EMA/659440/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/002252/II/0048

Invented name: Zinforo

International non-proprietary name: ceftaroline fosamil

Marketing authorisation holder (MAH): Pfizer Ireland Pharmaceuticals

Note

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

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List of abbreviations

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
CABP	community-acquired bacterial pneumonia
CAP	community-acquired pneumonia
CE	clinically evaluable
CHMP	committee for medicinal products for human use
CO	clinical overview
CrCl	creatinine clearance
cSSTI	complicated skin and soft tissue infection
EOT	end of treatment
ESBLs	extended spectrum β lactamases
ESRD	end-stage renal disease
EU	European Union
IV	intravenous
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MITTE	modified intent-to-treat efficacy
mMITTE	microbiological modified intent-to-treat efficacy
MRSA	methicillin-resistant *Staphylococcus aureus*
PBP	penicillin-binding proteins
PISP	penicillin-intermediate *Streptococcus pneumoniae*
PK	pharmacokinetics
PM	post-marketing
PORT	Pneumonia Outcomes Research Team
PRSP	penicillin-resistant *Streptococcus pneumoniae*
PT	preferred term
PTA	probability of target attainment
q8hr	every 8 hours
q12h	every 12 hours
q24h	every 24 hours
RSI	reference safety information
SAEs	serious adverse events

SmPC	summary of product characteristics
SOC	system organ class
SP	*Streptococcus pneumoniae*
TEAEs	treatment emergent adverse events
TRAEs	treatment related adverse events
TOC	test-of-cure
US	United States
USPI	United States package insert

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Ireland Pharmaceuticals submitted to the European Medicines Agency on 28 August 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of the indication for the treatment of community acquired pneumonia (CAP) to include concurrent bacteraemia due to *Streptococcus pneumoniae* (SP) for all age groups, based on the results of previously submitted studies: FOCUS 1 (study P903-08) and FOCUS 2 (study P903-09), paediatric CAP study (study P903-31) and relevant post-marketing safety experience with ceftaroline for bacteraemic *Streptococcus pneumoniae* CAP. As a consequence sections 4.1 and 5.1 of the SmPC are proposed to be updated.

No RMP has been provided within this application.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on Paediatric requirements

The development of this product has complied with all measures in the agreed paediatric investigation plan PIP P/0176/2018. All studies in the agreed paediatric investigation plan PIP P/0176/2018 were conducted after the entry into force of that Regulation, the Summary of Product Characteristics reflects the results of studies conducted in compliance with this agreed paediatric investigation plan.

In accordance with Article 23a of Regulation (EC) No 1234/2008, this statement indicating compliance with the agreed completed paediatric investigation plan PIP P/0176/2018 is included in the technical dossier.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of the indication for the treatment of community acquired pneumonia (CAP) to include concurrent bacteraemia due to *Streptococcus pneumoniae* (SP) for all age groups, based on the results of previously submitted studies: FOCUS 1 (study P903-08) and FOCUS 2 (study P903-09), paediatric CAP study (study P903-31) and relevant post-marketing safety experience with ceftaroline for bacteraemic *Streptococcus pneumoniae* CAP.

☒ is not recommended for approval.

The CHMP is of the opinion that the current product information supports the use of Zinforo in the treatment of patients with CSTTI / CAP with concurrent bacteraemia. Following assessment, the CHMP however does not consider that the sub-analysis data submitted by MAH provides further scientific value or guidance to prescribers to justify the proposed amendment of the product information.

The MAH is therefore invited to an oral explanation to further justify how the data submitted supports the proposed amendments to the product information, particularly given that the current indication, together with information in Section 4.4 on any safety concerns and the current information in 5.1, is considered by the CHMP to adequately support the use of Zinforo in a broad indication which does not exclude bacteraemia.

Having taken note of the CHMP position, the MAH took the decision on 30/11/2020 to withdraw the application.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are not recommended at this stage.

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

The CHMP is of the opinion that the current product information supports the use of Zinforo in the treatment of patients with CSTTI / CAP with concurrent bacteraemia. Having taken note of the CHMP position, the MAH took the decision on 30/11/2020 to withdraw the application.

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'

4. Scientific discussion

4.1. Introduction

The most common causative agent of community acquired pneumonia (CAP) in adults and children is *S. pneumoniae* which causes about half of the cases. The usual pathomechanism of CAP is microaspiration that leads to pneumococcal colonisation of the nasopharynx. In rare cases, pneumococci can invade from nasopharynx to bloodstream and thus cause bacteraemia together with pneumonia (sometimes referred to as invasive pneumonia).

Pneumococcal disease occurs at all ages, but incidence rates show a steep rise, in particular after 70 years of age. Another but smaller peak occurs at age below 2 years (*D. Weycker 2010*)[11]. Whether invasive pneumonia has worse outcome than non-invasive pneumonia is less clear. Some studies report on short-term mortality in adults (i.e. in-hospital or 30-day mortality) of non-invasive pneumococcal pneumonia varying from 5 to 13% and of invasive pneumonia from 13 to 21% (*S.P. van Mens2015[12]; S.H. Lin, 2011[13]*). However, there are also studies that have not seen differences in outcome regardless whether pneumococcal CAP is accompanied by bacteraemia or not (*Cristin Q. Fritz 2019)[14]*. Risk factors for a fatal outcome include high age and presence of underlying conditions such as chronic cardiovascular, lung, liver or kidney disease (*A.J. van Hoek2012).*

The prevalence of invasive pneumonia in children is low and ranges between 1.1% to 7.1% (it was 5.1% in a recent meta-analysis (Tam et. al. *2015*)[16]. The rates of invasive pneumococcal pneumonia in adults have been higher than in children. Of all CAP in adults, around 20–30% is invasive pneumococcal pneumonia while 70–80% is non-invasive (*D.S. Fedson, 2013), M.A. Said, 2013; C.H.van Werkhoven, 2016*). Non-invasive pneumococcal pneumonia is usually diagnosed by a positive lower respiratory tract culture, or a positive urinary antigen test (UAT) for *S. pneumoniae* in the absence of a positive blood culture while for invasive pneumonia positive blood culture is required.

British Thoracic Society (BTS), Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) and European guidelines recommend combined treatment with a beta-lactam plus a macrolide for CAP requiring hospital admission (*W.S. Lim, 2009; M. Woodhead 2011*). The beneficial effect of combined therapy was reviewed in a meta-analysis published in 2014, and authors concluded that from observational studies the addition of a macrolide might reduce the mortality risk of patients with CAP. Nevertheless, a recent cluster-randomised, crossover trial with strategies rotated in 4-month periods (beta-lactam, beta-lactam plus macrolide or fluoroquinolone), concluded that beta-lactam monotherapy for CAP requiring hospital admission was not inferior to other strategies regarding 90-day mortality. Therefore, the debate about the need for combined treatment in patients with CAP is still open, particularly for those with moderate to severe CAP. There are no specific guidelines for treatment of invasive pneumococcal disease including CAP with bacteraemia but combination rather than monotherapy with beta-lactam and macrolide is recommended especially in severe cases based on expert opinion (*Domínguez-Alegría AR, Pintado V, Barbolla I. RevClinEsp.2018; 218:244-252*).

The current label of ceftaroline fosamil states that Zinforo is indicated for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia in neonates, infants, children, adolescents and adults. This indication is broad; and both invasive (with bacteraemia) and non-invasive CAP caused by any microorganisms are already covered.

4.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

4.2.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) has been submitted. This is justified by the applicant as Zinforo is already approved in the EU for the treatment of CAP and is currently being used by CAP patients with concurrent bacteraemia due to *Streptococcus pneumoniae*. As existing CAP patients with concurrent bacteraemia due to *Streptococcus pneumoniae* are currently being treated with Zinforo, no increase in use is expected upon approval, therefore no environmental risk assessment is provided in this Type II variation for Zinforo. This justification is acceptable.

4.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of ceftaroline fosamil.

No new non-clinical data have been submitted in this application, which is considered acceptable.

4.3. Clinical aspects

4.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

4.3.2. Clinical pharmacology

No new clinical pharmacology data are submitted that impact the benefit/risk profile of ceftaroline fosamil.

4.4. Clinical efficacy

Ceftaroline fosamil was approved for use in adults for the treatment of cSSTI and CAP in the EU (Zinforo) in August 2012. Approval in neonates (birth to < 2 months) for the same 2 indications was granted in the EU in July 2019. Use of high dose ceftaroline fosamil in adolescents and adults for the treatment of cSSTI known or suspected to be caused by *Staphylococcus aureus* with a ceftaroline MIC of 2 or 4 mg/L was approved in February 2017. Approval for paediatric patients for the same dose and condition was granted in the EU in July 2019.

The original clinical development program for ceftaroline focused on patients with cSSTI and CAP. No new studies have been submitted. The extension of the indication to include bacteraemic SP (*Streptococcus pneumoniae*) CAP is based on:

- Analysis of efficacy and safety data for a subpopulation of adult patients with bacteraemic SP CAP from two Phase 3, multicentre, randomised, double-blind, comparative studies with ceftaroline versus ceftriaxone: Study P903-08 and Study P903-09.
- A descriptive summary of efficacy and safety data for bacteraemic SP CAP patients aged 2 months to < 18 years from one paediatric CAP study: Study P903-31.

- Relevant post-marketing (PM) safety experience with ceftaroline for CAP with SP bacteraemia.

The data provided to support the extension of the indication are aligned with the communication received from the Committee for Medicinal Products for Human Use (CHMP) (meeting date: 28 January 2015) (Zinforo Pre-submission Meeting Minutes).

Table 5.4.1 Summary of Ceftaroline Clinical Studies for CAP with SP bacteraemia

Study ID Phase Locations	Study Dates	Primary Study Objectives	Study Design	Study Drug Details	No. Subjects Randomized/ completed/ SP bacteraemic CAP[a]	M/F Mean Age (range)	Diagnosis	Primary Endpoints
P903-08 Phase 3 Argentina, Austria, Brazil, Bulgaria, Estonia, France, Georgia, Germany, Hungary, Lithuania, Malaysia, Poland, Romania, Russia, Serbia, South Africa, Spain, Switzerland, Thailand, Ukraine, US	January 2008 to December 2008	To determine non-inferiority in the clinical cure rate for ceftaroline compared with that for ceftriaxone at TOC (8 to 15 days after EOT) in the CE and MITTE populations in adult patients with CAP.	Multicentre, randomized, double-blind, comparative, efficacy, and safety study	Ceftaroline fosamil: 60-min IV infusions of 600 mg q12h Ceftriaxone: 30-min IV infusions of 1 g q24h 5 to 7 days	Ceftaroline: 305/277/7 Ceftriaxone: 309/283/5 Total: 614/560/12	Ceftaroline: 187/104 61.0 years (20 to 94 years) Ceftriaxone: 191/109 61.2 years (18 to 91 years)	Patients with clinical and radiographic evidence of pneumonia who required IV therapy and hospitalization; PORT risk classes III and IV (note that some patients in PORT risk class II were recruited prior to Protocol Amendment 2; these patients were excluded from the MITTE population).	Clinical cure rate at the TOC visit in the CE and MITTE populations

P903-09 Phase 3 Argentina, Austria, Bulgaria, Chile, Germany, Hungary, India, Latvia, Mexico, Peru, Poland,	July 2007 to August 2008	To determine non-inferiority in the clinical cure rate of ceftaroline compared with that for ceftriaxone at TOC (8 to 15 days after EOT) in CE and	Multicentre, randomized, double-blind, comparative, efficacy, and safety study	Ceftaroline fosamil: 60-min IV infusions of 600 mg q12h Ceftriaxone: 30-min IV infusions of 1 g q24h	Ceftaroline: 317/271/12 Ceftriaxone: 310/246/7 Total: 627/517/19	Ceftaroline: 175/114 60.6 years (18 to 99 years Ceftriaxone: 175/98 62.0 years (18 to 91 years)	Patients with clinical and radiographic evidence of pneumonia who required IV therapy and hospitalization; PORT risk classes III and IV (note that some patients in PORT risk class II were recruited prior to Protocol	Clinical cure rate at the TOC Visit in the CE and MITTE populations
Romania, Russia, Ukraine		MITTE Populations of adult patients with CAP.		5 to 7 days Both groups received oral clarithromycin 500 mg q12h on Day 1			Amendment 2; these patients were excluded from the MITTE population)	

P903-31 Phase 2/3 Argentina, Bulgaria, Georgia, Greece, Hungary, Poland, Spain, Ukraine, US	January 2013 to April 2014	To evaluate the safety and tolerability of ceftaroline versus ceftriaxone in pediatric subjects, ages 2 months to < 18 years, with community-acquired bacterial pneumonia (CABP) requiring hospitalization	Multicenter, randomized, observer-blinded, active-controlled study to evaluate safety, tolerability, PK, and efficacy	Ceftaroline fosamil: 60-min IV infusions q8h Doses: Children ≥ 6 months: 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg Children < 6 months: 8 mg/kg Ceftriaxone: 30-min IV infusion q12h Doses: 75 mg/kg/day up to a maximum of 4 g/day	Ceftaroline: 122/111/2 Ceftriaxone: 39/35/2 Total: 161/146/4	Ceftaroline: 56/51 4.26 years (0.2 to 17.0 years) Ceftriaxone: 19/17 3.98 years (0.4 to 16.0 years)	Male and female subjects 2 months to < 18 years of age, with clinical evidence of CAP requiring hospitalization and IV antibacterial therapy, and at least 1 of the following: organism consistent with a typical respiratory pathogen identified or isolated from a respiratory or blood culture, leukocytosis, > 15% immature white blood cells, leukopenia or hypoxemia.	Safety and tolerability of ceftaroline versus ceftriaxone in pediatric subjects, ages 2 months to < 18 years

4.4.1. Dose response study(ies)

NA

4.4.2. Main study(ies)

The primary objective in the main studies (P903-08 and P903-09) was the demonstration of non-inferiority of ceftaroline to ceftriaxone in patients with CAP in the primary efficacy endpoint of clinical cure rate at the Test-of-Cure (TOC) Visit in the modified intent-to-treat efficacy (MITTE) and CE Populations. These two Phase 3 studies are used for integrated analysis to support the submission of a Type II variation for the addition of concurrent bacteraemia in CAP due to *S. pneumoniae* (SP) in adults to the SmPC. The MAH presented comparison and post-hoc analyses results across these studies. In the analysis conducted for this submission, patients were classified as having bacteraemic SP CAP or non-bacteraemic SP CAP and were presented by individual studies and overall. Analysis of efficacy data for ceftaroline in the treatment of bacteraemic SP CAP was performed on a subpopulation of bacteraemic (N=31) and non-bacteraemic SP CAP patients (N=139) from these 2 Phase 3 studies to support the characterisation of efficacy for ceftaroline in the treatment of CAP.

In addition, the MAH presented data of bacteraemic SP CAP patients from paediatric (age 2 months to 18 years) Phase 2/3 Study P903-31. Because of the limited number of patients and differences in adult and paediatric study design, the paediatric study was not integrated with the other studies.

Study No P903-08 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

Ceftaroline for injection at a dose of 600 mg administered as a 1-hr IV infusion q12h for 5-7 days was non-inferior to ceftriaxone in the treatment of CABP caused by susceptible isolates of the following microorganisms: *S. aureus, Haemophilus influenzae, H. parainfluenzae, Klebsiella pneumoniae,* and *Escherichia coli*.

Altogether 57 patients had infection caused or suspected to be caused by *S. pneumoniae* of whom 12 patients were bacteraemic and were included into present analysis; 7 of them were treated with ceftaroline; 45 SP CAP patients were non-bacteraemic.

Study No P903-09 a Phase 3, Multicenter, 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

Altogether, 82 patients had infection caused or suspected to be caused by *S. pneumoniae* of whom 19 patients were bacteraemic and were included into present analysis; 12 of them were treated with ceftaroline; 63 SP CAP patients were non-bacteraemic.

Study P903-31 (Paediatric) a Phase 2/3, Multicenter, Randomized, Observer Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone in Pediatric Subjects With Community-acquired Bacterial Pneumonia Requiring Hospitalization

Altogether 33 patients had infection caused or suspected to be caused by *S. pneumoniae* of whom 4 were bacteraemic; 2 received ceftaroline and another 2 patients received ceftriaxone.

Assessor's comment

S. pneumoniae was not listed by the MAH in the summary of any of the adult studies referred to above, although S. pneumoniae is the most important susceptible microorganism. The MAH also applies for the extension of the indication to include concurrent bacteraemia due to S. pneumoniae. However, current CAP indication in the SmPC is nonspecific and does not in any way exclude treatment of patients with bacteraemia. Therefore the aim of this line extension is unclear.

The current and applied indication does not cover treatment of pneumococcocal bacteraemia (included into invasive pneumococcal disease). However, pneumococcal bacteraemia may also occur without identified source, especially in paediatric population. Still it may occur together with suspected pneumonia however no data are presented for this indication.

In study P903-31, only 2 bacteraemic paediatric patients were included, the number clearly insufficient to draw conclusions.

The applicant presents and discusses data for bacteraemic CAP but not necessarily for bacteraemia with CAP.

5.4.2.1 P903-08 and P903-09 integrated analysis

Methods

The general study design and population for studies **P903-08 and P903-09** were similar, and these studies were integrated for analysis.

These were a Phase 3 multinational, multicentre, randomised, double blinded studies that enrolled adult patients with CAP and employed the same methodology. The studies were identical in design, population, inclusion/exclusion criteria, comparator, and dosing regimens, with one exception - Study P903-08 included a brief initial course of oral clarithromycin (starting on Day 1 following randomisation) for both treatment groups at an approved dosage (500 mg q12h for a total of 2 doses) as adjunctive therapy to provide initial coverage against "atypical" pathogens".

Both studies compared ceftaroline to ceftriaxone for 5 to 7 days. According to the protocol, blood cultures were recommended to be obtained at baseline and repeated if the previous blood culture was positive or if medically indicated (Day 1, Day 2; Day 3; Days 4-6; EOT; TOC and LFU). Blood for culture was not obtained at the TOC visit if the subject was deemed a failure at the EOT visit.

<u>Study P903-08</u>

*S. pneumoniae was t*he most commonly isolated pathogen (57/155, 36.8%) in the mMITTE population. Among the *S. pneumoniae* isolates, MDRSP (defined as resistance to two or more classes of antibiotics, including penicillin, macrolides, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim/sulfamethoxazole, and second generation cephalosporins), was rare (two in ceftaroline group and one in ceftriaxone group) and no PRSP was identified according to CLSI 2008 breakpoints for non-meningeal pneumococcal infections. Approximately 65% of *S. pneumoniae* were identified with the urinary antigen test for *S. pneumoniae,* and some of these were positive on culture*.* Of those positive by respiratory or blood culture, approximately 30% had a positive streptococcal urinary antigen. A wide distribution of *S. pneumoniae* serotypes was identified.

Overall approximately 11% (17/155) of subjects in this population had bacteraemia at baseline in both treatment groups. The most commonly isolated pathogen from blood culture was *S. pneumoniae* (12/155, 70.6%).

Study P903-09

Approximately 75% of subjects in the mMITTE population had growth of at least one typical pathogen from a respiratory specimen, 15% from blood, and approximately 24% from pneumococcal urinary antigen testing. The most commonly isolated pathogen was *S. pneumoniae* (82/178, 46.1%). Among the *S. pneumoniae* isolates, ten (2 in the ceftaroline group and 8 in the ceftriaxone group) were identified as MDRSP and no PRSP were identified according to CLSI 2008 breakpoints for non-meningeal pneumococcal infections. A wide distribution of *S. pneumoniae* serotypes was identified. No serotype was found in more than 4 subjects in each treatment group. Approximately 50% of *S. pneumoniae* were identified with the urinary antigen test for *S. pneumoniae* and some of these were positive by culture. Of those positive by respiratory or blood culture, approximately 25% had a positive streptococcal urinary antigen. A higher percentage of subjects in the ceftaroline group had bacteraemia, 16.7% (15/90) compared with the ceftriaxone group 12.5% (11/88). The most commonly isolated pathogen from blood culture was *S. pneumoniae* (19/178, 73.0%).

In the analysis conducted for this submission, patients were classified as having bacteraemic SP CAP (e.g. those with positive blood cultures) or non-bacteraemic SP CAP (e.g. those with negative blood cultures) and were presented by individual studies and overall. No formal statistical hypotheses were tested; evaluation of the data consisted primarily of summary displays (ie, descriptive statistics). Efficacy results are descriptive and limited to small patient numbers.

In order to support the submission of a Type II variation for the addition of concurrent bacteraemia in CAP due to SP to the indication, efficacy data from the mMITTE and ME populations were integrated. No formal statistical hypotheses were conducted for this analysis; evaluation of the data consisted primarily of summary displays (ie, descriptive statistics).

Analysis populations

mMITTE (Microbiological Modified Intent-to-Treat Efficacy) population	All randomised patients who receive any amount of study drug, who were classified as PORT Risk Class III or IV, and who had at least one typical bacterial organism consistent with a CAP pathogen identified from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid).
ME (Microbiologically Evaluable) population	A subset of the clinically evaluable (CE) and mMITTE populations who met minimal disease criteria for CAP and all evaluability criteria, who had at least one "typical" bacterial pathogen that has been isolated from an appropriate microbiological specimen, and including patients 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 patient's outcome.

A descriptive summary of efficacy for bacteraemic SP CAP patients by PORT class score is also included.

A descriptive summary of efficacy data for bacteraemic SP CAP patients from one paediatric CAP study (Study P903-31) is discussed below in section 5.4.2.2.

Assessor's comment

The MAH presents a subgroup analysis of two adult studies with the aim of applying the addition of SP bacteraemia to the approved indication of CAP. No new studies were performed but patients with CAP caused by S. pneumoniae were re-analysed and compared in two groups – those with bacteraemia and those without. The outcome that was compared was that of CAP. In two studies there were in total of 31 adult patients and in the paediatric study (discussed separately below, please see section 5.4.2.2) - 4 paediatric patients with bacteraemia. Thus the number of CAP SP bacteraemia patients is very small.

To justify the proposed variation to the indication, the Applicant makes references to minutes of Zinforo COVERS pre-submission Agency Meeting from January 28, 2015 where among other issues advice was also sought on the use of ceftaroline in patients with bacteraemia that occurs in association with, or is suspected to be associated with CAP or cSSTI. The Agency comments were as follows: : "the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections is not intended to be applicable for new or recently approved drugs (like ceftaroline) as this was meant for harmonization of the SmPC for older antibiotics. The guidance is there because certain member states were not willing to remove bacteraemia from their labels. Generally, the CHMP does not like to endorse drugs for use in bacteraemia patients. If an application is made, data need to be split by organism, indication and study. Pivotal data and comparative trial data are key – observational data are not acceptable. It is although acceptable to use data from q8h and q12h and should provide both mMITT and ME. No set number of patients are required; compelling comparative data are important. The indication may be pathogen specific, for example, S. aureus bacteraemia associated with a cSSTI. This would be seen as a precedent setting application, CHMP need to very carefully evaluate the data and set their decision in context. This would be to ensure that all future approvals for the inclusion of bacteraemia were consistent."

Bacteraemia with only one microorganism (S. pneumoniae) associated with only one indication (CAP) is applied by the MAH to be included to the indication. This is considered to have minimal, if any, clinical relevance. It remains unclear why only S. pneumoniae bacteraemia is applied for and other causative microorganisms (i.e S. aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, and Escherichia coli) are not. Furthermore as mentioned above, current label already covers S. pneumoniae bacteraemia that is associated with CAP because label does not specify whether patients with bacteraemia should be treated or not.

Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections states the following regarding non-pathogen-specific bacteraemia: „It may be possible to accumulate sufficient clinical data to support an indication for use of an antibacterial agent in the treatment of bacteraemia that is associated with specific types of infection, with or without restriction to certain pathogens. For example, in the case of agents that have been in use for many years and are indicated for use in a broad range of infections the total evidence may be considered sufficient for an indication that reads. Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above (i.e. referring to the list of indications approved). If no concern arises from review of the subset with accompanying bacteraemia then no statement is made about use in such patients in the SmPC except to mention the limited experience. If the antibacterial agent has been evaluated in several indications and the total number of bacteraemic patients treated across these indications is deemed sufficient (e.g. ~50 or more) to support a conclusion that efficacy is comparable to that in other patients or, at least, comparable to that of other treatments, then the addition of the sentence could be considered appropriate." The context of this recommendation has been discussed above (in the Agency advice from the pre-submission meeting).

Study participants

This was a post-hoc analysis. The patients were classified as having bacteraemic SP CAP (total n=31, 19 on ceftaroline, 12 on ceftriaxone) or non-bacteraemic SP CAP (n=108). In addition there were 4 paediatric patients with SP CAP (2 in each treatment arm).

Efficacy of ceftaroline in the treatment of bacteraemic SP CAP was evaluated in a pooled subpopulation from two previously submitted adult studies (Studies P903-08 and P903-09).

Assessor's comment

The MAH has assessed only bacteraemic S. pneumoniae CAP patients and compared them to the non-bacteraemic SP CAP patients. Thus, the evaluation covers only bacteraemia of one microorganism in one site of infection. All patients had confirmed CAP and there were no patients with suspected CAP. The number of bacteraemic SP CAP patients on ceftaroline in pooled analyses was very low – only 19 patients received ceftaroline. The total number of patients with bacteraemia was smaller than suggested by guidance documents (n=31 vs n>50). It is the assessors` understanding that number of bacteraemic patients was not predefined.

Treatments

In studies P903-08 and P903-09 subjects were randomly assigned to receive either IV ceftaroline fosamil or IV ceftriaxone for 5 to 7 days for CAP. The 600-mg q12h dose of ceftaroline fosamil administered over 1 hour was divided into two 300-mg doses administered over 30 minutes in order to preserve the blind, as ceftriaxone was to be administered as a 1-g dose administered over 30 minutes q24h. In the ceftriaxone group, placebo was administered to match Infusion 2 of the first daily dose and Infusions 1 and 2 of the second daily dose of ceftaroline fosamil.

Ceftaroline fosamil dosing regimens could be adjusted to 400 mg q12h for subjects with moderate renal impairment. The ceftriaxone dose did not require adjustment for mild or moderate renal impairment.

In both treatment groups in study P903-08, two doses of oral clarithromycin (500 mg) q12h (± 2 hours), defined as adjunctive therapy, were administered on Study Day 1 with study drug therapy. Subjects may have received a single dose of clarithromycin if hospitalised in the evening of Study Day 1.

At any time, the dose of ceftaroline fosamil (including the initial dose) could be adjusted by unblinded pharmacy staff or unblinded study staff.

Table 5.4.2.1 Study Drug Dosing Overview (Standard/Adjusted for Renal Impairment)

Treatment Group	***First Daily Dose***		***Second Daily Dose***	
	Infusion 1 *30 (± 10) min*	*Infusion 2* *30 (± 10) min*	*Infusion 1* *30 (± 10) min*	*Infusion 2* *30 (± 10) min*
Ceftaroline	Ceftaroline fosamil (300 mg/200 mg)	Ceftaroline fosamil (300 mg/200 mg)	Ceftaroline fosamil (300 mg/200 mg)	Ceftaroline fosamil (300 mg/200 mg)
Ceftriaxone	Ceftriaxone (1 g)	Placebo	Placebo	Placebo

The ceftaroline fosamil dosing regimen for paediatric patients in study P903-31 was based on age and weight and administered q12h (standard dosing) or q8h as a 60-minute infusion.

Ceftaroline fosamil

Children ≥ 6 months: 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg q8h

Children 2 to < 6 months: 8 mg/kg q8h

Ceftriaxone: 30-min IV infusion q12h; Doses: 75 mg/kg/day up to a maximum of 4 g/day

Assessor's comment

The current guidelines by IDSA recommend a β-lactam (eg, a 3rd-generation cephalosporin) plus macrolide in combination for treatment of inpatient patients with CAP. Ceftriaxone is recommended to be given once or twice daily. In addition, ceftriaxone and ceftaroline are both cephalosporins with similar antibacterial spectrum, the choice of comparator is suitable. The doses correspond to those suggested in guidelines. There are no specific recommendations for patients with bacteraemic SP pneumonia.

Objectives of the subpopulation analysis (bacteraemic SP CAP patients)

This post-hoc sub-analysis aimed to evaluate efficacy in patients with SP bacteraemic CAP in the mMITTE and ME population. The primary analysis was the clinical response rate at test-of-cure (TOC).

Outcomes/endpoints

Clinical cure rate of CAP in patients with SP bacteraemic CAP vs non-bacteraemic CAP at the TOC visit in the mMITTE and ME population.

Clinical cure - total resolution of all signs and symptoms of the baseline CAP or improvement to such an extent that further antimicrobial therapy was not necessary.

Subgroup analysis on clinical response rate at TOC was performed by PORT class (III and IV).

Blood for culture were recommended to be obtained at baseline; repeat blood for culture was obtained if the previous blood culture was positive or if medically indicated (Day 1, Day 2; Day 3; Days 4-6; EOT; TOC and LFU). Blood for culture was not obtained at the TOC visit if the subject was deemed a failure at the EOT visit.

Per-Pathogen Microbiological Response

A microbiological outcome at the TOC visit was determined in the mMITTE and ME populations for each pathogen isolated at baseline. Microbiological outcome categories at TOC are eradication, presumed eradication, persistence, presumed persistence, and indeterminate. Favourable microbiological outcomes are eradication or presumed eradication. Unfavourable microbiological outcomes are persistence or presumed persistence.

Table 5.4.2.2 Microbiological Outcome Categories at TOC

Outcome[1]	Definition
Eradication	An appropriate source specimen[2] demonstrated absence of the original baseline pathogen
Presumed eradication	An appropriate source specimen was not available to culture, and the subject was assessed as a clinical cure
Persistence	Appropriate source specimen demonstrates continued presence of the original baseline pathogen
Presumed persistence	An appropriate source specimen was not available to culture and the subject was assessed as a clinical failure
Indeterminate	An appropriate source specimen was not available to culture and the subject's clinical response was assessed as indeterminate

Per-Subject Microbiological Response

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

Assessor's comment

The subgroup analysis of bacteraemic and non-bacteraemic SP CAP patients from two previously submitted Phase 3 studies was performed to evaluate the efficacy of ceftaroline versus ceftriaxone, in the treatment of bacteraemic SP CAP. The outcome of this analysis included the assessment of clinical cure of CAP. The MAH has not provided microbiological data in terms of resolution of bacteraemia for this submission. The MAH should clarify the microbiological outcome of the bacteraemic patients (the eradication day, incl Day 1, Day 2; Day 3; Days 4-6; EOT; TOC or LFU) and specify the meaning of "Presumed eradication" (only clinical cure or eradication before TOC already) ***(OC).***

Sample size

In the analysis conducted for this submission, patients were classified as having bacteraemic SP CAP or non-bacteraemic SP CAP and were presented by individual adult studies P903-08 and P903-09 and overall. No formal statistical hypotheses were conducted; evaluation of the data consisted primarily of summary displays (i.e., descriptive statistics). Efficacy results are descriptive and limited by small patient numbers: 31 adult patients from 2 studies overall (19 of them in ceftaroline group). Of the 139 SP CAP patients included in this pooled analysis, 31 (22.3%) had associated bacteraemia. The proportion of patients with bacteraemia was comparable between the two studies, with a higher proportion in the ceftaroline-treatment groups.

Table 5.4.2.3 Number of All Patients with *Streptococcus pneumoniae* Associated with Bacteraemia by Each Study in the mMITTE Population

Study	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Overall n/N (%)
Study P903_08 (Focus 1)	7/27 (25.9)	5/30 (16.7)	12/57 (21.1)

Study P903_09 (Focus 2)	12/42 (28.6)	7/40 (17.5)	19/82 (23.2)
Total	19/69 (27.5)	12/70 (17.1)	31/139 (22.3)

Abbreviations: mMITTE = microbiological modified intent-to-treat efficacy; N = number of patients; n = number of subjects in specific category.

Percentages are based on the total number of patients in the treatment group (N).

Table 5.4.2.4. Summary of all subjects with *S. pneumoniae* associated with Bacteraemia by each study - ME population

Study	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Overall n/N (%)
Study P903_08 (Focus 1)	7/24 (29.2)	5/27 (18.5)	12/51 (23.5)
Study P903_09 (Focus 2)	10/39 (25.6)	6/32 (18.8)	16/71 (22.5)
Total	17/63 (27.0)	11/59 (18.6)	28/122 (23.0)

Assessor's comment

Of the 139 Streptococcus pneumoniae CAP patients from studies P903-08 and P903-09 included in the pooled analysis, 31 (22.3%) had associated bacteraemia in mMITTE population.

As mentioned already under the methods section, according to the addendum to the guideline on the evaluation of medicinal products indicated for the treatment of bacterial infection, the suggested total number of bacteraemic patients treated across the indications should be ~50 or more to support a conclusion of efficacy. The MAH has not specified upfront the number of patients with bacteraemic pneumonia in either adult studies; and this could be a reason that the number was lower than suggested in guidelines.

Statistical methods

The data are purely descriptive and no formal statistical tests could be applied.

No formal statistical hypotheses were conducted; evaluation of the data consisted primarily of summary displays (ie, descriptive statistics).

Results

Baseline data

Of the 139 SP CAP patients included in this pooled analysis, 31 (22.3%) had associated bacteraemia. The proportion of patients with bacteraemia was comparable between the two studies, with a higher proportion in the ceftaroline-treatment groups. These proportions were similar for the ME population.

The mMITTE and ME populations overall and by bacteraemia classification were similar with regard to age and gender distribution, with slight differences in some baseline medical history characteristics. There was a higher percentage of patients with CAP SP bacteraemia classified to Port Risk Class IV compared to III (25.8% [III] vs 74.2% [IV] in the mMITTE analysis set); in contrast, in patients with SP CAP without bacteraemia, more were classified to Port Risk Class III (58.3% [III] vs 41.7% [IV]).

The assessment of clinical signs and symptoms in patients with SP bacteraemia and no SP bacteraemia by treatment group in the mMITTE analysis set are presented Table 5.4.2.7.

Table 5.4.2.5 Demographic Characteristics (mMITTE Analysis Set)

	Bacteraemic SP CAP			**Non-Bacteraemic SP CAP**		
	Ceftaroline	**Ceftriaxone**	**Total**	**Ceftaroline**	**Ceftriaxone**	**Total**
	(N=19)	**(N=12)**	**(N=31)**	**(N=50)**	**(N=58)**	**(N=108)**
Age (years) N	19	12	31	50	58	108
Mean	62.6	60.1	61.6	62.8	62.4	62.6
SD	15.53	15.63	15.36	18.23	14.63	16.32
Median	66	63	64	66	63	65.5
Min, Max	32, 87	25, 87	25, 87	23, 99	21, 89	21, 99
Sex Male	12 (63.2)	10 (83.3)	22 (71.0)	31 (62.0)	37 (63.8)	68 (63.0)
Female	7 (36.8)	2 (16.7)	9 (29.0)	19 (38.0)	21 (36.2)	40 (37.0)
Race White	18 (94.7)	11 (91.7)	29 (93.5)	46 (92.0)	57 (98.3)	103 (95.4)
Black or African American Asian	1 (5.3) 0 (0.0)	1 (8.3) 0 (0.0)	2 (6.5) 0 (0.0)	0 (0.0) 2 (4.0)	1 (1.7) 0 (0.0)	1 (0.9) 2 (1.9)
American Indian or Alaska Native Other	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	1 (2.0) 1 (2.0)	0 (0.0) 0 (0.0)	1 (0.9) 1 (0.9)
PORT Risk Class III	4 (21.1)	4 (33.3)	8 (25.8)	30 (60.0)	33 (56.9)	63 (58.3)
IV	15 (78.9)	8 (66.7)	23 (74.2)	20 (40.0)	25 (43.1)	45 (41.7)

Abbreviations: CAP = community-acquired pneumonia; mMITTE = microbiological modified intent-to- treat efficacy; N = number of patients; PORT = Pneumonia Outcomes Research Team; SD = standard deviation; SP = *Streptococcus pneumoniae*.

Percentages are based on the total number of patients in the treatment group (N). Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Table 5.4.2.6 Demographic Characteristics (ME Analysis Set)

	Bacteraemic SP CAP			**Non-Bacteraemic SP CAP**		
Demographic Characteristic	**Ceftaroline (N=17)**	**Ceftriaxone (N=11)**	**Total (N=28)**	**Ceftaroline (N=46)**	**Ceftriaxone (N=48)**	**Total (N=94)**
Age						
Mean	62.1	58.8	60.8	61.9	61.1	61.5
SD	15.83	15.73	15.59	18.55	14.62	16.57
Median	66	62	64	64	60.5	61
Min, Max	32, 87	25, 87	25, 87	23, 99	21, 89	21, 99
Sex n (%)						
Male	11 (64.7)	10 (90.9)	21 (75.0)	30 (65.2)	28 (58.3)	58 (61.7)
Female	6 (35.3)	1 (9.1)	7 (25.0)	16 (34.8)	20 (41.7)	36 (38.3)
Race n (%)						
White	16 (94.1)	10 (90.9)	26 (92.9)	42 (91.3)	48 (100)	90 (95.7)
Black or African American	1 (5.9)	1 (9.1)	2 (7.1)	0	0	0
Asian	0	0	0	2 (4.3)	0	2 (2.1)
American Indian or Alaska Native	0	0	0	1 (2.2)	0	1 (1.1)
Other	0	0	0	1 (2.2)	0	1 (1.1)
Port Risk Class n (%)						

III	4 (23.5)	4 (36.4)	8 (28.6)	27 (58.7)	28 (58.3)	55 (58.5)
IV	13 (76.5)	7 (63.6)	20 (71.4)	19 (41.3)	20 (41.7)	39 (41.5)

Abbreviations: ME = Microbiologically evaluable; n = Number of patients in the category or analysis; N = Number of patients; SD = Standard deviation; SP = S pneumoniae.

Note: Non-Bacteraemic SP CAP is "No bacteraemia" in the source table.

MIC values for ceftaroline and ceftriaxone were compared between SP isolates collected from bacteraemic and non-bacteraemic SP CAP patients in the mMITTE population. The MIC_{90} was lower for ceftaroline compared to ceftriaxone. Baseline MIC trends were similar for the ME population.

Table 5.4.2.7 Baseline MIC (µg/mL) of SP isolates from FOCUS 1 and FOCUS 2 to Ceftaroline - mMITTE Population

	Bacteraemic SP CAP		**Non-Bacteraemic SP CAP**	
	Ceftaroline	**Ceftriaxone**	**Ceftaroline**	**Ceftriaxone**
Susceptibility				
Number Isolated	19	12	50	58
Number Tested	18	11	21	25
MIC Range	0.015 - 0.015	0.015 - 0.030	0.015 - 0.120	0.015 - 0.120
MIC50	0.015	0.015	0.015	0.015
MIC90	0.015	0.015	0.015	0.060

Number Isolated = Count of subjects with non-missing pathogen with missing / non-missing MIC value.

Number Tested = Count of subjects with non-missing pathogen/MIC values.

MIC50 = The minimum inhibitory concentration of the study drug being tested that inhibits 50% of the respective pathogen.

MIC90 = The minimum inhibitory concentration of the study drug being tested that inhibits 90% of the respective pathogen.

Abbreviations: MIC = minimum inhibitory concentration; mMITTE = microbiological modified intent-to-treat efficacy; SP = *Streptococcus pneumoniae*.

Table 5.4.2.8 Baseline MIC (µg/mL) of SP isolates from FOCUS 1 and FOCUS 2 to Ceftriaxone - mMITTE Population

	Bacteraemic SP CAP		**Non-Bacteraemic SP CAP**	
	Ceftaroline	**Ceftriaxone**	**Ceftaroline**	**Ceftriaxone**
Susceptibility				
Number Isolated	19	12	50	58
Number Tested	18	11	21	25
MIC Range	0.015 - 0.060	0.015 - 0.250	0.015 - 1.000	0.015 - 2.000
MIC50	0.015	0.030	0.015	0.015

MIC90	0.030	0.120	0.030	1.000

Number Isolated = Count of subjects with non-missing pathogen with missing / non-missing MIC value.

Number Tested = Count of subjects with non-missing pathogen/MIC values.

MIC50 = The minimum inhibitory concentration of the study drug being tested that inhibits 50% of the respective pathogen.

MIC90 = The minimum inhibitory concentration of the study drug being tested that inhibits 90% of the respective pathogen.

Abbreviations: MIC = minimum inhibitory concentration; mMITTE = microbiological modified intent-to-treat efficacy; SP = *Streptococcus pneumoniae*.

Assessor's comment

All SP strains were susceptible to study antibiotics.

Outcomes and estimation

The results of clinical responses of CAP at TOC for the mMITTE and ME analysis sets were similar. Ceftaroline clinical cure rates were 78.9% and 82.4% in the SP bacteraemic mMITTE and ME analysis sets, respectively and were similar to non-bacteraemic SP CAP. The clinical cure rates in ceftaroline arm were numerically higher than the ceftriaxone arm with no differences in bacteraemic and non-bacteraemic patients (Table 5.4.2.9).

Table 5.4.2.9 Clinical Response at TOC (mMITTE Analysis Set) of studies P903-08 and P903-09

	Bacteraemic SP CAP			Non-Bactaeremic SP CAP		
Clinical response	Ceftaroline	Ceftriaxone	Total	Ceftaroline	Ceftriaxone	Total
P903_08						
N	7	5	12	20	25	45
Clinical cure	6 (85.7)	3 (60.0)	9 (75.0)	18 (90.0)	17 (68.0)	35 (77.8)
Clinical failure	1 (14.3)	2 (40.0)	3 (25.0)	2 (10.0)	8 (32.0)	10 (22.2)
Indeterminate	0	0	0	0	0	0
P903_09						
N	12	7	19	30	33	36
Clinical cure	9 (75.0)	5 (71.4)	14 (73.7)	26 (86.7)	23 (69.7)	49 (77.8)
Clinical failure	2 (16.7)	2 (28.6)	4 (21.1)	4 (13.3)	7 (21.2)	11 (17.5)
Indeterminate	1 (8.3)	0	1 (5.3)	0	3 (9.1)	3 (4.8)
Total						
N	19	12	31	50	58	108

Clinical cure	15 (78.9)	8 (66.7)	23 (74.2)	44 (88.0)	40 (69.0)	84 (77.8)
Clinical failure	3 (15.8)	4 (33.3)	7 (22.6)	6 (12.0)	15 (25.9)	21 (19.4)
Indeterminate	1 (5.3)	0	1 (3.2)	0	3 (5.2)	3 (2.8)

Table 5.4.2.10 Clinical Response at TOC (ME Analysis Set) of studies P903-08 and P903-09

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
Clinical response	Ceftaroline	Ceftriaxone	Total	Ceftaroline	Ceftriaxone	Total
P903_08						
N	7	5	12	17	22	39
Clinical cure	6 (85.7)	3 (60.0)	9 (75.0)	15 (88.2)	15 (68.2)	30 (76.9)
Clinical failure	1 (14.3)	2 (40.0)	3 (25.0)	2 (11.8)	7 (31.8)	9 (23.1)
P903_09						
N	10	6	16	29	26	55
Clinical cure	8 (80.0)	4 (66.7)	12 (75.0)	25 (86.2)	19 (73.1)	44 (80.0)
Clinical failure	2 (20.0)	2 (33.3)	4 (25.0)	4 (13.8)	7 (26.9)	11 (20.0)
Total						
N	17	11	28	46	48	94
Clinical cure	14 (82.4)	7 (63.6)	21 (75.0)	40 (87.0)	34 (70.8)	74 (78.7)
Clinical failure	3 (17.6)	4 (36.4)	7 (25.0)	6 (13.0)	14 (29.2)	20 (21.3)

There was concordance between the microbiological and clinical responses of all patients with SP bacteraemia except for 1 patient. This patient, in the ceftriaxone treatment group, had persistent symptoms at the end of treatment and was considered a clinical failure at the TOC visit. However, blood cultures taken on Study Day 7 were negative, and the patient had a microbiological response of eradication at the TOC visit. Of note most patients had microbiological response as presumed eradication.

Based on the MAH analysis of the subpopulations, ceftaroline was as effective as ceftriaxone in treating patients with both bacteraemic SP CAP and non-bacteraemic SP CAP.

Microbiological response

Table 5.4.2.11 Pooled FOCUS 1(P903_08), FOCUS 2 (P903_09): Listing of per-patient microbiological response at TOC visit in the mMITTE population subjects with Streptococcus pneumoniae bacteraemia

Treatment	SB Micro Response at TOC visit
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftriaxone	Presumed Persistence
Ceftaroline	Presumed Persistence
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftriaxone	Presumed Persistence
Ceftriaxone	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftriaxone	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftriaxone	Presumed Persistence

Treatment	SB Micro Response at TOC visit
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Persistence
Ceftriaxone	Eradication
Ceftaroline	Presumed Eradication
Ceftaroline	Presumed Persistence
Ceftaroline	Presumed Eradication
Ceftaroline	Indeterminate
Ceftaroline	Presumed Eradication

Table 5.4.2.12 Pooled FOCUS 1(P903_08), FOCUS 2 (P903_09): Listing of per-pathogen microbiological response at TOC visit in the mMITTE population subjects with Streptococcus pneumoniae bacteraemia

Treatment	Baseline Organism Name	Pathogen Micro Response at TOC visit
Ceftaroline	Streptococcus pneumoniae	Presumed Eradication
Ceftaroline	Streptococcus pneumoniae	Presumed Eradication
Ceftaroline	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication
Ceftaroline	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Persistence
Ceftaroline	Streptococcus pneumoniae	Presumed Persistence
Ceftaroline	Streptococcus pneumoniae	Presumed Eradication
Ceftaroline	Escherichia coli	Presumed Eradication
	Haemophilus parainfluenzae	Presumed Eradication
	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Enterobacter cloacae	Presumed Persistence
	Klebsiella pneumoniae	Presumed Persistence
	Streptococcus pneumoniae	Presumed Persistence
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication
Ceftaroline	Mycoplasma pneumoniae	
	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication
Ceftaroline	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Mycoplasma pneumoniae	
	Streptococcus pneumoniae	Presumed Eradication
Ceftriaxone	Streptococcus pneumoniae	Presumed Eradication

Assessor's comment

*With the exception of one patient the remaining were marked as "presumed eradication or presumed persistence". This may indicate that no repeated blood cultures were taken in vast majority of cases despite the recommendations given in the protocol. The MAH should clarify this (**OC**). There were 2 patients with infection caused by multiple microorganisms (Table 5.4.2.12). The MAH should clarify whether all these microorganisms were cultured from blood or were they found in different sites **(OC).***

Efficacy results of a subpopulation analysis of patients with bacteraemic SP CAP are descriptive and limited by small patient numbers and on response of CAP. Although the rates of clinical cure in ceftaroline arm tended to be numerically higher than in the ceftriaxone arm for both bacteraemic and non-bacteraemic patient subgroups, the small number of bacteraemic patients does not allow drawing conclusions on this indication. Of note, current CAP indication in the SPC does not exclude treatment of patients with bacteraemia or invasive CAP.

Ancillary analyses

Comparison of Results in Subpopulations

Clinical response at TOC was analysed by Port Class (III and IV). In the mMITTE analysis set, a higher percentage of patients with SP bacteraemia (both treatment groups) were classified as Port Class IV

compared to patients with non-bacteraemic CAP (23 of 31 [74.2%] patients compared to 45 of 108 [41.7%]). This was expected for a scoring system based on severity of illness.

In the mMITTE analysis set, 4 patients (100.0%) in the ceftaroline group in Port Class III had a clinical response of clinical cure at TOC compared favourably to the ceftriaxone treatment group (1/4, 25.0%). Non-bacteraemic SP CAP patients classified to PORT class III within the mMITTE population also had a numerically higher clinical cure in the ceftaroline treatment group (26/30, 86.7%) compared to the ceftriaxone treatment group (24/33, 72.7%). There results were similar for the ME population.

For bacteraemic SP CAP patients in Port Class IV, 11 of 15 (73.3%) in the ceftaroline group had a clinical response of clinical cure compared to the ceftriaxone treatment group (7/8, 87.5%). Non-bacteraemic SP CAP patients classified to PORT class IV within the mMITTE population had a numerically higher clinical cure response in the ceftaroline treatment group (18/20, 90.0%) compared to the ceftriaxone treatment group (16/25, 64.0%). These results were consistent with the ME population however it is noted that there are no SD or any other respective statistical information presented to describe the diffusiveness of the data.

Clinical response at TOC supports that ceftaroline is an effective treatment, even in patients classified to Port Class IV.

Table 5.4.2.13 Clinical Response at TOC (mMITTE Analysis Set) by PORT Class

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
Clinical response	Ceftaroline	Ceftriaxone	Total	Ceftaroline	Ceftriaxone	Total
Port III						
N	4	4	8	30	33	63
Clinical cure	4 (100)	1 (25.0)	5 (62.5)	26 (86.7)	24 (72.7)	50 (79.4)
Clinical failure	0	3 (75.0)	3 (37.5)	4 (13.3)	8 (24.2)	12 (19.0)
Indeterminate	0	0	0	0	1 (3.0)	1 (1.6)
Port IV						
N	15	8	23	20	25	45
Clinical cure	11 (73.3)	7 (87.5)	18 (78.3)	18 (90.0)	16 (64.0)	34 (75.6)
Clinical failure	3 (20.0)	1 (12.5)	4 (17.4)	2 (10.0)	7 (28.0)	9 (20.0)
Indeterminate	1 (6.7)	0	1 (4.3)	0	2 (8.0)	2 (4.4)

Table 5.4.2.14 Clinical Response at TOC in subjects with SP bacteraemia versus no SP bacteraemia in the mMITTE population by PORT Class (III and IV)

Study	Port Class	Clinical Response	Streptococcus pneumoniae Bacteremia			No Streptococcus pneumoniae Bacteremia		
			Ceftaroline	Ceftriaxone	Total	Ceftaroline	Ceftriaxone	Total
Focus 1 (P903_08)	III	n	1	2	3	15	12	27
		Clinical Cure	1 (100.0)	1 (50.0)	2 (66.7)	13 (86.7)	10 (83.3)	23 (85.2)
		Clinical Failure	0	1 (50.0)	1 (33.3)	2 (13.3)	2 (16.7)	4 (14.8)
	IV	n	6	3	9	5	13	18
		Clinical Cure	5 (83.3)	2 (66.7)	7 (77.8)	5 (100.0)	7 (53.8)	12 (66.7)
		Clinical Failure	1 (16.7)	1 (33.3)	2 (22.2)	0	6 (46.2)	6 (33.3)
Focus 2 (P903_09)	III	n	3	2	5	15	21	36
		Clinical Cure	3 (100.0)	0	3 (60.0)	13 (86.7)	14 (66.7)	27 (75.0)
		Clinical Failure	0	2 (100.0)	2 (40.0)	2 (13.3)	6 (28.6)	8 (22.2)
		Indeterminate	0	0	0	0	1 (4.8)	1 (2.8)
	IV	n	9	5	14	15	12	27
		Clinical Cure	6 (66.7)	5 (100.0)	11 (78.6)	13 (86.7)	9 (75.0)	22 (81.5)
		Clinical Failure	2 (22.2)	0	2 (14.3)	2 (13.3)	1 (8.3)	3 (11.1)
		Indeterminate	1 (11.1)	0	1 (7.1)	0	2 (16.7)	2 (7.4)
Total	III	n	4	4	8	30	33	63
		Clinical Cure	4 (100.0)	1 (25.0)	5 (62.5)	26 (86.7)	24 (72.7)	50 (79.4)
		Clinical Failure	0	3 (75.0)	3 (37.5)	4 (13.3)	8 (24.2)	12 (19.0)
		Indeterminate	0	0	0	0	1 (3.0)	1 (1.6)
	IV	n	15	8	23	20	25	45
		Clinical Cure	11 (73.3)	7 (87.5)	18 (78.3)	18 (90.0)	16 (64.0)	34 (75.6)
		Clinical Failure	3 (20.0)	1 (12.5)	4 (17.4)	2 (10.0)	7 (28.0)	9 (20.0)
		Indeterminate	1 (6.7)	0	1 (4.3)	0	2 (8.0)	2 (4.4)

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Table 5.4.2.15 Clinical Response at TOC (ME Analysis Set) by PORT Class

	Bacteraemic SP CAP			**Non-Bacteraemic SP CAP**		
Clinical response	**Ceftaroline**	**Ceftriaxone**	**Total**	**Ceftaroline**	**Ceftriaxone**	**Total**
Port III						
N	4	4	8	27	28	55
Clinical cure	4 (100)	1 (25.0)	5 (62.5)	23 (85.2)	20 (71.4)	43 (78.2)
Clinical failure	0	3 (75.0)	3 (37.5)	4 (14.8)	8 (28.6)	12 (21.8)
Port IV						
N	13	7	20	19	20	39
Clinical cure	10 (76.9)	6 (85.7)	16 (80.0)	17 (89.5)	14 (70.0)	31 (79.5)
Clinical failure	3 (23.1)	1 (14.3)	4 (20.0)	2 (10.5)	6 (30.0)	8 (20.5)

MAH claims that based on the subpopulation analysis, ceftaroline demonstrates high rates of clinical cure in patients with SP CAP, including patients with SP bacteraemia and patients classified to PORT class IV.

Other subgroup analyses using demographic characteristics (such as sex, race, geographic region, baseline disease severity, concomitant medications) were not explored, because the number of patients in the SP bacteraemia subpopulation in both studies was limited.

5.4.2.2 Study P903-31 (Paediatric patients)

Twenty percent of paediatric patients had positive results for *S. pneumoniae*. Respiratory specimens for microbiological testing were obtained from less than 8% of subjects at baseline; this is consistent with the challenge of collecting these samples from children and resulting in low pathogen recovery overall. Blood cultures were obtained from the majority (97.2%) of subjects and the number of positive blood cultures was low (4.2%), again consistent what has been seen in paediatric CAP.

There is limited data on efficacy of ceftaroline in the treatment of paediatric bacteraemic SP CAP patients (age 2 months to 18 years) from Study P903-31. This study had 4 patients with confirmed SP bacteraemia; 2 patients received ceftaroline and 2 patients received ceftriaxone. At TOC, none of these patients in the ceftaroline group were clinically cured compared to 1 patient in the ceftriaxone group.

Further evaluation of the two bacteraemic SP CAP paediatric patients treated with ceftaroline was undertaken.

One patient was a 4-year-old female admitted with a left lower lobe CAP. She was deemed a "Non-Responder" on Study Day 4 based on unstable respiratory rate, though her clinical symptoms showed general improvement. She was continued on ceftaroline until Study Day 8 (16 Jan 2104) when ceftaroline was discontinued due to insufficient therapeutic effect and replaced with oral clarithromycin and IV amoxicillin-clavulanate.

The other patient was a 3-year-old female admitted with severe pleuropneumonia on the left side, atelectasis and vomiting. She was initially treated with ceftaroline and was considered a Responder at Study Day 4. During the first week on study, the subject was severely ill, but her condition was stable. The following weekend, her general condition deteriorated; she was dyspnoeic and required oxygen. An increased volume of pleural fluid was found on ultrasound and chest x-ray revealed atelectasis of her whole left lung, which was compressed by pleural fluid and the mediastinum was shifted to the right. On Study Day 8, the subject received a blood transfusion and a pleural drainage which was effective. The subject completed IV ceftaroline on Study Day 14: however, she still required antibiotics and was switched to amoxicillin-clavulanate. She went on to develop an empyema and required a thoracic surgical procedure (decortication). She ultimately was discharged from the hospital on Study Day 34.

Assessor's comment

Efficacy results are descriptive and limited to small patient numbers, by only one diagnosis (CAP) and one microorganism (S. pneumoniae).

In addition, the paediatric CAP study P903-31 included only 2 patients who received ceftaroline. Neither of these patients in ceftaroline group were clinically cured compared to 1 patient in the ceftriaxone group. The low number of paediatric bacteraemic SP CAP patients is not surprising (Medicine (Baltimore). 2017 Jun; 96(22): e7028)[13] and may reflect the low yield of blood cultures in these patients or it may have occurred by chance.

The overall data is insufficient to conclude that ceftaroline is efficacious in both paediatric and adult bacteraemic SP CAP patients. In addition, the MAH has not provided data on CAP bacteraemia cases caused by other microorganisms.

4.4.3. Conclusions on the clinical efficacy

The MAH presents a type 2 variation to extend marketing authorisation of CAP to bacteraemic SP CAP. The need for this extension is not clear as current indication is broad enough and does not specify whether it is bacteraemic or non-bacteraemic CAP. What is not covered by current indication is pneumococcal bacteraemia without source, the disease that is characteristic for *S. pneumoniae* and is mostly seen in children. It is assessors' understanding that the applicant has not provided sufficient evidence to extend indication to pneumococcal bacteraemia.

The applicant has not conducted specific studies to extend already existing indication to bacteraemic SP CAP. The post-hoc analysis of already submitted data was performed and in total of 31 adult patients and 4 paediatric patients with pneumococcal CAP and bacteraemia were identified and included into this analysis. These patients were compared with those who had pneumococcal pneumonia (mostly defined by urinary antigen test or by sputum cultures) without bacteraemia. The analysis was performed for each study separately and then also as pooled analysis of two adult studies. Paediatric study was analysed separately. There was no formal statistical analysis and the primary endpoint was clinical cure of CAP. According to the protocol the blood cultures had to be taken in all patients at baseline and then repeated in those with positive cultures until cultures turn negative.

The adult studies showed that in terms of main endpoints (clinical cure of CAP in mMITTE population) the response rate was numerically higher in those with non-bacteraemic as compared to bacteraemic-CAP (78.9% vs 88.0% in ceftaroline and 66.7% vs 69.0% in ceftriaxone arm). The response was numerically slightly better in patients treated with ceftaroline as compared to ceftriaxone. Similar trends were seen in ME population. In terms of resolution of bacteraemia vast majority of patients were categorised into presumed eradication category which makes assessor to believe that repeated blood cultures as suggested in the protocol were not taken. The findings that patients with bacteraemic and non-bacteraemic SP CAP have similar response is consistent with recent studies (REF). In terms of PORT classes it was not surprising that number of patients with PORT III was smaller in bacteraemic patients as compared with non-bacteraemic patients. In patients of PORT IV the clinical response was again numerically higher in non-bacteraemic patients treated with ceftaroline while no such differences were observed in those treated with ceftriaxone. Small numbers should be noted, however.

Among paediatric patients only two in ceftaroline group had pneumococcal CAP with bacteraemia and another two were in ceftriaxone group. Both ceftaroline treated patients had clinical outcome assessed as failure. The numbers were too small to consider these results as conclusive.

In conclusion, patients with SP bacteraemic CAP were assessed during the post-hoc analysis in terms of CAP and not on resolution of bacteraemia. These data in 31 patients show that that clinical cure rate was similar in bacteraemic and non-bacteraemic patients with CAP as expected. There is no need to extend or specify current indication of CAP to bacteraemic SP CAP as current indication is broad and unspecific and thus covers non-bacteraemic as well as bacteraemic CAP. Furthermore the data are insufficient to recommend using of ceftaroline in patients with pneumococcal bacteraemia when CAP (or any other site of infection) is suspected. As mentioned above *S. pneumoniae* bacteraemia can also occur without clear source of infection in children and data are too limited to extend indication to pneumococcal bacteraemia.

4.5. Clinical safety

Introduction

This submission presents evidence in support of an extension of indication to include the addition of secondary bacteraemia in community acquired pneumonia (CAP) due to *Streptococcus pneumoniae*

(SP).
This Summary of Clinical Safety (SCS) presents:

- A summary of pooled safety data for a sub-population of adult patients with SP bacteraemia associated with CAP from two Phase 3, multicentre, randomised, double-blind, comparative studies with ceftaroline versus ceftriaxone; FOCUS 1 (Study P903-08) and FOCUS 2 (Study P903-09).
- A descriptive summary of safety data for bacteraemic patients from one paediatric CAP study (Study P903-31)
- Relevant post-marketing (PM) experience with ceftaroline fosamil for CAP with SP bacteraemia

The following points summarise the safety of ceftaroline fosamil for the treatment of secondary bacteraemia in CAP due to SP:

- Ceftaroline fosamil at a dose of 600 mg administered as a 1-hour IV infusion every 12 hours (q12h) for 5 to 7 days is effective and well tolerated in the treatment of CAP with SP bacteraemia.
- There were no new or unexpected safety findings, the safety profile observed in patients with SP bacteraemia associated with CAP being consistent with the known profile for ceftaroline fosamil as therapy for CAP in adults.

Study P903-08 was a Phase 3, multicentre, randomised, double-blind, comparative safety and efficacy study of intravenous (IV) ceftaroline fosamil versus IV ceftriaxone for 5 to 7 days for treatment of adults with CAP. All patients also received two doses of oral adjunctive therapy (clarithromycin) starting on Day 1 following randomisation.

Study P903-09 was a Phase 3, multicentre, randomised, double-blind, comparative safety and efficacy study of IV ceftaroline fosamil versus IV ceftriaxone administered for 5 to 7 days for treatment of adults with CAP.

Safety was evaluated in two pooled subpopulations from the above studies: a subset of the Microbiological Modified Intent-to-Treat Efficacy (mMITTE) population and Microbiologically Evaluable (ME) population, consisting of only those patients with CAP due to SP, with or without concomitant bacteraemia.

- mMITTE population - all randomised patients who receive any amount of study drug, who were classified as PORT Risk Class III or IV, and who had at least one typical bacterial organism consistent with a CAP pathogen identified from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid). Patients with Mycoplasma pneumoniae or Chlamydophila pneumoniae as the sole causative pathogen of infection, and all patients with Legionella pneumophila infection were excluded from the mMITTE population.
- ME population - a subset of the mMITTE subpopulation, who met minimal disease criteria for CAP and all evaluability criteria, including patients 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 patient's outcome. The ME population is a subset of the clinically evaluable (CE) and mMITTE populations and included patients in the CE population who also had at least one "typical" bacterial pathogen that has been isolated from an appropriate microbiological specimen.

The primary objective of the pooled analysis presented in this SCS was to evaluate the safety of ceftaroline in a subpopulation of adult CAP patients with SP bacteraemia.

Patient exposure

Summary statistics for safety data will be provided and are limited by patient numbers.

Safety data were comparable between the mMITTE and ME subpopulations.

Of the 139 pneumococcal CAP patients included in the pooled safety analysis, 31 (22.3%) had associated bacteraemia. The proportion of patients with bacteraemia was comparable between the two studies, with a higher proportion in the ceftaroline-treatment groups. These proportions were comparable for the ME population.

Table 5.5.1. Summary of All Patients with *S. pneumoniae* Associated with Bacteraemia by Each Study in the mMITTE Population

Study	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Overall n/N (%)
Study P903_08 (Focus 1)	7/27 (25.9)	5/30 (16.7)	12/57 (21.1)
Study P903_09 (Focus 2)	12/42 (28.6)	7/40 (17.5)	19/82 (23.2)
Total	19/69 (27.5)	12/70 (17.1)	31/139 (22.3)

Source: Appendix Table 1.1.
Abbreviations: N = number of patients, n = number of subjects in specific category, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population.
Percentages are based on the total number of patients in the treatment group (N).

Exposure to ceftaroline or comparator was comparable between drug treatment groups and between populations with and without bacteraemia, with a median duration of treatment of 7 days.

According to the Table 5.5.2, over 90% of patients received study drug for the protocol-specified 5 to 7 days. Six (6) patients (6/139, 4.3%) received study drug for less than 5 days. The extent of exposure was comparable for the ME subpopulation.

Table 5.5.2. Days on Study Drug in the mMITTE Population for Patients with Bacteraemic SP CAP Versus Non-Bacteraemic SP CAP

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
Days on Study Drug Distribution	**Ceftaroline (N=19)**	**Ceftriaxone (N=12)**	**Total (N=31)**	**Ceftaroline (N=50)**	**Ceftriaxone (N=58)**	**Total (N=108)**
<3	0	0	0	0	1 (1.7)	1 (0.9)
≥3 - <5	1 (5.3)	0	1 (3.2)	1 (2.0)	3 (5.2)	4 (3.7)
≥5 - 8	18 (94.7)	12 (100)	30 (96.8)	49 (98.0)	54 (93.1)	103 (95.4)
>8	0	0	0	0	0	0
Mean	6.84	6.92	6.87	6.70	6.52	6.60
SD	0.96	0.29	0.76	0.81	1.20	1.04
Median	7.00	7.00	7.00	7.00	7.00	7.00
Min, Max	3.0, 8.0	6.0, 7.0	3.0, 8.0	4.0, 8.0	1.0, 8.0	1.0, 8.0
n	19	12	31	50	58	108

Source: Appendix Table 8.1.
Abbreviations: N = number of patients, n = number of subjects in specific category, SD = standard deviation, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Demographic and Other Characteristics of Study Population

Table 5.5.3. Demographic and Baseline Characteristics in the mMITTE Population for Patients with Bacteraemic SP CAP Versus Non-Bacteraemic SP CAP

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
	Ceftaroline (N=19)	Ceftriaxone (N=12)	Total (N=31)	Ceftaroline (N=50)	Ceftriaxone (N=58)	Total (N=108)
Age (years)						
N	19	12	31	50	58	108
Mean	62.6	60.1	61.6	62.8	62.4	62.6
SD	15.53	15.63	15.36	18.23	14.63	16.32
Median	66	63	64	66	63	65.5
Min, Max	32, 87	25, 87	25, 87	23, 99	21, 89	21, 99
Sex						
Male	12 (63.2)	10 (83.3)	22 (71.0)	31 (62.0)	37 (63.8)	68 (63.0)
Female	7 (36.8)	2 (16.7)	9 (29.0)	19 (38.0)	21 (36.2)	40 (37.0)
Race						
White	18 (94.7)	11 (91.7)	29 (93.5)	46 (92.0)	57 (98.3)	103 (95.4)
Black or African American	1 (5.3)	1 (8.3)	2 (6.5)	0 (0.0)	1 (1.7)	1 (0.9)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)	2 (1.9)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.9)
PORT Risk Class						
III	4 (21.1)	4 (33.3)	8 (25.8)	30 (60.0)	33 (56.9)	63 (58.3)
IV	15 (78.9)	8 (66.7)	23 (74.2)	20 (40.0)	25 (43.1)	45 (41.7)

Source: Appendix Table 3.1.
Abbreviations: N = number of patients, SD = standard deviation, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population, PORT = Pneumonia Outcomes Research Team.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Across the mMITTE subpopulation, most patients were male (90/139, 64.7%) and white (132/139, 95.0%) with a median age ranging from 63 to 66 years. Age and race demographics were comparable between bacteraemic and non-bacteraemic populations and between drug treatment groups.

Within the bacteraemic population, there was a lower proportion of males in the ceftaroline treatment group (63.2%) versus the ceftriaxone treatment group (83.3%). Demographic and baseline characteristics were comparable for the ME subpopulation.

Table 5.5.4. Baseline Risk Factors and Markers of Disease Severity Clinical Parameters - mMITTE Population

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
	Ceftaroline (N=19)	Ceftriaxone (N=12)	Total (N=31)	Ceftaroline (N=50)	Ceftriaxone (N=58)	Total (N=108)
Patients with any Relative Medical History	6 (31.6)	5 (41.7)	11 (35.5)	22 (44.0)	31 (53.4)	53 (49.1)
Structural Lung Disease (1)	4 (21.1)	4 (33.3)	8 (25.8)	13 (26.0)	21 (36.2)	34 (31.5)
Gastroesophageal Reflux	2 (10.5)	0	2 (6.5)	3 (6.0)	1 (1.7)	4 (3.7)
Asthma	1 (5.3)	0	1 (3.2)	3 (6.0)	4 (6.9)	7 (6.5)
Chronic Sinusitis	1 (5.3)	0	1 (3.2)	0	1 (1.7)	1 (0.9)
Alcohol Abuse (2)	0	0	0	1 (2.0)	1 (1.7)	2 (1.9)
Prior Pneumonia	4 (21.1)	2 (16.7)	6 (19.4)	7 (14.0)	10 (17.2)	17 (15.7)
Smoking History						
Never Smoked	7 (36.8)	3 (25.0)	10 (32.3)	25 (50.0)	22 (37.9)	47 (43.5)
Smoked	12 (63.2)	9 (75.0)	21 (67.7)	25 (50.0)	36 (62.1)	61 (56.5)
Currently Smoking	5 (26.3)	6 (50.0)	11 (35.5)	18 (36.0)	20 (34.5)	38 (35.2)
CURB						
0	1 (5.3)	1 (8.3)	2 (6.5)	11 (22.0)	7 (12.1)	18 (16.7)
1	8 (42.1)	3 (25.0)	11 (35.5)	23 (46.0)	29 (50.0)	52 (48.1)
2	9 (47.4)	5 (41.7)	14 (45.2)	14 (28.0)	16 (27.6)	30 (27.8)
3	1 (5.3)	3 (25.0)	4 (12.9)	2 (4.0)	6 (10.3)	8 (7.4)
4	0	0	0	0	0	0
n (non-missing)	19 (100.0)	12 (100.0)	31 (100.0)	50 (100.0)	58 (100.0)	108 (100.0)
Mean (SD)	1.5 (0.70)	1.8 (0.94)	1.6 (0.80)	1.1 (0.81)	1.4 (0.83)	1.3 (0.82)
Median	2.0	2.0	2.0	1.0	1.0	1.0
Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0
CURB-65						
0	0	1 (8.3)	1 (3.2)	5 (10.0)	2 (3.4)	7 (6.5)
1	3 (15.8)	2 (16.7)	5 (16.1)	15 (30.0)	19 (32.8)	34 (31.5)
2	13 (68.4)	4 (33.3)	17 (54.8)	21 (42.0)	25 (43.1)	46 (42.6)
3	2 (10.5)	3 (25.0)	5 (16.1)	9 (18.0)	10 (17.2)	19 (17.6)
4	1 (5.3)	2 (16.7)	3 (9.7)	0	2 (3.4)	2 (1.9)
5	0	0	0	0	0	0
n (non-missing)	19 (100.0)	12 (100.0)	31 (100.0)	50 (100.0)	58 (100.0)	108 (100.0)
Mean (SD)	2.1 (0.71)	2.3 (1.22)	2.1 (0.92)	1.7 (0.89)	1.8 (0.87)	1.8 (0.88)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, Max	1.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 3.0	0.0, 4.0	0.0, 4.0
Pulmonary Infiltrate Status						
None	0	0	0	0	0	0
One Lobe	15 (78.9)	9 (75.0)	24 (77.4)	36 (72.0)	40 (69.0)	76 (70.4)
Multi Lobes	4 (21.1)	3 (25.0)	7 (22.6)	14 (28.0)	18 (31.0)	32 (29.6)
Pleural Effusion						
Yes	3 (15.8)	4 (33.3)	7 (22.6)	12 (24.0)	9 (15.5)	21 (19.4)
No	16 (84.2)	8 (66.7)	24 (77.4)	38 (76.0)	49 (84.5)	87 (80.6)
Co-Morbid Conditions						
Baseline Renal Status (based on CrCl (mL/min))						
Normal (>80)	5 (26.3)	2 (16.7)	7 (22.6)	19 (38.0)	19 (32.8)	38 (35.2)
Mild (50 <CrCl ≤80)	8 (42.1)	4 (33.3)	12 (38.7)	17 (34.0)	26 (44.8)	43 (39.8)
Moderate (30 <CrCl ≤50)	6 (31.6)	6 (50.0)	12 (38.7)	11 (22.0)	12 (20.7)	23 (21.3)
Severe (≤30)	0	0	0	3 (6.0)	1 (1.7)	4 (3.7)
Hypoxia and/or Fever						
Hypoxia (PaO_2 <60 or O_2 sat <90%)	4 (21.1)	1 (8.3)	5 (16.1)	8 (16.0)	12 (20.7)	20 (18.5)
Fever	7 (36.8)	5 (41.7)	12 (38.7)	15 (30.0)	15 (25.9)	30 (27.8)
Both Hypoxia and Fever	2 (10.5)	3 (25.0)	5 (16.1)	15 (30.0)	15 (25.9)	30 (27.8)

Source: Appendix Table 4.3.1.

Abbreviations: N = number of patients, SD = standard deviation, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population, CrCl = creatine clearance, CURB = Confusion, Urea nitrogen, Respiratory rate, Blood pressure, CURB-65 = Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older.

Percentages are based on the total number of patients in the treatment group (N).

(1) Structural lung disease was defined as any clinically-significant parenchymal or bronchial disease, e.g. chronic obstructive pulmonary disease (including emphysema or chronic bronchitis), bronchiectasis, and pulmonary fibrosis.

(2) Alcohol abuse is defined as an average daily intake of greater than 3 units, or a maximum weekly intake of greater than 21 units (one unit equals half a pint of beer or one measure of spirits).

Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Baseline risk factors and markers of disease severity are summarised in Table 5.5.4.

Over 40% (64/139) of patients had relevant medical history. This was lower in the ceftaroline treatment group compared to the ceftriaxone treatment group in both the bacteraemic (31.6% versus 41.7%) and non-bacteraemic (44.0% versus 53.4%) populations and was most commonly structural lung disease (42/139, 30.2%).

The bacteraemic population presented with a higher occurrence of smoking history compared to the non-bacteraemic population (67.7% versus 56.5%). The proportion of patients with a history of smoking was lower in the ceftaroline treatment group compared to the ceftriaxone treatment group in both the bacteraemic (63.2% versus 75.0%) and non-bacteraemic (50.0% versus 62.1%) populations.

For certain baseline characteristics and markers of disease severity, the bacteraemic population were classified as more severe:

- More than half of all patients (94/139, 67.6%) had renal impairment (CrCl <80mL/min).

  A higher proportion of bacteraemic patients had moderate renal impairment compared to non-bacteraemic patients (38.7% versus 21.3%). This was higher in the ceftriaxone-treated bacteraemic group compared to the ceftaroline-treated bacteraemic group (50.0% versus 31.6%).

- A higher proportion of bacteraemic patients were classified as PORT Risk Class IV compared to non-bacteraemic patients (74.2% versus 41.7%)

  The proportion was highest for the ceftaroline-treated bacteraemic group (78.9%).

- A higher proportion of bacteraemic patients were classified in CURB classes 2 and 3 compared to non-bacteraemic patients (58.1% versus 35.2%).

- A higher proportion of patients with bacteraemia had fever compared to non-bacteraemic patients (38.7% versus 27.8%).

These baseline risk factors and markers of disease severity were comparable for the ME subpopulation.

The microbiological parameters for the mMITTE population are presented in Table 5.5.5. Most patients had typical pathogens that were mono-microbial infections, and this was comparable between the bacteraemic and non-bacteraemic populations, and between drug treatment groups. These microbiological parameters were comparable for the ME subpopulation.

Table 5.5.5. Markers of Disease Severity: Microbiological Parameters - mMITTE Population

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
	Ceftaroline (N=19)	Ceftriaxone (N=12)	Total (N=31)	Ceftaroline (N=50)	Ceftriaxone (N=58)	Total (N=108)
Patients with Bacteraemia at Baseline	19 (100.0)	12 (100.0)	31 (100.0)	0	0	0
Presence of Atypical Pathogen[a]						
Yes (typical and atypical)	5 (26.3)	1 (8.3)	6 (19.4)	5 (10.0)	8 (13.8)	13 (12.0)
No (typical pathogen(s) only)	14 (73.7)	11 (91.7)	25 (80.6)	45 (90.0)	50 (86.2)	95 (88.0)
Infection Type (Typical Only)						
Mono-microbial	14 (73.7)	11 (91.7)	25 (80.6)	42 (84.0)	42 (72.4)	84 (77.8)
Poly-microbial	5 (26.3)	1 (8.3)	6 (19.4)	8 (16.0)	16 (27.6)	24 (22.2)

Source: Appendix Table 4.4.1.
a. Atypical CAP pathogens include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumoniae*.
Abbreviations: N = number of patients, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Assessor's comment:

The Applicant has included to the pooled safety analysis 139 Streptococcus pneumoniae CAP patients from studies P903-08 and P903-09; and 31 of them had bacteraemia. The higher proportion of patients was in ceftaroline treatment groups. Overall, the number of patients is too low to provide any specific safety data in this subgroup.

Provided subgroup data does not change the benefit-risk profile of ceftaroline.

Adverse events

A total of 69/139 patients (49.6%) reported any treatment emergent adverse event (TEAE) during the study period, of which 29/139 (20.9%) were study drug related.

The ceftaroline-treated bacteraemic group reported a higher proportion of TEAEs (57.9% versus 36.0%) and drug-related TEAEs (21.1% versus 12.0%) compared with the ceftaroline-treated non-bacteraemic group. This is likely related to the more severe baseline characteristics and markers of disease severity in this subpopulation of patients.

Overall, the two ceftriaxone treatment groups (bacteraemic and non-bacteraemic combined) reported a higher proportion of TEAEs (57.1% versus 42.0%) and drug-related TEAEs (27.1% versus 14.5%) compared to the two ceftaroline treatment groups.

SAEs were reported for 19/139 (13.7%) of patients. These were comparable between the bacteraemic and non-bacteraemic groups (16.1% versus 13.0%), with a higher proportion in the two ceftriaxone treatment groups (12/70, 17.1%) compared to the two ceftaroline treatment groups (7/69, 10.1%). SAEs were low in the ceftaroline-treated bacteraemic group (10.5%). No SAEs were considered study drug related.

Four (4) patients (2.9%) had treatment discontinued, of which one was considered study drug related in the ceftaroline-treated non-bacteraemic group (blood creatine increased).

Discontinuations due to TEAEs were low and comparable.

No deaths were reported. Reported AEs and deaths (none) were comparable for the ME subpopulation.

Table 5.5.6. Summary of Adverse Events - mMITTE Population

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
	Ceftaroline (N=19)	Ceftriaxone (N=12)	Total (N=31)	Ceftaroline (N=50)	Ceftriaxone (N=58)	Total (N=108)
Number of Patients with:						
Any TEAE	11 (57.9)	6 (50.0)	17 (54.8)	18 (36.0)	34 (58.6)	52 (48.1)
Any study drug-related TEAE	4 (21.1)	3 (25.0)	7 (22.6)	6 (12.0)	16 (27.6)	22 (20.4)
Any SAE	2 (10.5)	3 (25.0)	5 (16.1)	5 (10.0)	9 (15.5)	14 (13.0)
Any study drug-related SAE	0	0	0	0	0	0
Discontinuations due to TEAE	1 (5.3)	0	1 (3.2)	2 (4.0)	1 (1.7)	3 (2.8)
Discontinuations due to study drug-related TEAE	0	0	0	1 (2.0)	0	1 (0.9)
Deaths	0	0	0	0	0	0

Source: Appendix Table 7.1.1.
Abbreviations: N = number of patients, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population, TEAE = treatment emergent adverse event; SAE = serious adverse event.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Common Adverse Events

The majority of TEAEs were assessed as mild (39/69, 56.5%) to moderate (25/69, 36.2%) in severity and unrelated to study drug. TEAEs were comparable for the ME subpopulation.

TEAEs were higher in frequency in the ceftaroline-treated bacteraemia group (42.1% mild, 15.8% moderate) compared to the ceftaroline-treated non-bacteraemic group (26.0% mild, 10.0% moderate). This is likely related to the more severe baseline characteristics and markers of disease severity in this sub-population of patients.

The most common TEAEs being reported by at least 3 patients in any subpopulation or treatment group is presented in Table 5.5.7 by System Organ Class (SOC) and Preferred Term (PT). These were: nausea, pneumonia, headache and phlebitis. TEAEs were comparable for the ME subpopulation.

The TEAEs reported are consistent with the known safety profile of ceftaroline fosamil (Zinforo EU SmPC).

Five (5/69, 7.2%) patients had severe TEAEs. All of these occurred in the comparator group, were unrelated to drug treatment, and one of which was in the bacteraemia group (pneumonia). The severe TEAEs in the non-bacteraemic group were: 1 patient with acute myocardial infarction and hypertensive crisis, 1 patient with pneumonia, 1 patient with prostate cancer, and 1 patient with chronic obstructive pulmonary disease.

Table 5.5.7. Treatment Emergent Adverse Events Reported by at least 3 Patients in the Ceftaroline group or Comparator Group - mMITTE Population

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
System organ class / Preferred term	Ceftaroline (N=19)	Ceftriaxone (N=12)	Total (N=31)	Ceftaroline (N=50)	Ceftriaxone (N=58)	Total (N=108)
Gastrointestinal disorders						
Nausea	0	0	0	0	6 (10.3)	6 (5.6)
Infections and infestations						
Pneumonia	0	1 (8.3)	1 (3.2)	1 (2.0)	3 (5.2)	4 (3.7)
Nervous system disorders						
Headache	0	0	0	3 (6.0)	3 (5.2)	6 (5.6)
Vascular disorders						
Phlebitis	3 (15.8)	0	3 (9.7)	4 (8.0)	2 (3.4)	6 (5.6)

Source: Table Appendix 7.2.1.
Abbreviations: N = number of patients, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Serious adverse event/deaths/other significant events

There were no deaths reported in the subpopulation analysis for this study.

Other Serious Adverse Events

SAEs were reported for 19/139 (13.7%) of patients and none of these were considered study drug related (Table 5.5.6). Two (2) SAEs occurred in the ceftaroline-treated bacteraemic group (10.5%) compared to 3 in the ceftriaxone-treated bacteraemic group (25.0%). For the ceftaroline-treated bacteraemic group these were: pleural effusion and peripheral ischaemia. For the ceftriaxone-treated bacteraemic group these were: multiple myeloma, acute pulmonary oedema and endocarditis, and pleural effusion and pneumonia.

The most frequent SAEs being reported by at least 2 patients in any subpopulation or treatment group are shown in Table 5.5.8. These were Infections and Infestations (a lower proportion in the ceftaroline-treated groups compared to the comparator groups) and Respiratory, thoracic and mediastinal disorders (a slightly higher proportion in the bacteraemic group compared to the non-bacteraemic group). Reported SAEs were comparable for the ME subpopulation.

Table 5.5.8. SAEs Reported by at least 2 Patients in the mMITTE Population for Patients with Bacteraemic SP CAP versus Non-Bacteraemic SP CAP

	Bacteraemic SP CAP			Non-Bacteraemic SP CAP		
	Ceftaroline (N=19)	Ceftriaxone (N=12)	Total (N=31)	Ceftaroline (N=50)	Ceftriaxone (N=58)	Total (N=108)
Infections and infestations	0	2 (16.7%)	2 (6.5%)	1 (2.0%)	5 (8.6%)	6 (5.6%)
Endocarditis	0	1 (8.3%)	1 (3.2%)	0	0	0
Hepatitis C	0	0	0	0	1 (1.7%)	1 (0.9%)
Lung abscess	0	0	0	0	1 (1.7%)	1 (0.9%)
Pneumonia	0	1 (8.3%)	1 (3.2%)	1 (2.0%)	3 (5.2%)	4 (3.7%)
Respiratory, thoracic and mediastinal disorders	1 (5.3%)	2 (16.7%)	3 (9.7%)	3 (6.0%)	2 (3.4%)	5 (4.6%)
Acute pulmonary oedema	0	1 (8.3%)	1 (3.2%)	0	0	0
Chronic obstructive pulmonary disease	0	0	0	0	1 (1.7%)	1 (0.9%)
Pleural effusion	1 (5.3%)	1 (8.3%)	2 (6.5%)	1 (2.0%)	1 (1.7%)	2 (1.9%)
Pulmonary embolism	0	0	0	2 (4.0%)	0	2 (1.9%)

Source: Appendix Table 9.1.
Abbreviations: N = number of patients, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population, SAE = serious adverse event.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Other Significant Adverse Events

AEs that led to discontinuation are shown in Table 5.5.9. Four (4) patients (2.9%) had treatment discontinued.

One event that led to discontinuation was considered mild and study drug related in the ceftaroline-treated non-bacteraemic group (blood creatine increased).

Three (3) patients discontinued treatment due to SAEs that were not considered drug related.

One patient was in the ceftaroline-treated bacteraemic group (peripheral ischaemia), one patient was in the ceftaroline-treated non-bacteraemic group (pulmonary embolism), and one patient was in the comparator-treated non-bacteraemic group (pneumonia).

Table 5.5.9. Incidence of Adverse Events That Led to Discontinuation of Any Study Drug - mMITTE Population

	Bacteraemic SP CAP		Non-Bacteraemic SP CAP	
	Ceftaroline (N=19)	Ceftriaxone (N=12)	Ceftaroline (N=50)	Ceftriaxone (N=58)
Patients with at least one AE leading to discontinuation of any study drug				
Respiratory, thoracic and mediastinal				
Pulmonary embolism	0	0	1 (2.0)	0
Vascular disorders				
Peripheral ischaemia	1 (5.3)	0	0	0
Investigations				
Blood creatine increased	0	0	1 (2.0)	0
Infections and infestations				
Pneumonia	0	0	0	1 (1.7)

Source: Appendix Table 7.8.
Abbreviations: N = number of patients, mMITTE = Microbiological Modified Intent-to-Treat Efficacy Population, AE = adverse event.
Percentages are based on the total number of patients in the treatment group (N).
Note: Non-Bacteraemic SP CAP is "No SP Bacteraemia" in the source table.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Within the adult bacteraemic SP CAP population, 5 bacteraemic patients in the ceftaroline treatment group (5/69, 7.2%) and 1 bacteraemic patient in the ceftriaxone treatment group (1/70, 1.4%) had PCS (Potentially clinically significant) vital signs in the mMITTE subpopulation.

For the ceftaroline treatment group these were: high/low diastolic blood pressure, low heart rate, high systolic blood pressure and low systolic blood pressure. For the ceftriaxone treatment group these were: low diastolic blood pressure.

Review of PCS post-baseline laboratory values for selected parameters, and shifts over time, showed overall low incidence and no meaningful differences between bacteraemic patients in the two drug treatment groups. No safety concerns were identified based on mean values or trends for vital signs values.

Assessor's comment:

The most common TEAEs were nausea, pneumonia, headache and phlebitis. These are listed ADRs, except of pneumonia, which is the drug indication. In the bacteraemic-group was reported a higher proportion of TEAEs and drug-related TEAEs, which is in line with the more severe disease.

SAEs number was low and no SAEs were considered study drug related.

Four patients discontinued treatment, but only one was related to study drug (in the ceftaroline-treated non-bacteraemic group – mild blood creatinine increased, listed ADR of ceftaroline). No deaths were reported. Provided subgroup data does not change the benefit-risk profile of ceftaroline.

Laboratory findings

Within the adult bacteraemic SP CAP population, 6 bacteraemic patients in the ceftaroline treatment group (6/69, 8.7%) and 4 bacteraemic patients in the ceftriaxone treatment group (4/70, 5.7%) had PCS post-baseline clinical laboratory values in the mMITTE subpopulation.

For the ceftaroline treatment group these were: high alkaline phosphatase, high platelet count, low haemoglobin, low red blood cell count, high alkaline phosphatase and high GGT, high creatine kinase, high GGT and low potassium.

For the ceftriaxone treatment group these were: low haematocrit, low red blood cell count and low potassium, high platelet count, low white blood cell count, and low albumin and low calcium.

Overall, low incidences of PCS haematology, chemistry, or coagulation laboratory values were observed, and no meaningful differences were observed between bacteraemic patients in the two treatment groups. Furthermore, no safety issues were identified based on mean values or trends for haematology, chemistry, and coagulation values.

No patient met potential Hy's law criteria.

Assessor's comment:

No significant safety issues were identified.

Safety in special populations

Within the Zinforo paediatric clinical study P903-31 [CAP], a total of 4 patients had positive baseline blood cultures for SP. All subsequent data described in this section refers to only these 4 bacteraemic patients from Study P903-31.

Two (2) patients received ceftaroline fosamil, and two (2) patients received the comparator drug ceftriaxone.

A total of 16 TEAEs were reported by 3/4 patients (75.0%, compared to 54.8% of bacteraemic patients in the adult subpopulation). Two (2) of these patients were in the ceftaroline treatment group and 1 patient was in the ceftriaxone treatment group. AEs were generally mild to moderate in severity (13/16, 81.3%) and unrelated to study drug.

Two (2) patients experienced a total of 3 severe TEAEs; 1 patient was in the ceftaroline treatment group (infectious pleural effusion), and 1 patient was in the ceftriaxone treatment group (thrombocytosis and left lower lob lung thrombus). These TEAEs were considered not treatment related; all the events were resolving or resolved by the last study visit.

No TEAEs were considered treatment related in the ceftaroline treatment group. Within the ceftriaxone treatment group, 2 TEAEs (increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST)) were considered treatment related.

No AEs led to premature discontinuation of study treatment in this subgroup.

Three (3) patients in the bacteraemic subgroup experienced a SAE; 2 patients were in the ceftaroline treatment group and 1 patient was in the ceftriaxone treatment group. All SAEs were considered unrelated to study drug and were resolved by the last study visit.

In the ceftaroline treatment group, a 4-year-old white female received IV ceftaroline from Study Day 1 to Study Day 8 and experienced a SAE of moderate gastroenteritis on Study Day 12.

A 3-year-old white female received IV ceftaroline from Study Day 1 to Study Day 14 and experienced a SAE of severe infectious pleural effusion on Study Day 16.

In the ceftriaxone treatment group, a 4-year-old white male experienced a SAE of severe pulmonary thrombosis on Study Day 29.

There were no deaths in this subset of patients.

No bacteraemic patient in the ceftaroline treatment group had PCS laboratory values.

Safety data in the subset of paediatric patients with SP bacteraemia is very limited. However, no new safety findings were identified based on review of 4 paediatric patients (2 in the ceftaroline treatment group and 2 in the ceftriaxone treatment group and 2 in the ceftriaxone treatment group) who had positive baseline blood cultures for SP in the paediatric clinical studies.

Assessor's comment:

The paediatric patient numbers were too small to make any conclusions. However, there were no unexpected safety findings. Provided data does not change the benefit-risk profile of ceftaroline.

Post marketing experience

It is estimated that approximately 695,603 patients, equivalent to 13,836 patient-years, were exposed to ceftaroline fosamil worldwide since the product was first approved on 29 October 2010 in the US (EU approval on 23 August 2012). The method used for calculating patient exposure was consistent with that used in aggregate reports.

The estimated patient exposure is based on worldwide sales of 9,738,444 vials containing 600 mg of ceftaroline fosamil and on the assumption that the average dose and duration of treatment is 600 mg every 12 hours for 7 days (equals fourteen 600 mg vials) in adults with normal renal function across all approved indications.

The number of vials sold in the US is based on the data provided by Allergan Sales, LLC (sources: IQVIA, formerly IMS Health Inc. for patient visits; data available from launch date through March 2019). The number of vials sold in the EU, Latin America and Rest of the World (ROW) is based on actual Pfizer sales data through April 2019.

Cumulative estimated exposure by region is presented in Table 5.5.10. Cumulative estimated exposures by indication, gender and age group, available only for US, are summarised in Table 5.5.11.

Table 5.5.10. Cumulative Estimated Exposure by Region

	US	EU	Latin America	ROW
Vials sold	8,363,744	447,680	398,950	528,070
Estimated exposure (patient-years)	11,953[a b]	613[c]	547[c]	723[c]

a. Calculated for number of vials sold: Number of vials sold/1.917/365 patient-years
b. US calculation: a factor of 1.917 for patient-years was used.
c. EU, Latin America and ROW calculation: (Number of vials sold/14 vials)/52.14 weeks in a year.
US = United States; EU = European Union; ROW = Rest of the World.

Table 5.5.11. Cumulative Estimated US Exposure by Indication, Gender and Age Group

	Indication		Sex		Age (years)			
	CAP	cSSTI	M	F	≤17	18-64	65-74	≥75
Vials sold (US)	1,685,850	6,677,894	4,798,633	3,565,104	19,190	5,041,615	1,913,854	1,389,080
Estimated exposure (patient-years)[b,c]	2,409	9,544	6,858	5,095	27	7,205	2,735	1,985

a. Information available from US data only. Source: Allergan Sales, LLC (licensing partner)
b. Calculated for number of vials sold: Number of vials sold/1.917/365 patient-years
c. US calculation: a factor of 1.917 for patient-years was used.
CAP = community-acquired pneumonia; cSSTI = complicated skin and soft tissue infection; M = male; F = female.

Summaries of Post-Marketing Data from the Safety Database

A cumulative search of post-marketing (PM) AEs in cases reporting use of ceftaroline fosamil for secondary bacteraemia in CAP due to SP was conducted through 30 April 2019.

The safety database was initially searched for ceftaroline fosamil cases reporting the following MedDRA v 22.0 PT indications: *Streptococcal bacteraemia, Bacteraemia, or Sepsis*; 39 cases were retrieved from this search. The 39 cases were further reviewed to identify those potentially indicative of ceftaroline fosamil use for secondary bacteraemia in CAP due to SP.

On review, 13 relevant cases were identified, representing 1.6% of the cumulative (801) ceftaroline fosamil PM cases received through 30 April 2019:

- 1 case reported the use of ceftaroline fosamil in a patient with severe streptococcal pneumonia complicated with bacteraemia;
- 12 cases in which the pathogen was not clearly identified and bacteraemia due to pneumonia could not be excluded – these patients were conservatively included in the analysis.

Detailed case level characteristics of the relevant PM cases are summarised in Table 5.5.12. Medical history, co-suspect and concomitant medications were not reported in these cases.

Table 5.5.12. Relevant Cases from Spontaneous Sources through 30 April 2019 (N = 13)

Characteristics	Details	No. of cases
Country Where Event Occurred	United States	5
	Australia, Germany	2 each
	France, Hong Kong, Poland, Russian Federation	1 each
Medical confirmation[a]	Medically confirmed	13
Case Seriousness	Serious	3
	Nonserious	10
Age (n = 1)	54 years	1
	Unknown	12
Sex	Female	3
	Male	2
	Unknown	8
Case Outcome	Resolved	1
	Resolving	2
	Unknown	10

a. Medically confirmed cases are cases reported by a healthcare professional defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations. Non-medically confirmed cases are reported by a consumer defined as a person who is not a healthcare professional such as a patient, lawyer, friend or relative of a patient or carer.

Table 5.5.13. MedDRA Preferred Terms Reported in Cases Indicative of Use for Secondary Bacteraemia in CAP due to *Streptococcus pneumoniae*

SOC and PT	Number of events
Injury, poisoning and procedural complications	**13**
Off label use	7
Product use in unapproved indication	5
Incorrect product administration duration	1
Skin and subcutaneous tissue disorders	**2**
Drug reaction with eosinophilia and systemic symptoms	1
Rash	1
General disorders and administration site conditions	**1**
Condition aggravated	1
Blood and lymphatic system disorders	**1**
Neutropenia	1
Total	*17*

CAP = community-acquired pneumonia

In 10 out of 13 cases, only off label use terms were reported. In the remaining 3 cases, the patients experienced a total of 4 AEs: Drug reaction with eosinophilia and systemic symptoms, Neutropenia, Rash and Condition aggravated (1 each). The reported AEs are consistent with information included in the ceftaroline fosamil EU SmPC.

The PT Condition aggravated was reported for a 54-year-old female patient who was diagnosed with severe streptococcal pneumonia complicated with bacteraemia. She initially responded to treatment with ceftaroline fosamil 600 mg bid; subsequently, at unspecified time after starting ceftaroline fosamil, her condition deteriorated, presenting with low blood pressure. Ceftaroline fosamil was continued and her condition improved again on the third day after admission to the intensive care unit, following treatment with unspecified inotropes and intravenous human immunoglobulin.

Limited information is available concerning the remaining 2 patients who developed AEs while receiving ceftaroline fosamil for bacteraemia of unspecified origin (no pathogen, no indication of previous infection) with unspecified duration of therapy:

- Drug reaction with eosinophilia and systemic symptoms started approximately 2 weeks after initiation of ceftaroline fosamil therapy; ceftaroline fosamil was discontinued at unspecified time and the event was resolving at the time of reporting.
- Non-serious Rash and Neutropenia occurred with a latency of 37 days and ceftaroline fosamil was withdrawn at unspecified time; Neutropenia resolved while the outcome of Rash was unknown.

No new safety concerns regarding the use of ceftaroline fosamil for secondary bacteraemia in CAP due to SP have been identified from assessment of these cases. The MAH will continue to review the safety of ceftaroline fosamil, including all reports of adverse experiences and will revise the product documents if an evaluation of the safety data yields significant new information.

Assessor's comment:

The case of drug reaction with eosinophilia and systemic symptoms concerns bacteraemia of unspecified origin. DRESS is not listed.

Conclusions of Post Marketing Safety Analysis

Based upon routine post-marketing pharmacovigilance monitoring there are no new emerging safety concerns identified in this dataset and the benefit/risk profile of ceftaroline fosamil remains favourable.

Assessor's comment:

No new safety concerns were identified; however the number of patients with bacteraemic SP CAP was extremely low to draw any conclusions.

4.5.1. Conclusions on clinical safety

The Applicant has included to the pooled safety analysis 139 *Streptococcus pneumoniae* CAP patients from studies P903-08 and P903-09; and 31 of them had with bacteraemia. The higher proportion of patients was in the ceftaroline treatment groups. Overall, the number of patients is too low to provide any specific safety data in this subgroup.

The paediatric patient numbers were too small to make any conclusions (4 in total, 2 on ceftaroline and 2 on ceftriaxone group).

There were no unexpected safety findings.

Provided data does not change the benefit-risk profile of ceftaroline.

4.5.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

5. Changes to the Product Information

The initial proposal to update the wording in section 4.1 has been withdrawn. The Applicant proposal that bacteraemia information be included in section 5.1 is not supported as the sub-analysis data provided by MAH is not considered to provide further scientific value or guidance to prescribers and therefore not in accordance with the SmPC guideline which refers to 'exceptional cases' where the secondary or post-hoc analyses could be included in the SmPC when these are of sufficient relevance to prescribers (Section 5.1, page 20, https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf) - in particular given that the current broad indication is already understood to include patients with bacteraemia. No changes are therefore proposed to the product information.

Assessor`s comment

In their comments in the first round, the CHMP members pointed out to the current regulatory practice of not including information about bacteraemia under sections 4.1. or 5.1 of the SmPC unless information from the secondary analysis is of high importance to guide usage, mainly identifying specific concerns. The Rapporteur agrees that the proposed update of section 5.1. is not sufficiently justified in light of the SmPC guideline. Current labelling supports the use of Zinforo in cases of secondary bacteraemia without any need for subsequent revision of SmPC and there are no concerns that need to be reflected in the SmPC in this regard.

5.1.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The applicant is seeking to extend the indication to CAP with bacteraemia (also called invasive pneumonia in the literature) caused by *S. pneumoniae*. CAP with bacteraemia occurs in 20-30% of adult patients and in about 1-7% of paediatric patients. Although there are no specific treatment guidelines for treatment of invasive pneumococcal pneumonia similar antibiotic regimens as for non-invasive pneumonia are recommended and include beta-lactam +/- macrolide. While monotherapy may be recommended for non-invasive CAP for invasive CAP experts tend to suggest combination therapy. The data whether CAP with bacteraemia has different outcome than CAP without bacteraemia is still debatable. It is characteristic of *S. pneumoniae* that it may cause pneumococcal disease (bacteraemia) without known site of infection, especially in children.

6.1.2. Available therapies and unmet medical need

See 7.1.1.

6.1.3. Main clinical studies

The applicant has not conducted any specific studies to extend already existing indication of CAP. The existing indication is broad and covers all microorganisms and does not exclude patients with bacteraemia. The *post hoc* analysis of already submitted studies (adult studies PO903-08, PO903-09 and paediatric study PO903-31) was performed and in total 31 adult patients and 4 paediatric patients with pneumococcal CAP and bacteraemia were identified and included into this analysis. These patients were compared with those who had pneumococcal pneumonia (most defined by urinary antigen test or by sputum cultures) without bacteraemia. The analysis was performed for each study separately and then also as pooled analysis of two adult studies. Paediatric study was analysed separately. There was no formal statistical analysis and the primary endpoint was clinical cure of CAP. According to the protocol the blood cultures had to be taken in all patients at baseline and then repeated in those with positive cultures until cultures turn negative.

6.2. Favourable effects

The adult studies showed that in terms of main endpoints (clinical cure of CAP in mMITTE population and in pooled analysis) the response was numerically slightly higher in those with non-bacteraemic as compared to bacteraemic CAP (78.9% vs 88.0% in ceftaroline and 66.7% vs 69.0% in ceftriaxone arm). The response was also numerically higher in patients treated with ceftaroline as compared to ceftriaxone. Similar trends were seen in in ME population. In terms of resolution of bacteraemia vast majority of patients were categorised into presumed eradication category, which makes assessor to believe that repeated blood cultures, as suggested in the protocol, were not taken. The findings that patients with bacteraemic and non-bacteraemic SP CAP have similar response are consistent with recent studies (REF). In terms of PORT classification it was not surprising that number of patients with PORT III was smaller in bacteraemic patients as compared with non-bacteraemic patients. In patients of PORT IV the clinical response was again numerically higher in non-bacteraemic patients treated with

ceftaroline while no such differences were observed in those treated with ceftriaxone. Small numbers should be noted, however.

In paediatric study only two patients treated with ceftaroline had pneumococcal CAP with bacteraemia and another two were treated with ceftriaxone. The low percentage of bacteraemic patients is in line with other studies that also have shown low rate of bacteraemic children with CAP. Both ceftaroline treated patients had clinical outcome assessed as failure. The numbers were too small to be conclusive.

No new safety concerns were identified.

6.3. Uncertainties and limitations about favourable effects

There is no need to extend current indication of CAP to bacteraemic SP CAP as current indication is unspecific and thus already covers non-bacteraemic as well as bacteraemic CAP.

Studies were not designed to compare bacteraemic CAP to non-bacteraemic. As a result, the number of patients with CAP and bacteraemia was small – in total of 31 adults (19 received ceftaroline fosamil) and 4 children (2 received ceftaroline fosamil). Thus no adequate conclusions can be drawn.

The data are insufficient of using ceftaroline in patients with pneumococcal bacteraemia when CAP (or any other site of infection) is only suspected and not confirmed. Bacteraemia without clear site of infection is characteristic to pneumococci and occurs mostly in children. There is a risk that if bacteraemia is mentioned in the label the SPC will be misinterpreted and ceftaroline will be used for paediatric patients without confirmed CAP. The efficacy of ceftaroline in invasive pneumococcal disease has not been demonstrated and needs further studies. The fact that both bacteraemic children treated with ceftaroline had failure outcome is of concern, but due to very small patient numbers these results are inconclusive.

The studied outcome was the one for CAP and not designed to look specifically resolution of bacteraemia. Although one could speculated, that these two outcomes match, the time of bacterial clearance should have been reported, as it is likely that longer duration of bacteraemia results in worse outcome. It is assessor's speculation that repeated blood cultures as defined in the protocol were not taken.

6.4. Unfavourable effects

There were bacteraemic children and both had failure outcome. However, these results cannot be considered conclusive because the number of patients was very small.

6.5. Uncertainties and limitations about unfavourable effects

See above.

6.6. Benefit-risk assessment and discussion

6.6.1. Importance of favourable and unfavourable effects

The applicant is seeking for specifying current label of ceftaroline indicated for treatment of CAP to CAP with bacteraemia caused by *S. pneumoniae*. The reason behind this change is not clear as current label is not specific and thus CAP patients with bacteraemia or without are already covered. In addition it is noted that the Draft of the "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3" states that for pathogen-specific bacteraemia, it is not considered that

an indication for treatment of bacteraemia can be substantiated by a trial that enrols patients with bacteraemia due to a specific pathogen regardless of the primary focus of infection. Such trials are not recommended because i) most patients will be treated for a site-specific infection, whether known or unknown, with associated bacteraemia and the outcome will be related to source control and ii) the trial will not be designed or powered to assess efficacy in sub-groups defined by primary foci or unknown source.

6.6.2. Balance of benefits and risks

The benefit-risk balance of Zinforo in its approved indication remains unchanged and the CHMP is of the opinion that the current product information supports the use of Zinforo in the treatment of patients with CSTTI / CAP with concurrent bacteraemia.

6.7. Conclusions

The benefit-risk balance of Zinforo in its approved indication remains unchanged and the CHMP is of the opinion that the current product information supports the use of Zinforo in the treatment of patients with CSTTI / CAP with concurrent bacteraemia.

According to the responses submitted, the applicant agreed not to change the current wording in section 4.1 and proposed to update section 5.1 to reflect the current knowledge in the treatment of patients with secondary bacteraemia. However, following assessment of the submitted data, the CHMP does not consider that the sub-analysis data submitted by MAH provides further scientific value or guidance to prescribers and is therefore not in accordance with the SmPC guideline which refers to 'exceptional cases' where the secondary or post-hoc analyses could be included in the SmPC when these are of sufficient relevance to prescribers (Section 5.1, page 20, https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf) - in particular given that the current broad indication is already understood to include patients with bacteraemia. This is maintained as a Major Objection.

7. 3rd CHMP Request for Supplementary Information to be addressed in an Oral Explanation

Major objection

The CHMP is of the opinion that the current product information supports the use of Zinforo in the treatment of patients with CSTTI / CAP with concurrent bacteraemia. Sub-analysis data submitted by the MAH however was not considered to provide further scientific value or guidance to prescribers to justify the proposed amendment of the product information.

The MAH is therefore invited to an oral explanation to further justify how the data submitted supports the proposed amendments to the product information, particularly given that the current indication, together with information in Section 4.4 on any safety concerns and the current information in 5.1, is considered by the CHMP to adequately support the use of Zinforo in a broad indication which does not exclude bacteraemia.

Other concerns

None

8. Rapporteur assessment of the MAH responses to the 1st Request for Supplementary Information

Major objections

Clinical efficacy aspects

Question

1. The applicant is seeking to extend the indication to CAP with concurrent bacteraemia (also called invasive pneumonia in the literature) caused by *S. pneumoniae* for all age groups. Current label of ceftaroline fosamil (Zinforo) states that Zinforo is indicated for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia in neonates, infants, children, adolescents and adults. As this CAP indication is broad and both invasive (with bacteraemia) and non-invasive CAP caused by any microorganisms are already covered, the proposal for singling out one microorganism in one site of infection is not justified considering the clinical aspects and is not in line with the current guidelines and principles for the treatment of bacterial infections. In addition, there is a risk that ceftaroline could be promoted for patients with bacteraemia without clear CAP (e.g. suspected CAP) and thus be used in cases in which there are very limited data. Use of ceftaroline in paediatric patients with bacteraemia is even less clear as both patients in paediatric study failed. Considering these issues, the applicant should justify the proposed extension of indication

Summary of MAH answer

The MAH agrees that available clinical data support the broader bacteraemia indication compared to what was initially submitted in the Type II variation seeking only an extension of the CAP indication to include patients with concurrent SP bacteraemia.

The MAH's preferred position to address the major objection would be to add bacteraemia text to Section 4.1 of the Zinforo EU Summary of Product Characteristics (SmPC), the same as what has been included recently for the Vaborem SmPC. However, following receipt of the Rapporteur's Preliminary Assessment Report and the 27 March 2020 teleconference with EMA representatives and Rapporteurs, the MAH understands that the EMA believe including bacteraemia text in Section 4.1 of the SmPC is not necessary. Therefore, in the absence of any text related to bacteraemia in the European Public Assessment Report (EPAR) and current SmPC, the MAH proposes adding text to Section 5.1 of the SmPC to clarify Zinforo use in the treatment of patients with bacteraemia associated with cSSTI/CAP from the Phase 3 clinical trials.

The current Zinforo SmPC or EPAR does not provide healthcare professionals (HCPs) with a confirmation that this product is suitable for cases with concurrent bacteraemia. In addition, the SmPC does not provide details on Phase 3 studies. Whilst the MAH understands that the EMA's preference is to not include bacteraemia text in line with the antibacterial guideline, HCPs may not be aware of the regulatory requirements. Specifically, the Zinforo EPAR does not add details on bacteraemic patients, it only provides fragmented data, mostly on *S. pneumoniae* efficacy from Studies P903-08 and P903-09 being reported. As some other available antibiotics have additional wording regarding bacteraemia, this may create confusion for prescribers and may result in situations, whereby patients in which positive blood cultures are received after initiation of ceftaroline, may be switched unnecessarily to another treatment, or patients not started on ceftaroline if they are known to have secondary bacteraemia.

In fact, the MAH receives a considerable amount of questions from HCPs related to the use of Zinforo in bacteraemia through different channels (medical information, sales representatives, customer facing

medical colleagues). As an example, the Medical Information database (including EU countries with the United Kingdom, Norway, and Switzerland) recorded 23 enquiries in 2019. This represents 5.72% of total for all Zinforo enquiries received in that year. The MAH believes that providing more details from pivotal studies on cases of secondary bacteraemia in cSSTI and CAP in the SmPC will support the appropriate use of the product.

Overall Bacteraemia Experience From the Ceftaroline Fosamil Phase 3 Clinical Trials

The MAH's initial submission to extend the indication for CAP to include concurrent bacteraemia due to SP was limited to Phase 3 clinical data in CAP patients with SP bacteraemia. The MAH performed an analysis of clinical data from all patients with concurrent bacteraemia associated with CAP or cSSTI from the Phase 3 ceftaroline fosamil development program. The MAH has provided supporting documentation for the overall bacteraemic versus non-bacteraemic patients from the previous Phase 3 studies.

The number of patients with baseline bacteraemia associated with CAP and cSSTI from the 6 ceftaroline fosamil Phase 3 studies was analysed. Overall, of the 1976 patients included in the pooled analysis, 138 patients had concurrent bacteraemia at baseline, of which 72 were treated with ceftaroline fosamil. Although the clinical trials included no randomisation by bacteraemic status at baseline, the proportion of CAP/cSSTI patients with bacteraemia was similar across treatment groups.

Table 1: Summary of All Bacteraemic and Non-Bacteraemic Patients by Indication in the mMITT Population

Indication	Phase 3 CT	Bacteraemic patients		Non-bacteraemic patients	
		Ceftaroline n/N	Ceftriaxone n/N	Ceftaroline n/N	Ceftriaxone n/N
CAP	FOCUS 1 (P903-08) FOCUS 2 (P903-09) Asia CAP (D3720C00002)	26/53	27/53	225/477	252/477
		Ceftaroline n/N	Vanc + Az n/N	Ceftaroline n/N	Vanc + Az n/N
cSSTI	CANVAS 1 (P903-06) CANVAS 2 (P903-07) COVERS, High Dose (D3720C00001)	46/85	39/85	741/1361	620/1361
Total		72/138	66/138	966/1838	872/1838

Abbreviations: N = number of patients; n = number of patients in specific category; Vanc + Az = vancomycin +

aztreonam.

Demographics and Baseline Characteristics

Across the mMITT population, most patients were male and White, with a median age ranging from 51 to 62 years. Age range, sex, and race demographics were generally similar between drug treatment groups and between bacteraemic and non-bacteraemic populations, except for mean age, which was slightly higher in the bacteraemic group compared to the non-bacteraemic group (57.3 years compared to 51.8 years).

A higher proportion of bacteraemic CAP patients were classified as PORT Risk Class IV compared to non-bacteraemic patients (71.7% compared to 30.6%), likely related to the more severe baseline characteristics in this subpopulation of patients and expected for a scoring system based on severity of illness. Demographic and baseline characteristics were comparable for the ME subpopulation.

Efficacy

Clinical Response

Table 2: Clinical Response at TOC in Patients With Bacteraemia Versus No Bacteraemia (mMITT Population Excluding Site 1314 from Asia CAP Study)

Clinical response	**Bacteraemic patients N (%)**			**Non-bacteraemic patients N (%)**		
	Ceftaroline N = 72	**Comparator N = 66**	**Total N = 138**	**Ceftaroline N =966**	**Comparator N =872**	**Total N =1838**
Clinical cure	55 (76.4)	51 (77.3)	106 (76.8)	822 (85.1)	717 (82.2)	1539 (83.7)
Clinical failure	14 (19.4)	13 (19.7)	27 (19.6)	79 (8.2)	92 (10.6)	171 (9.3)
Indeterminate	3 (4.2)	2 (3.0)	5 (3.6)	49 (5.1)	45 (5.2)	94 (5.1)
Missing	0	0	0	16 (1.7)	18 (2.1)	34 (1.8)

Percentages are based on the total number of patients in the treatment group (N). Abbreviations: N = number of patients

Clinical cure rates were similar in bacteraemic patients across drug treatment groups. These clinical cure rates were lower compared to the clinical cure rates in non-bacteraemic patients. Clinical cure rates were comparable for the ME population.

Table 3: Clinical Response at TOC in subjects with bacteraemia versus no bacteraemia (ME Population excluding site 1314 for Asia CAP study)

Clinical response	**Bacteraemic patients N (%)**			**Non-bacteraemic patients N (%)**		
	Ceftaroline N = 64	Comparator N = 51	Total N = 115	Ceftaroline N =794	Comparator N =716	Total N =1510
Clinical cure	50 (78.1)	40 (78.4)	90 (78.3)	726 (91.4)	636 (88.8)	1362 (90.2)
Clinical failure	14 (21.9)	11 (21.6)	25 (21.7)	68 (8.6)	80 (11.2)	148 (9.8)

When analysed by indication and by study, the clinical cure rates for bacteraemic patients were generally similar to comparator, and similar between bacteraemic and non-bacteraemic subgroups and with the overall population (both patients with and without bacteraemia). However, efficacy conclusions are limited by smaller patient numbers.

Table 4: Clinical Response at TOC in Patients With Bacteraemia Versus No Bacteraemia by study (mMITT Population Excluding Site 1314 from Asia CAP Study)

Study	Clinical response	Bacteraemic patients N (%)			Non-bacteraemic patients N (%)		
		Ceftaroline	Comparator	Total	Ceftaroline	Comparator	Total
D3720C00001	N	17	15	32	231	121	352
	Clinical cure	13 (76.5)	9 (60.0)	22 (68.8)	186 (80.5)	99 (81.8)	285 (81.0)
	Clinical failure	3 (17.6)	5 (33.3)	8 (25.0)	18 (7.8)	13 (10.7)	31 (8.8)
	Indeterminate	1 (5.9)	1 (6.7)	2 (6.3)	27 (11.7)	9 (7.4)	36 (10.2)
D3720C00002	N	3	5	8	74	90	164
	Clinical cure	2 (66.7)	3 (60.0)	5 (62.5)	63 (85.1)	63 (70.0)	126 (76.8)
	Clinical failure	1 (33.3)	1 (20.0)	2 (25.0)	8 (10.8)	20 (22.2)	28 (17.1)
	Indeterminate	0	1 (20.0)	1 (12.5)	3 (4.1)	7 (7.8)	10 (6.1)
P903_06	N	20	10	30	251	253	504
	Clinical cure	16 (80.0)	10 (100.0)	26 (86.7)	219 (87.3)	216 (85.4)	435 (86.3)
	Clinical failure	3 (15.0)	0	3 (10.0)	18 (7.2)	13 (5.1)	31 (6.2)
	Indeterminate	1 (5.0)	0	1 (3.3)	8 (3.2)	13 (5.1)	21 (4.2)
	Missing	0	0	0	6 (2.4)	11 (4.3)	17 (3.4)
P903_07	N	9	14	23	259	246	505
	Clinical cure	8 (88.9)	14 (100.0)	22 (95.7)	225 (86.9)	214 (87.0)	439 (86.9)
	Clinical failure	1 (11.1)	0	1 (4.3)	16 (6.2)	15 (6.1)	31 (6.1)
	Indeterminate	0	0	0	8 (3.1)	10 (4.1)	18 (3.6)

	Missing	0	0	0	10 (3.9)	7 (2.8)	17 (3.4)
P903_08	N	8	11	19	67	71	138
	Clinical cure	6 (75.0)	8 (72.7)	14 (73.7)	60 (89.6)	54 (76.1)	114 (82.6)
	Clinical failure	2 (25.0)	3 (27.3)	5 (26.3)	5 (7.5)	15 (21.1)	20 (14.5)
	Indeterminate	0	0	0	2 (3.0)	2 (2.8)	4 (2.9)
P903_09	N	15	11	26	84	91	175
	Clinical cure	10 (66.7)	7 (63.6)	17 (65.4)	69 (82.1)	71 (78.0)	140 (80.0)
	Clinical failure	4 (26.7)	4 (36.4)	8 (30.8)	14 (16.7)	16 (17.6)	30 (17.1)
	Indeterminate	1 (6.7)	0	1 (3.8)	1 (1.2)	4 (4.4)	5 (2.9)

Within the CAP indication, clinical cure rates were lower in the bacteraemic subgroups compared to the non-bacteraemic subgroups; however, between treatment arms, clinical cure rates were higher in ceftaroline-treated patients compared to patients treated with the comparator. Given the small number of patients, it is difficult to draw conclusions in this subgroup.

Table 5: Clinical response at TOC in bacteraemic CAP patients was analysed by PORT Risk Class (III and IV). Though the denominators are small, the clinical cure rate for ceftaroline and comparator by PORT score was generally similar in the Phase 3 CAP studies.

Port class	**Clinical response**	**Bacteraemia**			**No bacteraemia**		
		Ceftaroline	**Comparator**	**Total**	**Ceftaroline**	**Comparator**	**Total**
II	n	0	1	1	9	14	23
	Clinical cure	0	1 (100.0)	1 (100.0)	7 (77.8)	12 (85.7)	19 (82.6)
	Clinical failure	0	0	0	2 (22.2)	1 (7.1)	3 (13.0)
	Inderterminate	0	0	0	0	1 (7.1)	1 (4.3)
III	n	6	7	13	144	164	308
	Clinical cure	6 (100.0)	4 (57.1)	10 (76.9)	127 (88.2)	124 (75.6)	251 (81.5)
	Clinical failure	0	3 (42.9)	3 (23.1)	15 (10.4)	32 (19.5)	47 (15.3)
	Inderterminate	0	0		2 (1.4)	8 (4.9)	

				0			10 (3.2
IV	n Clinical cure Clinical failure Inderterminate	20 12 (60.0) 7 (35.0) 1 (5.0)	18 12 (66.7) 5 (27.8) 1 (5.6)	38 24 (63.2) 12 (31.6) 2 (5.3)	72 58 (80.6) 10 (13.9) 4 (5.6)	74 52 (70.3) 18 (24.3) 4 (5.4)	146 110 (75.3) 28 (19.2) 8 (5.5)
V	n Clinical cure Clinical failure Inderterminate	0 0 0 0	1 1 (100.0) 0 0	1 1 (100.0) 0 0	0 0 0 0	0 0 0 0	0 0 0 0

Clinical response at TOC in the mMITT and ME populations were further analysed by baseline pathogen. The predominant baseline pathogens isolated from blood specimens were S. aureus (n=29) and S. pneumoniae (n=19). As expected, all S. pneumoniae blood isolates were from CAP patients while most S. aureus isolates were from cSSTI patients. All other baseline blood pathogens identified in the bacteraemic subgroup were isolated in no more than 6 patients each. Similar clinical cure rates were observed in the mMITT and ME populations for the pathogens that were most frequently isolated. Clinical cure rates were high for S. aureus (mMITT population: bacteraemic group: 82.8%; non-bacteraemic group: 86.6%) and S. pneumoniae (mMITT population: bacteraemic group: 78.9%; non-bacteraemic group: 84.8%) in patients treated with ceftaroline. As expected with small denominators, variability was observed by pathogen, but clinical cure rates were broadly similar between treatment groups.

Microbiological Response

Table 7: Per Patient Microbiological Response at TOC in subjects with bacteraemia versus no bacteraemia (mMITT Population excluding site 1314 for Asia CAP study)

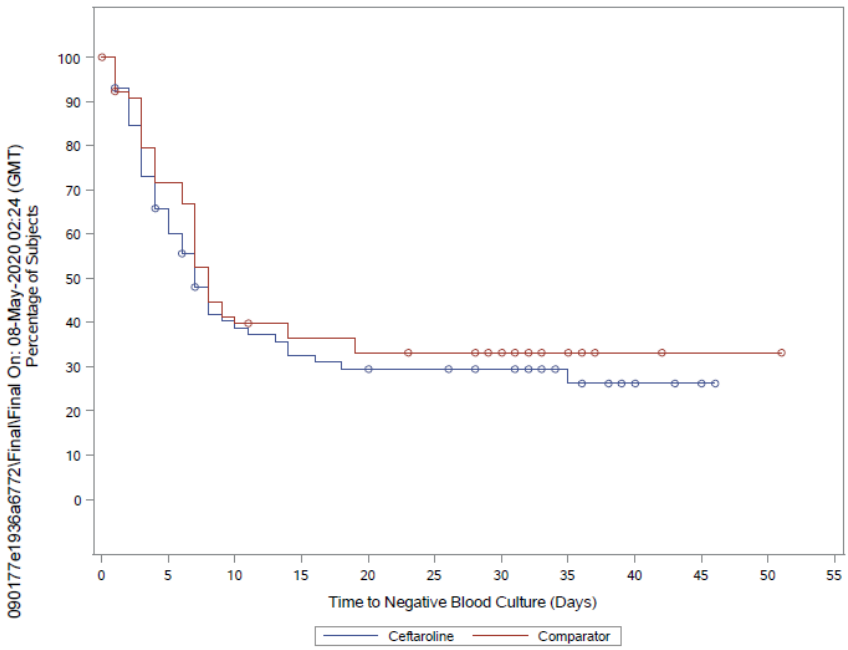
Microbiological Response	**Bacteraemia**			**No Bacteraemia**		
	Ceftaroline	**Comparator**	**Total**	**Ceftaroline**	**Comparator**	**Total**
N	72	66	138	966	872	1838
Favourable	56 (77.8)	54 (81.8)	110 (79.7)	825 (85.4)	719 (82.5)	1544 (84.0)
Eradication	1 (1.4)	3 (4.5)	4 (2.9)	18 (1.9)	17 (1.9)	35 (1.9)
Presumed eradication	55 (76.4)	51 (77.3)	106 (76.8)	807 (83.5)	702 (80.5)	1509 (82.1)

Unfavourable Persistence Presumed persistence	13 (18.1) 1 (1.4) 12 (16.7)	10 (15.2) 0 10 (15.2)	23 (16.7) 1 (0.7) 22 (15.9)	76 (7.9) 15 (1.6) 61 (6.3)	90 (10.3) 17 (1.9) 73 (8.4)	166 (9.0) 32 (1.7) 134 (7.3)
Inderterminate	3 (4.2)	2 (3.0)	5 (3.6)	65 (6.7)	63 (7.2)	128 (7.0)

Patient-level microbiological response rates at TOC in the mMITT and ME populations were generally similar between treatment groups, by indication and across indication. For patients treated with ceftaroline, 56/72 (77.8%) bacteraemic patients and 825/966 (85.4%) non-bacteraemic patients had a favourable microbiological response at TOC in the mMITT population.

Per-pathogen microbiological response rates in the mMITT and ME populations were generally similar between treatment groups, by indication and across indication, though comparisons are limited by small numbers for any given pathogen.

In bacteraemia patients who achieved negative blood culture, the median time (in days) to first negative blood culture was 7 days (range 1-35 days) for patients treated with ceftaroline and 8 days (range 1-19 days) for patients treated with comparator.



Studies D3720C00001, D3720C00002, P903_06, P903_07, P903_08 and P903_09 are included in this table.
mMITT=Microbiological Modified Intent To Treat; CAP=Community Acquired Pneumonia;
Only subjects with baseline blood culture positive were included in this analysis.
PFIZER CONFIDENTIAL SDTM Creation: . (.) Output File: ./csr_figaro/scsc2660012a/t62 Date of Generation: 07MAY2020 (13:29)

Figure 1: Kaplan-Meier Plot of time to negative blood culture for bacteraemia patients (mMITT Population excluding site 1314 for Asia CAP study)

Safety

There were no new emerging safety issues identified during the analysis of adverse events (AEs) in the bacteraemic subpopulations.

Exposure to ceftaroline and comparator was similar between drug treatment groups and between bacteraemic and non-bacteraemic populations, with a median duration of treatment of 7.00 to 7.38 days across subgroups

Table 8: Summary of Adverse events for subjects with bacteraemia versus no bacteraemia (mMITT Population)

Number of Subjects with	**Bacteraemia**			**No Bacteraemia**		
	Ceftaroline (N = 72)	**Comparator (N = 66)**	**Total (N = 138**	**Ceftaroline (N = 969)**	**Comparator (N = 873)**	**Total (N = 1842)**
Any TEAE	42 (58.3)	35 (53.0)	77 (55.8)	391 (40.4)	377 (43.2)	768 (41.7)
Any study drug-related TEAE	20 (27.8)	9 (13.6)	29 (21.0)	170 (17.5)	168 (19.2)	338 (18.3)
Any SAE	10 (13.9)	15 (22.7)	25 (18.1)	49 (5.1)	37 (4.2)	86 (4.7)
Any study drug-related SAE	2 (2.8)	1 (1.5)	3 (2.2)	4 (0.4)	2 (0.2)	6 (0.3)
Treatment Discontinuations due to TEAE	5 (6.9)	3 (4.5)	8 (5.8)	25 (2.6)	21 (2.4)	46 (2.5)
Study Discontinuations due to TEAE	0	1 (1.5)	1 (0.7)	4 (0.4)	6 (0.7)	10 (0.5)
Treatment Discontinuations due to study drug-related TEAE	4 (5.6)	1 (1.5)	5 (3.6)	16 (1.7)	16 (1.8)	32 (1.7)
Study Discontinuations due to study drug-related TEAE	0	0	0	0	1 (0.1)	1 (0.1)
Deaths	0	1 (1.5)	1 (0.7)	6 (0.6)	4 (0.5)	10 (0.5)

Overall, bacteraemic patients reported a higher incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) than non-bacteraemic patients. This is likely related to the more severe baseline characteristics and markers of disease severity in this subpopulation of patients. As shown in Table 8 in bacteraemic patients any study drug related TEAEs and SAEs were numerically more frequent in ceftaroline as compared with comparator arm patients but small numbers should be noted.

Observed TEAEs were generally in line with the known safety profile of ceftaroline or consistent with the underlying indications. The majority of TEAEs were assessed as mild to moderate in severity and

unrelated to study drug. Within the ceftaroline-treated bacteraemic patients, no preferred term (PT) for all-causality TEAEs was reported in more than 4 (5.6%) patients and no PT for treatment-related TEAEs was reported in more than 3 (4.2%) patients. Four patients discontinued ceftaroline treatment due to a treatment-related TEAE (pruritus/rash generalised; hypersensitivity; clostridial infection; and dermatitis allergic) vs one patient is comparator arm. All treatment-related TEAEs in the ceftaroline treatment group were resolved.

The incidence of all-cause SAEs in bacteraemic patients treated with ceftaroline was lower compared to bacteraemic patients treated with comparator (13.9% versus 22.7%). The majority of SAEs were assessed as moderate in severity across both treatment groups, unrelated to study drug and were resolved. Within the ceftaroline-treated bacteraemic patients, no PT for all-causality SAEs was reported in more than 1 (1.4%) patient. Three ceftaroline-treated patients reported 1 SAE each that was severe in intensity: osteoarthritis, hypersensitivity, and clostridial infection. These 3 SAEs were all resolved; however, the latter 2 SAEs were considered related to treatment and led to discontinuation.

There were no deaths reported in ceftaroline-treated bacteraemic patients.

Paediatric Patients With Baseline Bacteraemia From the Ceftaroline Fosamil Paediatric cSSTI and CAP Clinical Trials

Efficacy

There are limited data on efficacy of ceftaroline fosamil in the treatment of paediatric patients (aged 2 months to <18 years) with bacteraemia associated with cSSTI or CAP from the ceftaroline fosamil paediatric clinical trials. The MAH's original bacteraemia submission included a summary of 4 patients (2 ceftaroline, 2 ceftriaxone) with confirmed SP bacteraemia who were enrolled in Study P903-31 (Paediatric CAP Study).

Across the paediatric studies comprising the ceftaroline fosamil development program, a total of 9 paediatric patients in the mMITT population had a positive baseline blood culture, identified as a typical pathogen. Baseline blood pathogens were as follows: SP – 6 patients; MRSA – 1 patient; MSSA – 1 patient; E. coli – 1 patient. Two (2) patients with SP bacteraemia were treated with comparator; the remaining 7 bacteraemia patients were treated with ceftaroline fosamil. Clinical response rates (Clinical cure) at TOC in the paediatric bacteraemia subgroup were 57.1%. However, the patient numbers are too small to draw any efficacy conclusions.

Table 9: Clinical Response Rates in Paediatric Patients with Concurrent Baseline Bacteraemia from Ceftaroline Fosamil Paediatric Clinical Trials (mMITT Population)

Indication	Study	Clinical Cure at TOC, n/N (%)		
		Ceftaroline	Comparator	Total
CAP	P903-24 P903-31	1 / 2 (50.5) 2 / 4 (50.0)	0 1 / 2 (50.0)	1 / 2 (50.0) 3 / 6 (50.0)
cSSTI	P903-23	1 /1 (100.0)	0	1 /1 (100.0)
Overall		4 / 7 (57.1)	1 / 2 (50.0)	5 / 9 (55.6)

The low number of paediatric patients with baseline bacteraemia enrolled in the ceftaroline fosamil paediatric studies may reflect low yield of blood cultures in these young patients or it may have occurred by chance. It is plausible, however, to extrapolate efficacy observed in adults with bacteraemia associated with cSSTI or CAP to the paediatric population, using the same rationale for

extrapolation of efficacy for the approved indications of cSSTI and CAP. The pathophysiology of bacteraemia associated with cSSTI/CAP is similar between adult and paediatric patients. The minimum inhibitory concentrations (MICs) of pathogens collected from clinical trials and surveillance programs are similar in adults and paediatric patients. Furthermore, Zinforo's mechanism of action targets the pathogen rather than human receptors/physiology; therefore, pharmacokinetic/ pharmacodynamic (PK/PD) targets are the same for both adult and paediatric patients. A robust population PK/PD model based on adult and paediatric clinical trial data was developed and supported the approved dosing regimens for treatment of cSSTI and CAP.

Safety

Within the ceftaroline fosamil paediatric multiple-dose clinical trials, a total of 9 patients had positive baseline blood cultures with an identified pathogen. Seven (77.8%) patients received ceftaroline, and 2 (22.2%) patients received the comparator drug.

Overall, a total of 26 TEAEs were reported by 4/9 (44.4%) patients. AEs were generally mild to moderate in severity (21/26, 80.8%) and unrelated to study drug.

For patients treated with ceftaroline, 3 patients each experienced 1 SAE (gastroenteritis, infectious pleural effusion, and pulmonary thrombosis); all events were assessed as not related and resolved. Only 1 patient within the ceftaroline treatment group was reported to have a treatment related AE; the severe, non-serious events of aspartate aminotransferase (AST) increased and alanine aminotransferase (ALT) increased starting on study Day 8 led to discontinuation of study treatment and were later resolved. Within ceftaroline-treated patients, no other AEs led to discontinuation of study treatment. There were no deaths in this subset of bacteraemic patients.

Safety data in the subset of paediatric patients with concurrent baseline bacteraemia are very limited. However, no new safety findings were identified based on review of the 9 paediatric patients with positive baseline blood cultures from the paediatric clinical studies.

In conclusion, the MAH claims that there have been a considerable number of questions from HCPs related to efficacy and availability of clinical trials data of Zinforo in bacteraemic patients. In the absence of bacteraemia text in clinical trial section of the EPAR, the MAH proposes to add the following summary text to the end of Section 5.1 of the SmPC to clarify concurrent bacteraemia experience from Zinforo clinical trials:

"Clinical efficacy in case of concurrent bacteraemia

A limited number of patients with concurrent bacteraemia were enrolled in clinical trials for the indications of complicated skin and soft tissue infections and community-acquired pneumonia. Among 6 adult studies, 85/1361 (6.2%) patients with cSSTI, and 53/477 (11.1%) patients with CAP were bacteraemic at baseline (mMITT population). The most commonly isolated pathogens in Zinforo-treated patients with concurrent bacteraemia and cSSTI or CAP were Staphylococcus aureus and Streptococcus pneumoniae, respectively. Overall, clinical cure rates in patients with concurrent bacteraemia who received Zinforo treatment were comparable to those seen in the comparator group as well as in the overall population for the respective indications of CAP and cSSTI."

Rapporteur Assessment

In the submitted responses the applicant has now changed the position and is not seeking extension of indication for the treatment of community acquired pneumonia (CAP) to include concurrent bacteraemia due to *Streptococcus pneumoniae* (SP) for all age groups. This is in line with both the view of the CHMP as well as the IDWP (Infection disease working party), that it is evident that Zinforo can be used for secondary bacteraemia without any additional revision on the wording in section 4.1.

The MAH has provided supporting documentation for the bacteraemic versus non-bacteraemic patients regardless of condition or infecting organism from the previous Phase 3 studies.

As a response to major objection the MAH proposes an update of section 5.1 of the SmPC to include data about bacteraemia associated with cSSTI/CAP regardless of infecting organism.

In total, there were 138 patients (72 ceftaroline-treated) with bacteraemia associated with CAP/cSSTI from six Phase 3 clinical trials. Efficacy results are descriptive and limited by small patient numbers. In general clinical response in patients with bacteraemia was lower than in those without but response (clinical cure) in patients treated with ceftaroline vs comparator was largely similar as expected with small denominators, variability was observed by pathogen and within indications.

As regards to safety data, the observed TEAEs were in line with the known safety profile of ceftaroline. Bacteraemic patients had more TEAEs and SAEs than non-bacteraemic patients. Treatment related AE and SAEs were numerically more common in patients treated with ceftaroline than with comparator. The majority of TEAEs were assessed as mild to moderate in severity and unrelated to study drug. No deaths were reported in ceftaroline-treated patients with bacteraemia. The most common related TEAEs' SOCs within the ceftaroline-treated bacteraemic adult patients were gastrointestinal disorders 5 (6.9%), skin and subcutaneous tissue disorders 4 (5.6%), nervous system disorders 3 (4.2%) and vascular disorders 3 (4.2%). The most common related TEAE PTs within the ceftaroline-treated bacteraemic adult patients were Phlebitis 3 (4.2%), Rash 2 (2.8%) and Headache 2 (2.8%). There were no new safety findings during this analysis.

The subset of paediatric patients with concurrent baseline bacteraemia was too limited, to draw any conclusions.

Similar to initial comments current label does not prevent using ceftaroline in patients with concomitant bacteraemia. The MAH, however, argues that prescribers are interested in efficacy of ceftaroline in patients with concomitant bacteraemia. The analyses provided by the MAH are not considered to provide sufficient value to justify the amendment of Section 5.1, given that the current indication, together with information in Section 4.4 on any safety concerns and the current information in 5.1, is considered by the CHMP to adequately reflect the use of Zinforo in a broad indication which does not exclude bacteraemia. The update of section 5.1 is not considered justified and cannot be accepted.

Conclusion

The MO is partially resolved with the applicant not pursuing the extension of the indication regarding CAP.

However, the proposal to update section 5.1 of the SmPC to include information regarding bacteraemia is not supported by the Rapporteur and this is maintained as an MO.

Other concerns

Clinical efficacy aspects

Question 2

The MAH should clarify the microbiological outcome of the bacteraemic patients in the studies P903-08 and P903-09 (the eradication day, including Day 1, Day 2; Day 3; Days 4-6; EOT; TOC or LFU) and specify the meaning of "Presumed eradication" (only clinical cure or eradication before TOC already).

The MAH should submit the microbiological data of eradication stratified by day (P903-08 and P903-09).

Summary of MAH answer

In Studies P903-08 and P903-09, the per-patient and per-pathogen microbiological outcomes at TOC in the mMITTE and ME populations were derived programmatically, using electronic data from the central laboratory and pathogen information determined by the Sponsor for each baseline isolate. The Microbiological Outcome Categories were follows:

Eradication - an appropriate source specimen (any sample that may yield the growth of a CAP pathogen, e.g. blood, respiratory specimens, or pleural fluid) demonstrated absence of the original baseline pathogen

Presumed eradication - an appropriate source specimen was not available to culture, and the subject was assessed as a clinical cure

Persistence - an appropriate source specimen demonstrated continued presence of the original baseline pathogen

Presumed persistence - An appropriate source specimen was not available to culture and the subject was assessed as a clinical failure

Indeterminate - an appropriate source specimen was not available to culture and the subject's clinical response was assessed as indeterminate

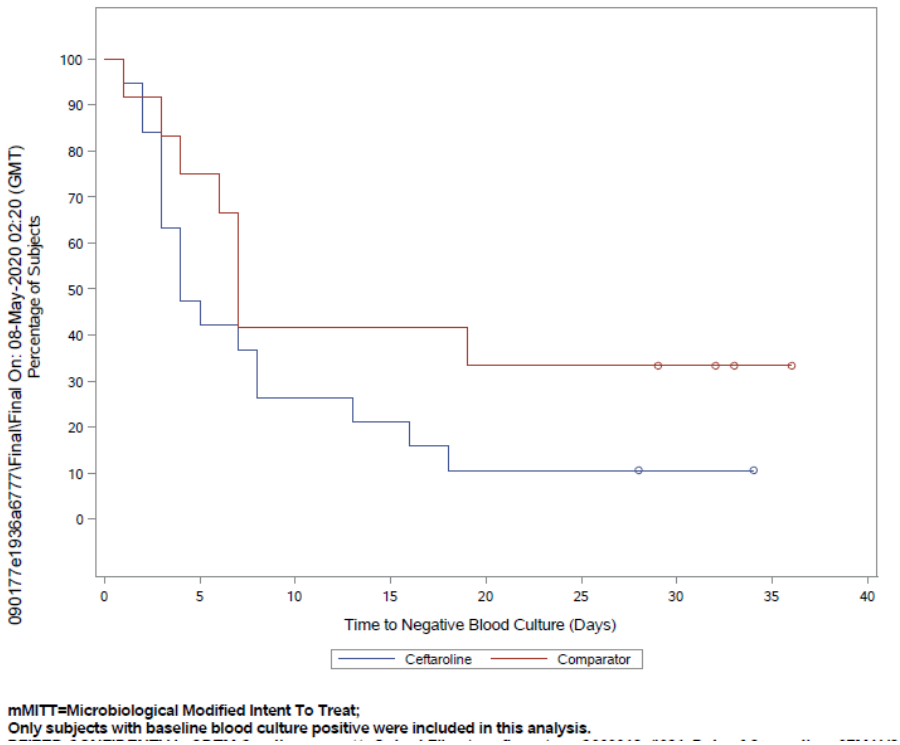
For the special case of pneumococcal infection identified via a urinary antigen test only, the microbiological outcome was always presumed from the clinical response, unless a postbaseline respiratory culture was positive for *S. pneumoniae*, in which case the microbiological outcome was persistence. For patients with coinfection with an atypical pathogen, the outcome for atypical pathogens was presumed from the clinical response, unless serology data at Late Follow-up were available.

The microbiological outcome was determined for a pathogen within a patient and a source (i.e. respiratory specimens or blood). If a pathogen was identified from multiple sources, the worst per-source outcome for that pathogen was used for per-pathogen microbiological outcome. Likewise, if multiple pathogens were identified for a patient, the worst per-pathogen outcome for that patient was used for per-patient microbiological outcome. The microbiological outcomes at TOC were only applicable to patients who were not clinical failures at end of therapy (EOT). Patients who were failures at EOT had the corresponding microbiological outcome determined from EOT cultures and carried forward to TOC. If no EOT culture was available for patients who were clinical failures at EOT, then the microbiological outcome at TOC was presumed persistence. Otherwise, the microbiological outcome at TOC was determined from cultures obtained at the TOC window. If no culture was available in the TOC window, then the microbiological outcome at TOC was presumed from the clinical response at TOC.

According to the conservative definitions applied for the microbiological outcome in the 2 studies, when no culture was available within the TOC window (8-10 days after stopping study drug), the microbiological outcome was presumed from the clinical response. To be considered as presumed eradication, the patient's clinical response must have been clinical cure at TOC. Protocol requirements for repeat blood cultures in both protocols were as follows: "Blood for culture was obtained if the previous blood culture was positive or if medically indicated. Blood for culture was not obtained at TOC if the subject was a failure at EOT". Patients with a positive blood culture at baseline were required to have follow-up cultures at subsequent study visits; however, once the follow-up blood cultures were negative, there was no additional requirement for blood cultures to be taken in the TOC window unless

the investigator determined there was a medical need. The majority of patients with baseline blood cultures positive for SP had follow-up negative blood cultures taken 1-7 days after baseline (i.e. on Study Days 2-8); and therefore, did not require cultures to be drawn during the TOC window according to the study protocols. This accounts for the preponderance of microbiological outcomes being presumed eradication rather than eradication at TOC.

For ceftaroline-treated patients with SP bacteraemia, the median time to negative blood culture was 4 days (range 1-18 days). For comparator-treated patients with SP bacteraemia, the median time to negative blood culture was 7 days (range 1-19 days). To further assess the rate at which blood cultures became negative in SP bacteraemic patients in Studies P903-08 and P903-09 who achieved negative blood culture, a "time-to-negative-culture" analysis was conducted.



mMITT=Microbiological Modified Intent To Treat;
Only subjects with baseline blood culture positive were included in this analysis.

Figure 2: Kaplan-Meier Plot of time to negative blood culture for Streptococcus pneumoniae bacteraemia patients (mMITT Population)

In summary, the preponderance of presumed eradication microbiological outcomes in patients with SP bacteraemic who were clinical cures at TOC is the result of the conservative definition for eradication which required that a negative blood culture be collected during the narrow TOC window. Because a majority of patients achieved negative culture prior to the TOC window (i.e. median of 4 days for patients treated with ceftaroline), an additional blood culture was not obtained at TOC, which was in line with the protocol requirements and expected in cases where the patient was improving clinically.

Rapporteur Assessment

Issue resolved.

Question 3

According to the data presented for studies P903-08 and P903-09, with the exception of one patient the remaining were marked as "presumed eradication or presumed persistence". This makes assessor to assume that no repeated blood cultures were taken in vast majority of cases despite the recommendations given in the protocol. The MAH should clarify this.

Summary of MAH answer

As noted in the previous response, protocols for Studies P903-08 and P903-09 specified that follow-up blood cultures were to be taken if the previous blood culture was positive or if they were medically indicated. Blood cultures were not mandatory at EOT or TOC unless previous blood cultures remained positive. A review of microbiological culture results indicates that follow-up blood cultures were taken in the majority of SP bacteraemic patients, which was consistent with protocol recommendations. Within ceftaroline-treated patients, there were 2 patients for whom post-baseline blood culture data are not available: 1 patient was a clinical cure at TOC, and 1 patient was a clinical failure with persistent symptoms of community-acquired bacterial pneumonia (CABP) at TOC.

Rapporteur Assessment
Issue resolved.

Question 4

There were 2 patients with infection caused by multiple microorganisms. The MAH should clarify whether all these microorganisms were cultured from blood or were they found in different sites.

Summary of MAH answer

One patient had both SP and *S. aureus* isolated from the baseline blood culture; no isolates were obtained from other culture sites. A follow-up blood culture taken on Day 8 was negative for both pathogens; no additional follow-up blood cultures were obtained. The patient was assessed as a clinical cure at both EOT and TOC visits. The per patient response was favourable, and the per pathogen microbiological outcome at TOC for both pathogens were presumed eradication.

One patient had both SP and *E. coli* isolated from the baseline blood cultures; no isolates were obtained from other culture sites. The patient had persistent symptoms of CABP at TOC and was considered a clinical failure. The per patient microbiological response was unfavourable. In the absence of follow-up blood cultures, the per pathogen microbiological outcome at TOC for both pathogens were presumed persistence.

Rapporteur Assessment
No further comments, issue is resolved.

9. CHMP member comments on the assessment of the 1st RSI responses

MS#1 comment: The rapporteur's assessment that no revisions are needed to section 4.1 is endorsed. Adding clinical data on treatment of bacteraemia to section 5.1 is not endorsed for the reasons indicated below. Additionally we have a specific SmPC comment.

Clinical Efficacy: MS#1 supports the opinion that the current CAP indication already covers treatment of patients with secondary bacteraemia and the agreement of the applicant that no revisions are needed in section 4.1 is thus endorsed. However the MEB is not convinced that the additional data on bacteraemia should be incorporated in section 5.1.

According to the draft antibacterial guideline (rev.3), clinical data should only be added to section 5.1 of the SmPC if considered directly relevant to the approved indications and secondary analyses should not usually be included unless the information is of high importance to guide usage.

As has been previously commented in the discussions on Zemdri (in which the applicant also proposed to include clinical data on treatment of patients with cUTI and concurrent bacteraemia in section 5.1 *(EMEA/H/C/004457*) extra information in the SmPC on the treatment of patients with concurrent bacteraemia is not needed unless there is a concern raised by the data available, in which case this concern should be placed in section 4.4.

Considering the draft antibacterial guideline (rev. 3) and considering previous discussions on Zemdri, MS#1 is not convinced that the data on the treatment of bacteraemic patients should be incorporated in section 5.1. Firstly, the secondary analyses are not considered to be directly relevant to the approved indication of CAP and are not needed to guide use of Zinforo in patients with bacteraemic CAP. Secondly, the secondary analysis did not result in specific concerns regarding the treatment of bacteraemic patients and if it did raise additional concerns, these should be incorporated in section 4.4.

SmPC, PIL, labelling: If the CHMP will allow for the addition of the bacteraemia data to section 5.1, the actual numbers of patients treated for bacteraemic CAP with ceftaroline, should be reflected as the number of adult bacteraemic SP CAP patients on ceftaroline in pooled analyses was very low – only 19 adult patients received ceftaroline.

MS#2 comment: The assessment and conclusions of the Rapporteur is agreed. MS#2 supports the opinion that the current wording in section 4.1 of the SmPC already covers the indication of secondary bacteraemia (linked to CAP and cSSTI) initially applied for. Thus, the agreement of the Applicant that no revisions are needed in section 4.1 is endorsed.

The update of section 5.1 to include clinical trial data with regard to the treatment of bacteraemia linked to CAP and cSSTI with Zinforo is also agreed. This is based on the fact that these data are considered of significant relevance and that mentioning of such data is in line with the draft Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3. The guideline states that clinical data from efficacy studies might be implemented in section 5.1 of the SmPC. Since the proposed wording of section 5.1 is a summary statement of clinical efficacy trials relevant to the treatment of bacteraemia linked to CAP and cSSTI including a description on the outcome of the trials, the addition is considered in line with the draft guideline and thus acceptable.

MS#3 comment: The Rapporteur's assessment that no revisions are needed to section 4.1 is endorsed. Adding clinical data on treatment of bacteraemia to section 5.1 is not endorsed for the reasons indicated further below.

SmPC, PL, labelling: In our opinion the design and the conduct of the studies included in this application, exclude the possibility for drawing a clear and valuable conclusion on the efficacy of ceftaroline in case of bacteraemia.

The diverging proposals for the amendment to section 5.1 of the SmPC made by the applicant and the Rapporteur illustrate this clearly:

The applicant proposes "*Overall, clinical cure rates in patients with concurrent bacteraemia who received Zinforo treatment were comparable to those seen in the comparator group as well as in the overall population for the respective indications of CAP and cSSTI.";*

The Rapporteur proposes *"The clinical cure rates were lower in bacteraemic patients (76.4% vs 77.3% in ceftaroline and comparator group accordingly) compared to the clinical cure rates in non-bacteraemic patients (85.1% vs 82.2% in ceftaroline and comparator group accordingly)."*

The draft of the "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3" states that *it is not considered that an indication for treatment of bacteraemia can be substantiated by a trial that enrols patients with bacteraemia due to a specific pathogen regardless of the primary focus of infection. Such trials are not recommended because i) most patients will be treated for a site-specific infection, whether known or unknown, with associated bacteraemia and the outcome will be related to source control and ii) the trial will not be designed or powered to assess efficacy in sub-groups defined by primary foci or unknown source.* Regarding Section 5.1 of the SmPC the GL states (see below): *Secondary analyses should not usually be included unless the information is of high importance to guide usage*

Furthermore, we do not find it appropriate to accept the result "presumed eradicated" as a marker for positive efficacy ("favorable") when the diagnosis in concern is bacteraemia. We may need to know whether control blood cultures were negative at a well-defined time point.

Another problem is the use of the word "comparator" instead of the names of the comparators. The applicant states in the rationale for the application that he wants to make it easier for the clinicians to decide which treatment would be suitable for his patient with bacteraemia. According to the Rapporteur's proposal the clinician would most probably prefer the comparator; however, he will not know which product was the comparator.

A third problem is the paragraph used in both proposals "*The most commonly isolated pathogens in ceftaroline fosamil-treated patients with concurrent bacteraemia and cSSTI or CAP were Staphylococcus aureus and Streptococcus pneumoniae, respectively."* Why only inform about the most commonly isolated pathogens in the ceftaroline group? If the frequencies of the different species differ between the two treatment arms, this could theoretically be an explanation for different efficacy in the two arms. So, either delete the sentence or add information about the comparator-group.

MS#4 comment: The conclusion that no revisions are needed to section 4.1 is endorsed.

As commented during the first round of assessment MS#4 is of the opinion that this "supplement" to syndrome-specific indications is redundant. MS#4 considers that it is sufficient that any concerns regarding the efficacy in the treatment of patients with a syndrome-specific indication associated with bacteraemia are expressed in section 4.4. Unless there are any concerns, no information with regards bacteraemia is needed in the SmPC. This has been discussed and agreed by the CHMP in earlier procedures (Zemdri). Introducing information with regards subgroup analyses of patients with concurrent bacteraemia in section 5.1 will be setting a new precedent. Therefore, MS#4 is of the opinion that the paragraph proposed for section 5.1 should be deleted.

Rapporteur comment: taking into account MSs comments received and the draft antibacterial guideline (rev.3), the proposal from the Applicant to update section 5.1 of the SmPC, to include statement about bacteraemia associated with cSSTI/CAP, is reconsidered by the Rapporteur and is not regarded justified. It is evident from the current SmPC that Zinforo can be used for secondary bacteraemia without any additional revision on the wording in sections 4.1 or 5.1.

Additionally, as observed for Zinforo, in general the clinical response in patients with bacteraemia was lower than in those without but response (clinical cure) in patients treated with ceftaroline vs

comparator was largely similar. The secondary analysis did not result in specific concerns regarding the treatment of bacteraemic patients, which in any case should be included under section 4.4, as also noted in the MSs comments. Therefore this proposal is not following the draft GL where it is stated that "*Secondary analyses should not usually be included unless the information is of high importance to guide usage.* "

To be in line with the previous approaches of the CHMP for similar cases and acknowledging the comments received, Rapporteur considers that in the absence of dedicated studies the proposed amendment to section 5.1 not sufficiently justified and not supported and is maintained as an MO. Hence the MO raised in the first round is considered as partially resolved.

10. Rapporteur assessment report of the MAH responses to the 2nd Request for Supplementary Information

Major objections

Clinical efficacy aspects

1. Current labelling supports the use of Zinforo in cases of secondary bacteraemia without any need for subsequent revision of SmPC. According to the responses submitted, the applicant has agreed not to change current wording in section 4.1 and has proposed to update section 5.1 to reflect the current knowledge in the treatment of patients with secondary bacteraemia. The analyses provided by the MAH are not considered to provide sufficient value to justify the amendment of Section 5.1, given that the current indication, together with information in Section 4.4 on any safety concerns and the current information in 5.1, is considered by the CHMP to adequately reflect the use of Zinforo in a broad indication which does not exclude bacteraemia.

Summary of Applicant's responses

The MAH acknowledges the CHMP comments. Secondary bacteraemia occurs in a significant number of patients with CAP or cSSTI and may be even more frequent in more severe patients that require hospitalisation. Indeed, up to 20% of CAP patients may suffer from concurrent bacteraemia.[1] If the bacteria involved are under the therapeutic range of Zinforo, these patients may benefit from treatment with Zinforo and, therefore, explicitly addressing this within the Product Information (PI) would seem "of high importance to guide usage", and consistent with EMA guidance in the draft "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3"[2] related to the inclusion of secondary analyses Section 5.1 of the SmPC.

The absence of a concurrent bacteraemia indication or absence of any bacteraemia-related text in the PI may lead HCPs to believe that there is not sufficient data to support the use of Zinforo in secondary bacteraemia. This misunderstanding may lead to unwanted outcomes, either with patients suitable for Zinforo treatment not being started on the drug or being unnecessarily switched to other agents, resulting in, as examples:

1. Patients being exposed at first instance to regimens with potentially lower efficacy compared to Zinforo.

   Zinforo showed excellent efficacy against main pathogens responsible for CAP in its Phase 3 studies.[3] Although the pivotal studies were not planned for demonstrating superiority, Zinforo achieved unadjusted clinical cure rate of 85.5% vs. 68.6% in the ceftriaxone group (P = 0.009) in the cohort of 139 subjects (69 ceftaroline, 70 ceftriaxone) with confirmed SP CAP. Notably, the microbiological response was 87.0% (60/69) and 72.9% (51/70) for ceftaroline and ceftriaxone, respectively (P=0.0003)[4]

   More importantly, ceftriaxone has limited activity against *Staphylococcus aureus* (SA), which seems particularly important in some CAP patients (as in patients with post-influenza CAP).[5] Zinforo has potent activity against SA, including methicillin-resistant *Staphylococcus aureus* (MRSA) and its clinical efficacy was tested in CAP (excluding patients with MRSA infection), with a clinical cure rate of 72% (18/25) vs. 60% (25/30) for ceftriaxone.

2. Patients being unnecessarily switched to an alternative antibiotic and thus potentially experiencing the adverse events (AEs) of that treatment.

A patient with a cSSTI suspected or documented to be caused by MRSA could be switched to vancomycin. There is established evidence of renal toxicities related with vancomycin, especially if preventive actions are not taken or the resistance of MRSA leads to increasing the dosage of vancomycin.[6] However such patients with suspected or confirmed secondary bacteraemia could be continued on Zinforo, if the HCP were confident about its use in that clinical setting.

In addition, the MAH is concerned that HCPs do not share the same level of awareness that patients with concurrent bacteraemia are included under the approved indications of cSSTI and CAP. Provided within our previous response dated 20 May 2020, the MAH advised that queries were received from medical information, sales representatives, and customer facing medical colleagues. The Medical Information database for only European Union (EU) countries recorded 23 enquiries in 2019, which represents 5.72% of total for all Zinforo enquiries received in that year. Due to current marketing codes of conduct, as secondary bacteraemia is not explicitly mentioned in the SmPC, many Pfizer country offices are not able to discuss the topic of secondary bacteraemia with HCPs via sales representatives, nor can they inform HCPs on secondary bacteraemia by any proactive communication channels.

Furthermore, older anti-infectives, including the comparator drugs used in the Zinforo Phase 3 clinical trials: ceftriaxone, vancomycin and aztreonam, have bacteraemia wording included in their respective PI, either as a statement referring to secondary bacteraemia ("(…) the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above")[7,8] or as a more inclusive indication of "Bacteraemia/septicaemia" as is the case for aztreonam.[9]

The MAH believes that the omission of wording in the Zinforo PI may lead HCPs to not use, or delay use of, Zinforo in patients with concurrent bacteraemia who could potentially benefit from treatment with Zinforo.

The MAH also notes the recent CHMP opinion received for secondary bacteraemia indication to the Zavicefta PI. The MAH understands that inclusion of concurrent bacteraemia text in Section 4.1 of the SmPC for Zavicefta was possible because such text was already included in the ceftazidime PI; however, HCPs likely do not share the same level of awareness or understanding of the regulatory guidance regarding the inclusion of bacteraemia text in Section 4.1. The discrepancy in bacteraemia text between the Zavicefta and Zinforo labels could inappropriately lead HCPs to believe that there is not adequate data to support the use of Zinforo in the case of secondary bacteraemia.

Additional confusion may result from the lack of alignment between the Teflaro United States Prescribing Information (USPI), containing selective concurrent bacteraemia indication: "Teflaro is indicated in adult and paediatric patients 2 months of age and older for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteraemia)".[10]

In summary, the MAH strongly believes that the absence of bacteraemia text in the current SmPC represents a significant issue. The strategy to include text into Section 5.1 would seem consistent with the draft "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3"[2]: "Secondary analyses should not usually be included unless the information is of high importance to guide usage". The MAH therefore proposes the following text to Section 5.1 of the SmPC, taking into account the comments received by the EMA within the updated AR dated 16 July 2020:

5.1 Pharmacodynamic properties

"*Clinical efficacy in case of concurrent bacteraemia*

A limited number of patients with concurrent bacteraemia were enrolled in clinical trials conducted for the indications of cSSTI and CAP. Among 6 adult studies, 85/1446 (5.9%) patients with cSSTI and 53/530 (10.0%) patients with CAP were bacteraemic at baseline, of which 72 patients were treated with ceftaroline fosamil. The clinical cure rates in patients with concurrent bacteraemia were 76.4% in the ceftaroline fosamil group and 77.3% in the comparator group (aztreonam/vancomycin for cSSTI and ceftriaxone for CAP). The clinical cure rates in non-bacteraemic patients were 85.1% and 82.2% in ceftaroline and comparator group (aztreonam/vancomycin for cSSTI and ceftriaxone for CAP), respectively."

Rapporteur Assessment

No new data have been submitted.

The MAH has submitted further arguments to support their request to include some text indicating the acceptance of the CHMP of the use of Zinforo in patients with concurrent bacteraemia.

As previously, the discrepancy between the product information of antibacterial agents authorised at different time-points is accepted.

Although the practical concern is well understood, the inclusion of the proposed data would create yet another configuration of product information that is not in line with the current regulatory practice.

The basis for acceptance of the use of the product in patients with concurrent bacteraemia is wider than the proposed text/reference and issues around the data proposed to be included have been discussed in the earlier rounds of assessment.

Based on the earlier CHMP position for similar cases and as there is no new data, the Rapporteur is of the opinion that the proposed text cannot be accepted for inclusion in section 5.1. of the SmPC. The public assessment report can be used as a reference to answer any queries to the MAH related to the topic.

Issue not resolved.

Supporting Rapporteur assessment: MS#1, MS#3, MS#4, MS#5

MS#4 comment: MS#4 supports the Rapporteur´s position in that the proposed paragraph for Section 5.1 should be deleted, the rationale for which has been provided in previous MS#4 comments.

However, MS#4 proposes to exclude, in the assessment report, any hints to the Applicant that this possibly could have been resolved by additional data.

Not supporting Rapporteur assessment:

MS#2: We still agree with the Applicant that the inclusion of clinical trial data concerning bacteraemia linked to CAP and cSSTI provides relevant and important information for the prescriber.

The inclusion of this information in section 5.1 does not contradict the requirements of the draft Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3, but rather is in accordance with the Guideline.

The wording as modified by the applicant is agreed with.

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