AEs. Two others received ceftaroline plus NXL104 and discontinued due to a generalised rash on days 8 and 9. In the IV Phase 2 cSSTI study 3 (4.5%) in the ceftaroline group discontinued due to gangrene (deemed unrelated), QTc interval prolonged (considered related; QTcB 470 ms baseline, 501 ms day 3 and 468 ms 10 days post EOT) and mononucleosis syndrome (considered related; unproven virologically and more likely due to drug).

In Phase 3 studies the most common TEAEs resulting in premature discontinuation of study drug or withdrawal from study were potential allergic reactions or were linked to the illnesses seen in the population treated (see table 29).

Table 29: TEAEs by discrete category of rash, hypersensitivity or pruritus which led to premature discontinuation of study drug or withdrawal from study in phase 3 studies for cSSTI and CAP

	cSSTI pool (Studies 06, 07)		CAP pool (Studies 08, 09)		Phase 3 pool (Studies 06, 07, 08, 09)	
Preferred term	Ceftaroline (N=692) n (%)	Vancomycin[a] (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n (%)	Ceftaroline (N=1305) n (%)	Pooled comparators (N=1301) n (%)
Subjects with at least 1 potential allergic TEAE	14 (2.0)	22 (3.2)	1 (0.2)	1 (0.2)	15 (1.1)	23 (1.8)
Any rash	7 (1.0)	13 (1.9)	0	0	7 (0.5)	13 (1.0)
Rash	2 (0.3)	4 (0.6)	0	0	2 (0.2)	4 (0.3)
Rash generalised	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
Dermatitis allergic	1 (0.1)	2 (0.3)	0	0	1 (0.1)	2 (0.2)
Rash maculopapular	2 (0.3)	0	0	0	2 (0.2)	0
Erythema	0	5 (0.7)	0	0	0	5 (0.4)
Generalised erythema	0	1 (0.1)	0	0	0	1 (0.1)
Any hypersensitivity	7 (1.0)	9 (1.3)	1 (0.2)	1 (0.2)	8	10 (0.8)
Hypersensitivity	3 (0.4)	6 (0.9)	1 (0.2)	0	4 (0.3)	6 (0.5)
Urticaria	1 (0.1)	2 (0.3)	0	1 (0.2)	1 (0.1)	3 (0.2)
Anaphylactic reaction	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactic shock	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0	0	0	1 (0.1)	0
Infusion site urticaria	0	1 (0.1)	0	0	0	1 (0.1)
Any pruritus	2 (0.3)	6 (0.9)	0	0	2 (0.2)	6 (0.5)
Pruritus	0	3 (0.4)	0	0	0	3 (0.2)
Pruritus generalised	2 (0.3)	3 (0.4)	0	0	2 (0.2)	3 (0.2)

[a] Plus aztreonam.

In the Phase 3 cSSTI pool 27 ceftaroline subjects discontinued prematurely compared to 33 vancomycin subjects while in 17 (4 severe) and 24 (3 severe) subjects in respective groups the TEAEs were considered to be treatment-related. In ceftaroline subjects the four severe related TEAEs included hypersensitivity, *C. difficile* colitis, anaphylactoid reaction and anaphylactic shock.

In the Phase 3 CAP pool 27 (4.4%) subjects in the ceftaroline group and 25 (4.1%) in the ceftriaxone group had at least one TEAE that resulted in premature discontinuation of study drug or withdrawal from study, including 2 and 3 in respective groups with pneumonia. Five subjects (2 and 3 in respective treatment groups) had related TEAEs that were assessed by the Investigator as severe. In the ceftaroline group these were cases of sudden death and fatigue.

Including the SAEs, 15 ceftaroline and 23 comparator subjects had a potential allergic reaction considered related to study drug (with 2 exceptions in the comparator group) that led to discontinuation. Almost all cases occurred in the cSSTI studies.

Post marketing experience

At the time of filing this application ceftaroline was approved only in the US. Ceftaroline was launched in the US in January 2011 and post-marketing safety data became available during the assessment period. As of 17 June 2011 there had been 17 AEs reported from 14 patients. The most frequently reported event was rash (7 reports). All other AEs were reported only once and each occurred in different subjects. There were two SAEs of malignant lung neoplasm and anaemia/worsening cellulitis.

2.6.1. Discussion on clinical safety

Including the SAEs, 15 ceftaroline and 23 comparator subjects had a potential allergic reaction considered related to study drug (with 2 exceptions in the comparator group) that led to discontinuation. However, almost all cases occurred in the cSSTI studies, in which ceftaroline was administered for longer than in CAP studies. This suggests that the risk of a hypersensitivity reaction concerning rash or pruritus increases with duration of exposure to ceftaroline.

The direct antiglobulin test positivity rates were higher with ceftaroline and, specifically, higher than observed with the cephalosporin comparator in CAP studies. The total safety database was deemed too small to draw any conclusions regarding the possible associated risk of haemolytic anaemia although no such risk has been detected thus far.

Further exploration of imbalances in white blood cells count shifts from normal to low and coagulation test shifts (especially for aPTT) did not reveal any obvious explanations for the observations of higher rates with ceftaroline. Thus far these changes have not been associated with bleeding events.

The available post-marketing safety data are still very limited but rash has predominated thus far.

2.6.2. Conclusions on the clinical safety

The CHMP agreed that overall the safety profile of ceftaroline does not currently give rise to any major concerns. The several issues needing careful follow-up (*C.difficile* associated diarrhoea, hypersensitivity/anaphylaxis, surveillance of bacterial resistance development, convulsions/seizures, potential drug-induced liver injury, haemolytic anaemia, renal impairment) are reflected in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, version from , which included a risk minimisation plan. The RMP was deemed to be comprehensive and of good quality by CHMP. The actions proposed were considered broadly proportionate to the risks associated with ceftaroline, most of which are recognized across the cephalosporin class.

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Important identified risks		
***Clostridium difficile* associated diarrhoea**	RPVA Signal management, evaluation, and review APVA Add to adverse event of special interest KUR list	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftaroline fosamil and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftaroline fosamil (see section 4.8). In such circumstance, the discontinuation of therapy with ceftaroline fosamil and the use of supportive measures together with the administration of specific treatment for Clostridium difficile should be considered.* Section 4.8, Undesirable effects of the SmPC lists the following terms: *Clostridium difficile colitis (see section 4.4)* *Diarrhoea*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Hypersensitivity / Anaphylaxis	RPVA Signal management, evaluation, and review APVA Add Anaphylaxis to adverse event of special interest KUR list	RRMA Section 4.3, Contraindications of the SmPC contains the following statements: *Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.* *Hypersensitivity to the cephalosporin class of antibacterials.* *Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems)* Section 4.4, Special warnings and precautions for use of the SmPC contains the following statements: *Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 and 4.8).* *Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftaroline fosamil. Zinforo is contraindicated in patients with a history of hypersensitivity to cephalosporins. In addition, it is contraindicated in patients with a history of an immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (see section 4.3). Zinforo should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or carbapenems.* *If a severe allergic reaction occurs during treatment with Zinforo, the medicinal product should be discontinued and appropriate measures taken.* Section 4.8, Undesirable effects of the SmPC lists the following terms: *Rash* *Pruritus* *Anaphylaxis (see sections 4.3 and 4.4)* *Hypersensitivity (e.g. urticaria, lip and face swelling) (see sections 4.3 and 4.4)*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Important potential risks		
Bacterial resistance development	RPVA Signal management, evaluation, and review Standard topic for discussion in PSUR	RRMA Section 4.1 Theurapeutic indications of the SmPC containsthe following statement: Consideration should be given to official guidance on the appropriate use of antibacterial agents.
	APVA Add to adverse event of special interest KUR list Resistance tracking programme Microbiologist participation in pre-SERM/SERM process Targeted follow-up lack of effect questionnaire for spontaneous reports - to determine need for expedited reporting.	Section 5.1, Pharmacodynamic properties of the SmPC contains susceptibility information by microorganism and also the following statement: *Resistance* *Ceftaroline is not active against strains of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-beta-lactamases or class C (AmpC) cephalosporinases. Organisms that express these enzymes and which are therefore resistant to ceftaroline and occur at very variable rates between countries and between healthcare facilities within countries. If ceftaroline is commenced before susceptibility test results are available then local information on the risk of encountering organisms that express these enzymes should be taken into consideration. Resistance may also be mediated by bacterial impermeability or drug efflux pump mechanisms. One or more of these mechanisms may co-exist in a single bacterial isolate.*
	Due to strict inclusion/exclusion criteria and clinical study designs, changes in bacterial resistance patterns will be difficult to track; therefore, efforts to monitor for such patterns will be reserved for the post-approval setting.	Product labels will provide information concerning non-susceptible organisms and instructions for proper use in an attempt to limit bacterial resistance development; however, ceftaroline resistance patterns beyond what is known presently, will not become apparent until after the launch of the product. Until such time, development of resistance will remain an important potential risk rather than an identified risk.

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Convulsions / Seizures	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Add to adverse event of special interest KUR list Targeted follow-up questionnaire/intake mechanism for proposed phase III CAP Asia-Pacific study D3720C00002 and post-marketing reports	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statements: *Patients with pre-existing seizure disorder* *Seizures have occurred in toxicology studies at 7-25 times human ceftaroline Cmax levels (see section 5.3). Clinical study experience with ceftaroline fosamil in patients with pre-existing seizure disorders is very limited. Therefore, Zinforo should be used with caution in this patient population.*
Drug induced liver injury	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Add to adverse event of special interest KUR list Targeted follow-up questionnaire/intake mechanism for proposed phase III CAP Asia-Pacific study D3720C00002 and post-marketing reports	RRMA Section 4.8, Undesirable effects of the SmPC lists the following terms: *Increased transaminases*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Haemolytic anaemia	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Add to adverse event of special interest KUR list Targeted follow-up questionnaire/intake mechanism for proposed phase III CAP Asia-Pacific study D3720C00002 and post-marketing reports (see Annex 7) Haptoglobulin and reticulocyte tests added to proposed phase III studies D3720C00002 and D3720C00001	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia* *The development of a positive direct antiglobulin test (DAGT) may occur during treatment with cephalosporins. The incidence of DAGT seroconversion in patients receiving ceftaroline fosamil was 10.7% in the pooled pivotal studies. In clinical studies there was no evidence of haemolysis in patients who developed a positive DAGT on treatment. However, the possibility that haemolytic anaemia may occur in association with cephalosporins including Zinforo treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Zinforo should be investigated for this possibility.* Section 4.8, Undesirable effects of the SmPC lists the following terms: *Coombs Direct Test Positive (see section 4.4)* *Anaemia*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Renal impairment (including potential drug interactions with nephrotoxic agents)	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Add to adverse event of special interest KUR list Targeted follow-up questionnaire/intake mechanism for proposed phase III CAP Asia-Pacific study D3720C00002 and post-marketing reports	RRMA Section 4.2, Posology and method of administration of the SmPC contains the following statements: *Renal impairment* *The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 ml/min, as shown below (see sections 4.4 and 5.2).* ***Creatinine clearance (ml/min)*** / ***Dosage regimen*** / ***Frequency*** *> 30 to ≤ 50* / *400 mg intravenously (over 60 minutes)* / *every 12 hours* *There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis (see Section 4.4).* Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Renal impairment* *There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis. Therefore, use of Zinforo is not recommended in these patient populations (see section 5.2).* Section 4.8, Undesirable effects of the SmPC lists the following terms: *Blood creatinine increased* Section 5.2, Pharmacokinetic properties of the SmPC contains the following statement: *Renal impairment* *Dosage adjustment is required in patients with moderate renal impairment (CrCL > 30 to 50 ml/min). There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and ESRD, including patients undergoing haemodialysis.*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Off-label use	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Literature reports of off-label use will be reviewed Proposed Paediatric Investigation Plan efficacy / safety studies Targeted follow-up lack of effect questionnaire inquires about pathogen and susceptibility.- for healthcare professionals (see Annex 7) Resistance surveillance programme - programme may also include isolates from other infection types and therefore explore off-label use.	RRMA Section 4.1, Therapeutic indications of the SmPC contains the following statements: *Zinforo is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):* *• Complicated skin and soft tissue infections (cSSTI)* *• Community-acquired pneumonia (CAP)* *Consideration should be given to official guidance on the appropriate use of antibacterial agents.* Section 4.2, Posology and method of administration of the SmPC contains the following statements: *For the treatment of cSSTI and CAP, the recommended dose is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older. The recommended treatment duration for cSSTI is 5 to 14 days and the recommended duration of treatment for CAP is 5 to 7 days.* *Paediatric population:* *The safety and efficacy of Zinforo in children aged birth to <18 years have not yet been established. No data are available (see section 5.2)*
Important missing information		

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Asian population exposure	RPVA Signal management, evaluation and review APVA Evaluation of PK data and safety data derived from proposed phase I PK and phase III CAP studies D3720C00005 and D3720C00002 studies, respectively. - Asia Pacific region.	None
Immunocompromised population	RPVA Signal management, evaluation and review APVA Proposed phase III cSSTI study D3720C00001 eligibility includes patients in immunocompromised states unless severely compromised – in development	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Limitations of the clinical data* *There is no experience with ceftaroline in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, those with PORT Risk Class V and/or CAP requiring ventilation at presentation, CAP due to methicillin-resistant S. aureus or patients requiring intensive care. Caution is advised when treating such patients.* *There is no experience with ceftaroline in the treatment of cSSTI in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, necrotizing fasciitis, perirectal abscess and patients with third degree and extensive burns. There is limited experience in treating patients with diabetic foot infections. Caution is advised when treating such patients.*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Lactation	RPVA Signal management , evaluation and review Standard topic for discussion in PSUR	RRMA Section 4.6, Fertility, pregnancy and lactation for use of the SmPC contains the following statement: *Breast-feeding* *It is unknown whether ceftaroline fosamilor ceftaroline is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zinforo therapy taking into account the benefit of therapy for the woman.*
Paediatric population exposure	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR	RRMA Section 4.2, Posology and method of administration of the SmPC contains the following statements: *The safety and efficacy of Zinforo in children aged birth to < 18 years have not yet been established. No data are available (see section 5.2).*
	APVA Evaluation of safety data produced by proposed PIP studies	Section 5.2, Pharmacokinetic properties of the SmPC contains the following statement: *The safety and efficacy of Zinforo in children aged birth to < 18 years have not yet been established.*
Pre-existing seizure disorder	RPVA Signal management, evaluation and review APVA Proposed phase III cSSTI study D3720C00001 eligibility includes patients with pre-existing seizure disorders – in development - AstraZeneca plans to add patients with pre-existing seizure disorders to all subsequent studies moving forward.	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Patients with pre-existing seizure disorder* *Seizures have occurred in toxicology studies at 7-25 times human ceftaroline Cmax levels (see section 5.3). Clinical study experience with ceftaroline fosamil in patients with pre-existing seizure disorders is very limited. Therefore, Zinforo should be used with caution in this patient population.*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Pre-existing severe renal impairment	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Proposed phase III cSSTI study D3720C00001 eligibility includes patients with a CrCl ≥ 20 mL/min Proposed phase I PK study D3720C00012 to determine the appropriate ceftaroline fosamil dosing regimen in patients with end-stage renal disease - in development	RRMA Section 4.2, Posology and method of administration of the SmPC contains the following statements: *Renal impairment* *The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 ml/min, as shown below (see sections 4.4 and 5.2).* ***Creatinine clearance (ml/min)*** / ***Dosage regimen*** / ***Frequency*** *> 30 to ≤ 50* / *400 mg intravenously (over 60 minutes)* / *every 12 hours* *There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis (see Section 4.4).* Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Renal impairment* *There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis. Therefore, use of Zinforo is not recommended in these patient populations (see section 5.2).* Section 4.8, Undesirable effects of the SmPC lists the following terms: *Blood creatinine increased* Section 5.2, Pharmacokinetic properties of the SmPC contains the following statement: *Renal impairment* *Dosage adjustment is required in patients with moderate renal impairment (CrCL > 30 to 50 ml/min). There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and ESRD, including patients undergoing haemodialysis.*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Pre-existing significant hepatic disease	RPVA Signal management, evaluation and review Standard topic for discussion in PSUR APVA Proposed phase III cSSTI studyD3720C00001 eligibility includes patients with pre-existing hepatic impairment unless classified as Child Pugh Stage C - in development	RRMA Section 4.2, Posology and method of administration of the SmPC contains the following statement: *No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2).* Section 4.8, Undesirable effects of the SmPC lists the following terms: *Increased transaminases* Section 5.2, Pharmacokinetic properties of the SmPC contains the following statements: *Biotransformation* *In pooled human liver microsomes, metabolic turnover was low for ceftaroline, indicating that ceftaroline is not metabolised by hepatic P450 enzymes.* *Hepatic impairment* *The pharmacokinetics of ceftaroline in patients with hepatic impairment has not been established. As ceftaroline does not appear to undergo significant hepatic metabolism, the systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairment. Therefore, no dosage adjustment is recommended for patients with hepatic impairment.*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Pregnancy exposure	RPVA Signal management, evaluation and review includes measures to request follow-up on all reports of pregnancy where there has been maternal and/or paternal exposure Standard topic for discussion in PSUR	RRMA Section 4.6, Fertility, pregnancy and lactation for use of the SmPC contains the following statement: *There are no or limited data from the use of ceftaroline fosamil in pregnant women. Animal studies conducted in rat and rabbit do not indicate harmful effects with respect to reproductive toxicity at exposures similar to therapeutic concentrations. Following administration throughout pregnancy and lactation in the rat, there was no effect on pup birth weight or growth, although minor changes in foetal weight and delayed ossification of the interparietial bone were observed when ceftaroline was administered during organogenesis (see section 5.3). .* *As a precautionary measure, it is preferable to avoid the use of Zinforo during pregnancy unless the clinical condition of the woman requires treatment with an antibiotic withZinforo's antibacterial profile*. Section 5.3, Preclinical safety data of the SmPC contains the following statement: *Reproductive toxicology* *Overall, no adverse effects on fertility or post natal development were observed in the rat at up to 5 times the clinical exposure. When ceftaroline was administered during organogenesis, minor changes in foetal weight and delayed ossification of the interparietal bone were observed in the rat at exposures below that observed clinically. However, when ceftaroline was administered throughout pregnancy and lactation, there was no effect on pup weight or growth. Ceftaroline administration to pregnant rabbits resulted in an increased foetal incidence of angulated hyoid alae, a common skeletal variation in rabbit foetuses at exposures similarto those observed clinically.*

Table 30 Summary of the Risk Management Plan

Safety concern	Agreed routine PV activities (RPVA)* - Agreed additional PV activities (APVA)**	Agreed routine risk minimisation activities (RRMA)*** - Product/medical information in the form of the SmPC
Potential for suboptimal dosing in patients with more severe systemic upset	RPVA Signal management, evaluation and review APVA Proposed phase 1 PK studies (D3720C00005 and D3720C00010) and phase III cSSTI study D3720C00001 use of q8h dosing strategy to ensure optimal efficacy - in development.	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Limitations of the clinical data* *There is no experience with ceftaroline in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, those with PORT Risk Class V and/or CAP requiring ventilation at presentation, CAP due to methicillin-resistant S. aureus or patients requiring intensive care. Caution is advised when treating such patients* *There is no experience with ceftaroline in the treatment of cSSTI in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, necrotizing fasciitis, perirectal abscess and patients with third degree and extensive burns. There is limited experience in treating patients with diabetic foot infections. Caution is advised when treating such patients.*
Efficacy in methicillin-resistant *Staphylococcus aureus* (MRSA) community acquired pneumonia	RPVA Signal management, evaluation and review APVA Proposed phase III/IV CAP study in adult (P903-25) and paediatric (P903-24) patients with methicillin resistant *Staphylococcus aureus* (MRSA) to be conducted by licensing partner. - in development	RRMA Section 4.4, Special warnings and precautions for use of the SmPC contains the following statement: *Limitations of the clinical data* *There is no experience with ceftaroline in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, those with PORT Risk Class V and/or CAP requiring ventilation at presentation, CAP due to methicillin-resistant S. aureus or patients requiring intensive care. Caution is advised when treating such patients*.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Table 31: Additional pharmacovigilance measures to be included in the RMP

Description	Due date
The MAH shall provide a dosing recommendation for patients with creatinine clearance <30mL/min following study (D3270C00012) in ESRD after evaluating the PK and safety data derived from the phase 1 PK study D3720C00012 to determine the appropriate ceftaroline fosamil dosing regimen in patients with end stage renal disease.	Final study report to be submitted **by 31 March 2014**
The MAH shall provide results from study D3720C00001. A Phase III, multi-centre, randomised, blinded, comparative study to evaluate the efficacy and safety of ceftaroline fosamil versus intravenous vancomycin plus aztreonam in the treatment of patients with complicated bacterial skin and soft tissue infections	Final study report to be submitted by **30 June 2014**

The importance of the two above mentioned studies resides in the need to generate data which would allow a dosage recommendation in terminally ill renal patients (study D3720C00012) and in immunocompromised patients (study D3720C00001), and ultimately the potential use of the product in these patients.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Ceftaroline was shown to be non-inferior to the selected comparative regimens in two Phase 3 studies in each of cSSTI and CAP. The study populations were adequately representative and the limitations of the populations are reflected in section 4.4 of the SmPC.

Unlike other cephalosporins, ceftaroline is active in preclinical studies (*in vitro* and *in vivo* infection models*)* against MRSA and PNSP due to its ability to bind to the altered PBPs in these organisms that commonly confer non-susceptibility to other beta-lactam agents.

Uncertainty in the knowledge about the beneficial effects

Ceftaroline was evaluated against control regimens in a strictly controlled setting and with a considerable list of exclusion criteria. There remains some doubt regarding the adequacy of the 600 mg BID regimen using 60-min infusion times to treat patients with very severe systemic disturbances that could impact on PK and therefore on PK/PD and ultimately on efficacy. In addition, this regimen is not predicted to cover MRSA that require > 1 mg/L ceftaroline for inhibition and currently perhaps one-fifth to one quarter of strains have MICs above this cut-off. The applicant is undertaking a comparative

study of 600 mg three times dailyin patients with co-morbidities associated with poor outcomes and will also monitor resistance in clinical isolates through a resistance surveillance programme. This is already included in the agreed risk management plan.

Ceftaroline has not been evaluated in patients with severe renal impairment so the appropriate dose in these patients is not established. The applicant will conduct a study in patients with sever renal impairment post-authorisation.

Ceftaroline has also not been studied in patients with hepatic impairment as the major route of elimination is renal.

Patients with diabetic foot infections were excluded from the cSSTI studies though a proportion of patients with diabetes were included so there is limited experience in treating patients with diabetic foot infections.

There is no experience with ceftaroline in the treatment of cSSTI in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, necrotizing fasciitis, perirectal abscess and patients with third degree and extensive burns. The applicant has to generate these data through the conduct of phase III trial D3720C00001 (see table 33. Additional pharmacovigilance measures to be included in the RMP).

Risks

Unfavourable effects

For the most part the safety profile of ceftaroline in the indications studied was comparable with that for the control regimens. As would be expected hypersensitivity reactions have been reported with this beta-lactam agent. There is a suggestion that longer duration of therapy may be associated with an increased risk of some types of allergic reactions. In addition, seroconversion to positive DAGT status has occurred, so far without a link to haemolysis. However, the total safety database is too limited to fully assess the risk.

Uncertainty in the knowledge about the unfavourable effects

As already pointed out, certain imbalances were noted for some types of AEs (gastrointestinal: nausea, diarrhoea (including *C.difficile* diarrhoea), hypersensitivity (pruritus, generalised pruritus, anaphylactoid reaction), headache) in the ceftaroline group vs. comparators These will be kept under review through the agreed pharmacovigilance measures..

Benefit-risk balance

Importance of favourable and unfavourable effects

Efficacy of ceftaroline has been adequately demonstrated in cSSTI and CAP. Unlike other cephalosporins, ceftaroline has demonstrated *in vitro* and *in vivo* activity in the treatment of MRSA and PNSP and so may be effective against a proportion of these organisms. However, clinical experience to date is limited. There are no major concerns regarding the safety of ceftaroline.

Benefit-risk balance

There are no outstanding issues. The applicant has addressed the D180 LoOI and provided reassurance regarding the acceptability of the data following the findings of the GCP inspection. The benefit-risk

balance is concluded to be favourable for CAP and cSSTI.

Discussion on the benefit-risk balance

The data have demonstrated the benefit of ceftaroline in the treatment of patients with cSSTI and CAP although there are some uncertainties whether the benefit is maintained in patients with severe infection (severe sepsis/septic shock, necrotizing fasciitis, perirectal abscess) and patients with third degree and extensive burns. There are also only limited data on the efficacy of ceftaroline against MRSA and PNSP but *in vitro* and *in vivo* data suggest ceftaroline is expected to have clinical activity against these organisms.

In general the safety profile of ceftaroline is good with 'rash' as the main adverse effect in post-marketing experience. There is some suggestion that the risk of hypersensitivity reactions may increase with length of treatment but as ceftaroline is proposed for short courses this does not adversely affect the benefit/risk balance.

Conclusion

The overall benefit-risk of Zinforo is positive for use in cSSTI and CAP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zinforo in the treatment of complicated skin and soft tissue infections (cSSTI) and of community-acquired pneumonia (CAP) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ceftaroline fosamil is qualified as a new active substance.