EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

REFUSAL ASSESSMENT REPORT

FOR

Zeftera ***(previously known as Zevtera)***

International Nonproprietary Name:

Ceftobiprole medocaril

Procedure No. EMEA/H/C/000883

Applicant: Janssen-Cilag International NV

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 15 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ceftobiprole medocaril, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 14 December 2006.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 21 September 2006 and 22 March 2007. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
A new application was filed in the following countries: United States on 18 May 2007.
The product was not licensed in any country at the time of submission of the application.

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

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: **János Borvendég**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 15 June 2007.
- The procedure started on 18 July 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 October 2007 (Annex 4.1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2007 (Annex 4.2).
- During the meeting on 12-15 November 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 November 2007 (Annex 4.3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 May 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 8 July 2008 (Annex 4.4).
- During the CHMP meeting on 21-24 July 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 4.5).
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 15 September 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 9 October 2008 (Annex 4.6).

- During the CHMP meeting on 20-23 October 2008, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant (Annex 4.7).
- The applicant submitted the responses to the CHMP consolidated second List of Outstanding Issues on 23 October 2008
- The Rapporteurs circulated the consolidated version of the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 14 November 2008 (Annex 4.8).
- During the meeting on 17-20 November 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zevtera on 20 November 2008.
- After the positive opinion was adopted, the applicant informed the CHMP that for the two pivotal studies BAP00154 and BAP00414 data from clinical investigators inspected by the US Food and Drug Administration were not considered reliable.
- The Rapporteurs circulated a post-Opinion Assessment Report on GCP issues on 16 December 2008.
- Consequently, the CHMP informed the European Commission on 18 December 2008 before the issuing of a Decision on GCP findings.
- The applicant submitted responses to the issues raised in the post-Opinion assessment report on 13 January 2009.
- The Rapporteurs circulated an updated post-Opinion Assessment Report on GCP issues on 16 January 2009, including a List of Questions to be addressed at an oral explanation.
- An oral explanation was given by the applicant on 21 January 2009.
- The CHMP agreed on a list of questions to be addressed by the applicant following the oral Explanation on 22 January 2009
- The CHMP requested the European Commission to return the opinion to further assess the benefit risk balance in light of ongoing and planned GCP inspections on 22 January 2009.
- The applicant submitted responses to the CHMP LoQ on 27 January 2009
- The Rapporteurs' circulated an updated Post-Opinion Assessment Reports of the applicant's Response to CHMP LoQ (January 2009) on 06 and 13 February 2009
- The applicant submitted responses to outstanding points in the updated Post-Opinion Assessment Report (42 site audit plan + microbiologic inclusion criteria #6) on 27 February 2009
- The CHMP then requested that GCP inspections be carried out on the pivotal studies BAP00154 and BAP00414. The final GCP inspection request, including the sites to be inspected and the inspection scope was adopted by the Committee on 19 March 2009.
- Following a positive outcome of the CHMP/NRG review on the acceptability of the invented name the applicant has requested on 10 February 2010 a change of the invented name to Zeftera.
- The applicant submitted responses to outstanding points in the updated Post-Opinion Assessment Report (42 site audit and EU GCP inspection) on 28 August 2009
- The applicant submitted updated responses to outstanding points in the updated Post-Opinion Assessment Report (42 site audit and EU GCP inspection, including information on FDA warning letter) on 11 September 2009

- The final integrated GCP inspection report was issued on 15 September 2009.
- The Rapporteurs' circulated an updated Post-Opinion Assessment Report on the response to CHMP Questions (January 2009) on 17 September 2009.
- The CHMP discussed and evaluated the outcome of the inspection and its impact on the assessment of the benefit risk balance during the September 2009 CHMP plenary session.
- The Rapporteurs circulated a further updated Post-Opinion Assessment Report on the response to CHMP Questions (January 2009) on 22 December 2009
- The Rapporteurs circulated a further updated Post-Opinion Assessment Report on the response to CHMP Questions (January 2009) on 15 January 2010
- An Oral Explanation was given by the applicant on 20 January 2010.
- The CHMP adopted a Question to be addressed by the applicant in writing on 20 January 2010.
- The applicant submitted the responses to the CHMP Question following the Oral Explanation on 28 January 2010.
- The Rapporteurs circulated the final further updated Post-Opinion Assessment Report on the response to CHMP Questions (January 2009) on 12 February 2010.
- The CHMP adopted on 18 February 2010 a revised opinion according to Art 6 of Regulation (EC) No 726/2004 of 31 March 2004.

1.3 Steps taken for the re-examination procedure

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

Rapporteur: **Dr Tomas Salmonson** Co-Rapporteur: **Dr Alar Irs**

- On 9 March 2010 Janssen-Cilag International NV submitted written notice to the European Medicines Agency to request a re-examination of the revised opinion.
- On 25 April 2010 the detailed grounds for the re-examination request were submitted to the European Medicines Agency.
- The Rapporteur's Assessment Report of the Grounds for the re-examination procedure was circulated to all CHMP members on 2 June 2010 (Annex 4.17). The Co-Rapporteur's Assessment Report of the Grounds for the re-examination procedure was circulated to all CHMP members on 3 June 2010 (Annex 4.18).
- A Scientific Advisory Group was consulted on 11 June 2010.
- An oral explanation was given by the applicant on 22 June 2010.
- During the meeting on 21-24 June 2010, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

Not applicable

3. SCIENTIFIC DISCUSSION

3.1 Introduction

Skin and soft tissue infections (SSTIs) comprise a broad range of clinical presentations. These infections are typically classified as complicated (cSSTIs) if they require surgical intervention, involve deeper soft tissue such as fascia or muscle, or occur in patients with significant underlying disease that complicates the response to treatment, e.g. diabetes mellitus, neoplastic disease, HIV or peripheral vascular disease. They include infections complicating local traumatic injury or bite injury, burns, surgical procedures, major abscesses, cellulitis, fasciitis, diabetic foot infection (DFI), infected ischemic or decubitus ulcers, complicated erysipelas.

In clinical practice, postoperative surgical site infections represent up to 25% of all nosocomial infections and their treatment generally requires hospitalization. The pathogens involved in cSSTIs mainly depend on the location of infection and reflect the bacterial flora at the anatomical site of the infection. Most frequently isolated pathogens in skin and soft tissue infections are gram-positive aerobes like *S. aureus* and *Str. pyogenes,* followed by gram-positive anaerobic species and gram-negative bacteria like *Pseudomonas* and *Enterobacter* species.

According to the SENTRY Antimicrobial Surveillance Program in the United States and Canada, the major pathogens isolated from skin and soft tissue infections include: *S. aureus* (45.9%), *P. aeruginosa* (10.8%), *Enterococcus sp*ecies (8.2%), *E. coli* (7.0%), *Enterobacter sp*ecies (5.8%), and *Klebsiella sp*ecies (5.1%). *Proteus mirabilis* (3.0) and *beta -hemolytic streptococci (5.1%)*[1]*.* Gram-negative bacteria are isolated more frequently in severe and polymicrobial infections.

Diabetic patients with infections involving the foot represent an important subgroup of patients with cSSTI. Compromised vasculature and neuropathy leading to traumatic injury of abraded skin on the foot as well as subtle deficiencies in immune responses have been recognised as the most important factors contributing to the high prevalence of these infections in diabetics.

Besides anti-microbial therapy, surgical intervention is commonly required in complicated skin and soft tissue, such as surgical debridement and/or incision and drainage of abscesses and amputation of diabetic foot.

Methicillin-resistant *S. aureus* (MRSA) prevalence in SSTI varies greatly among countries in Europe with an incidence of MRSA 1% to 10% in Germany, Sweden, Denmark, Finland, the Czech Republic, and Iceland, 10% to 25% in Austria, Belgium, and Luxembourg, and more than 25% in the United Kingdom, Spain, Ireland, Italy, Greece, Portugal, Bulgaria, and Malta. Since MRSA is also resistant to many other

[1]Rennie RP, Jones RN, Mutnick AH, and the SENTRY Program Study Group (North America). Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: Report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000). Diagn Microbiol Infect Dis 2003,45:287–293. EDMS-PSDB-6795896.

antimicrobial agents, both β –lactams and non-β-lactams (e.g clindamycin, rifampicin), more recently approved agents such as linezolid, daptomycin, and tigecycline, have been considered as appropriate, empiric treatment for infections suspected or proven to be caused by methicillin-resistant organisms. With a single exception, tigecycline, these agents have no or negligible activity against gram-negative bacteria.

Ceftobiprole has a bactericidal mode of action and has *in vitro* antimicrobial activity against multi-resistant staphylococci, including MRSA. It is active against most clinically important gram-positive (including MRSA) and various gram-negative bacteria.

Ceftobiprole medocaril has been developed as a prodrug due to solubility limitations of the active moiety, ceftobiprole. Ceftobiprole medocaril is very rapidly converted to ceftobiprole upon intravenous administration.

This β-lactam anti-bacterial agent has *in vitro* activity against a broad spectrum of gram-positive bacteria, including methicillin-resistant *Staphylococcus* species (MRSS), vancomycin-resistant *S. aureus* (VRSA), ampicillin-susceptible *Enterococcus faecalis*, and penicillin- and ceftriaxone-resistant *S. pneumoniae* (PRSP).

Ceftobiprole has poor activity against *Enterococcus faecium* and *Proteus vulgaris* and limited useful activity against β-lactamase-producing anaerobic bacteria, including *Bacteroides* species.

The claimed indication was:

"Zeftera is indicated for the treatment of complicated skin and soft tissue infections, including diabetic foot infections without concomitant osteomyelitis (see sections 4.4 and 5.1).

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

The originally *recommended dosage* regimen was 500 mg administered every 8 hours as a 120 minute intravenous infusion for:

- infections documented or suspected to be due to gram-negative bacteria or due to both gram-positive and gram-negative bacteria;
- diabetic foot infections without concomitant osteomyelitis.

In documented or suspected cases of gram-positive bacterial infection, 500 mg of Zeftera can be administered every 12 hours as a 60 minute intravenous infusion. The every 12-hour dosing regimen has not been studied in patients with diabetic foot infections.

The usual treatment duration is 7-14 days and should be guided by the severity, site of the infection and the patient's clinical response.

There is no experience in paediatric patients.

3.2 Quality aspects

Introduction

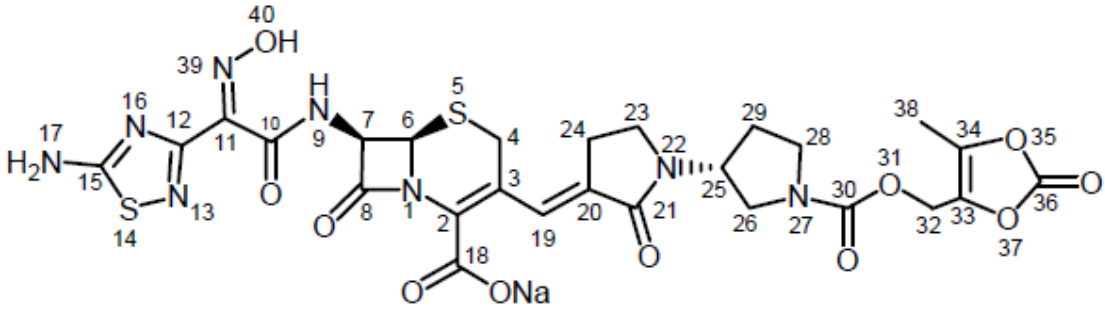
The medicinal product Ceftobiprole is presented as powder for solution for infusion, intended for intravenous administration after reconstitution and dilution. Ceftobiprole is presented as vials containing 500 mg ceftobiprole (which corresponds to 666.6 mg of ceftobiprole medocaril sodium) as active substance. The active ingredient is present as a sterile lyophilized powder.

Ceftobiprole is supplied in cartons containing 10 single use glass vials with rubber stopper and a flip-off aluminium seal.

Active Substance

The chemical name for ceftobiprole medocaril is : (6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxylimino)acetyl]amino]-3-[(*E*)-[(3'*R*)-1'-[[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy] carbonyl]-2-oxo[1,3'-bipyrrolidin]-3-ylidene]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, monosodium salt. The molecular formula is $C_{26}H_{25}N_8NaO_{11}S_2$ and the molecular weight is 712.64 g/mol

The molecular structure is given below:



Ceftobiprole medocaril is an amorphous white to yellowish or slightly brownish powder. Ceftobiprole medocaril does not show polymorphism but appears consistently in amorphous form. The substance is highly water soluble and very hygroscopic.

Ceftobiprole medocaril has been developed as a pro-drug due to solubility limitations of the active moiety, ceftobiprole. Ceftobiprole medocaril 666.6 mg corresponds to 500 mg of the active substance ceftobiprole.

The chemical structure of ceftobiprole medocaril has been confirmed using analytical data by elemental analysis, IR spectroscopy, NMR spectroscopy, UV-VIS spectroscopy, single crystal X-ray diffraction and mass spectrometry. All data are consistent with the proposed structure.

- Manufacture

The active substance is manufactured by a three step process. Detailed information about the manufacturing, validation and analytical controls of all manufacturing steps of the active substance has been supplied. The starting materials have been adequately characterized and the manufacturing process has adequately been validated.

All relevant impurities have been appropriately discussed and characterized. The levels of the impurities are considered acceptable and appropriate specifications have been set.

Information on stability studies conducted for ceftobiprole medocaril is provided. The stability data support the proposed retest period.

- Specification

The active substance specifications include appropriate tests for appearance, identifications (IR spectra and HPLC), assay and impurities (HPLC), residual solvents, water content, heavy metals, bacterial endotoxins and microbiological purity.

The impurity limits are acceptable and there is no concern in relation with safety or efficacy.

The batch analysis data support the proposed acceptance limits.

- Stability

Stability studies have been performed in accordance with the ICH requirements. The test parameters evaluated in these studies were appearance, assay, chromatographic purity and water content.

The active substance has also been subject to stress studies, to forced degradation studies and to photostability studies. The stability data provided justify the proposed retest period in the proposed storage conditions.

Medicinal Product

- Pharmaceutical Development

The medicinal product is a sterile, lyophilized powder for solution for infusion, formulated with commonly used pharmaceutical excipients. The development of the medicinal product is adequately explained.

- Adventitious Agents

None of the materials used in the manufacture of the medicinal product is of animal and/or human origin.

- Manufacture of the Product

The manufacturing process consists of the following steps: compounding, sterile filtration, sterile filling, lyophilisation, stoppering and capping. The manufacturing procedures ensure appropriate microbiological quality of the medicinal product at every step of the process.

The excipients used in the formulation are: citric acid monohydrate, sodium hydroxide, water for injection and nitrogen and comply with the monographs of the current PhEur.

Ceftobiprole medocaril is an amorphous material completely dissolved during the manufacture of the medicinal product. Although the end product is lyophilised it is reconstituted and diluted before use.

Critical process parameters during manufacturing have been identified and controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the finished product specifications.

- Product Specification

Appropriate finished product specifications have been set. The specifications for the finished product at release and shelf life are classical for this pharmaceutical form and include tests for appearance, identification (HPLC, IR) and assay of the active substance, uniformity of dosage units, reconstitution of the solution, water content, impurities, bacterial endotoxins and sterility. All tests included in the specification have been satisfactorily described and validated, according to the state of the art.

Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Batch analysis data show that the proposed specifications are met.

- Stability of the Product

Long term and accelerated stability studies have been carried out according to the ICH requirements. The parameters tested are the appearance of powder and cake, colour and clarity of reconstituted solution, reconstitution time, pH, particulate matter, water content, sterility and endotoxin content. Additionally, the assay and related substances are measured. The analytical methods used were identical to those used for the release specifications. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the proposed storage conditions.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Ceftobiprole is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation.

The Ceftobiprole powder for solution for infusion intended for marketing is well suited; the manufacturing process is under control and ensures both batch to batch reproducibility and compliance with standard procedures and specifications; the analytical methods have been validated and ensure consistent quality of the active substance and the finished product, the synthetic pathway is presented and the structure and impurity profile are well characterised and in line with current ICH guidelines. The stability data on the active substance supports the proposed re-testing period. The stability data of the finished product in the proposed commercial packages support the proposed shelf life.

At the time of the initial CHMP opinion there were some unresolved minor quality issues which had no impact on the benefit/risk profile. These minor issues have been resolved meanwhile.

3.3 Non-clinical aspects

Introduction

Ceftobiprole medocaril (BAL5788) is the water-soluble pro-drug of a novel cephalosporin, ceftobiprole (BAL9141).

Pilot studies were generally conducted as "non- Good Laboratory Practice (GLP) compliant", whilst pivotal toxicological studies were conducted according to GLP guidelines of the country where the study was performed.

Pharmacology

- Primary pharmacodynamics (in vitro/in vivo)

The primary targets of β-lactam antibiotics, including cephalosporins such as ceftobiprole, are penicillin-binding proteins (PBPs), membrane-associated bacterial enzymes involved in the last steps of peptidoglycan (cell wall) biosynthesis. Ceftobiprole showed good affinity for PBPs of *Staphylococcus aureus*, also for PBP2a of methicillin resistant strains, and for PBPs of *Streptococcus pneumoniae*. Ceftobiprole generally showed good affinity for PBPs 1, 2, 3 and 4 of gram-negative bacteria *E.coli* and *P.aeruginosa*.

Ceftobiprole exhibited good *in vitro* activity against gram-positive bacteria. Against *Staphylococcus aureus* MIC90 values were ≤ 4 µg/ml, also against methicillin/oxacillin resistant isolates. Ceftobiprole also inhibited in vitro activity against other staphylococci, against which MIC90 generally was ≤ 4 µg/ml. Against streptococci, MIC90 generally was ≤ 1 µg/ml. Against gram-negative bacteria, ceftobiprole showed good *in vitro* activity against ESBL-negative or ceftazidime susceptible isolates (MIC90 generally ≤ 0.5 µg/ml), but not against ESBL-positive or ceftazidime non-susceptible isolates (MIC90 > 256 µg/ml).

Ceftobiprole was active against MSSA, MRSA, *S.pyogenes*, *S.pneumoniae* (pen-S and pen-R), *E.coli*, *K.pneumoniae*, *E.cloacae*, *C.freundii*, *S.marcescens*, *P.mirabilis*, and *P.aeruginosa* in a murine septicaemia infection model. Ceftobiprole was active against *S.pneumoniae* (pen-S and pen-R), *H.influenzae* β-lactamase negative, *E.cloacae* ESBL negative, and *K.pneumoniae* ESBL negative, in murine respiratory tract infection models. Ceftobiprole was active against *P.aeruginosa* in a murine neutropenic thigh infection model. Furthermore, ceftobiprole was active against MRSA in endocarditis infection models in rats and rabbits, in a rabbit osteomyelitis infection model and against MRSA and MSSA in mice skin and soft tissue models. Complete eradication was shown of *S.pneumoniae* pen-R in a respiratory tract infection model in mice and of MRSA in endocarditis infection models in rats and in rabbits, in a murine skin and soft tissue model, and in a rabbit osteomyelitis infection model.

As yet, ceftobiprole shows a low potential for resistant mutant selection in *Staphylococcus aureus*. Regarding gram-negative bacteria, ceftobiprole was not stable to ESBLs, carbapenemase KPC-2, class B β-lactamases IMP-1 and VIM-2 and class D β-lactamase OXA-10. Ceftobiprole was stable to several class A non-ESBL β-lactamases and carbapenemase SME-3. Ceftobiprole seems fairly stable to AmpC β-lactamases, although rather high MICs were observed against AmpC-producing *P.aeruginosa*.
Single step resistance frequencies and AmpC induction were investigated in *Morganella morganii*, *Citrobacter freundii*, *Providencia stuartii*, *Enterobacter cloacae*, *Serratia marcescens* and *Pseudomonas aeruginosa.* Single step resistance was observed at frequencies of 10^{-9} – 10^{-6} and the resistance profile was comparable to that of cefepime and ceftazidime. In resistant mutants from *C.freundii* and *E.cloacae*, increased increased levels of AmpC β-lactamase were observed. In resistant mutants from *P.aeruginosa*, an upregulation of *mex*XY efflux pumps was observed.

In a neutropenic mouse thigh model, the time during which the drug concentration was above the MIC (%T>MIC) correlated best with *in vivo* efficacy. %T>MIC required for microbiologic static effect was 30% for gram-positive bacteria. For gram-negative bacteria *E.coli*, *K.pneumoniae* and *E.cloacae*, static

%T>MIC was on average <50%. For *P.aeruginosa*, it was higher than 50%. 30% and 50% were used as targets for gram-positive and gram-negative bacteria respectively. Fractional attainment rates for a dosing regimen of 500 mg, 2 hour-infusion every 8 h were 99.66% and 89.16% for 30% and 50% T>MIC targets respectively at a MIC value of 4 µg/ml. At a dosing interval of 12 h, for 30% T>MIC a TAR of 89.32% was achieved at MIC 4 µg/ml.

- Secondary pharmacodynamics

No data were provided on secondary pharmacodynamics. A general screen is considered not necessary; as a cephalosporin, ceftobiprole is a member of a well-known class. Provided publications indicate that it is not likely that ceftobiprole will cause a disulfiram-like action, which has been reported for some, but not all cephalosporins, since the publications indicate that a tetrazol-group is necessary for the disulfiram-like action to occur and ceftobiprole does not contain such a group.

- Safety pharmacology programme

Safety pharmacology studies were provided regarding the cardiovascular system, CNS system and respiratory system.

The package of studies on QT is limited. No effects on QT were observed in the hERG assay and in the *in vivo* cardiovascular study in the dog. However, in the hERG assay, the highest tested concentration was far below the expected human exposure because of solubility limitations. It seems though that sufficient efforts have been performed to try to achieve higher concentrations in the hERG assay. Slight increases in blood pressure and heart rate were observed in rats and marmosets after i.v. bolus injection. This effect seemed less prominent after i.v. infusion. No effects on QT were observed in dogs. However, this was a limited study with only 2 dogs and exposure only up to approximately 2.5 times the human Cmax. In one of the dogs, at the high dose, a ventricular premature complex was observed. This may have been due to chance, because sometimes these types of arrhythmias occur spontaneously in beagle dogs. Although the number of investigated dogs was limited, no further testing on QT is considered necessary, because for a cephalosporin, no QT-problems are expected and because clinically there is no indication for QT-problems.

No effect was observed on respiration in rats.

Based on the date of the single (intra-cerebroventricular) comparative study, ceftobiprole has similar convulsive potential as imipenem, but more potent convulsive activity than the comparator meropenem given icv. (ED50 values of 2,55 µg for BAL9141, 3.16 µg for imipenem, and 548,42 µg for meropenem). No i.v. comparative studies were performed. Since the capability of various beta-lactam antibiotics to cross the brain-blood barier is different, an iv comparative study would have great importance to make a more realistic comparison of convulsive activity of ceftobiprole, imipenem and meropenem. After i.v. administration of BAL5788 to mice, convulsions, tremors, behavioural changes, mortality and nephrotoxicity were observed from 250 mg/kg. At the NOEL of 125 mg/kg, estimated exposure based on Cmax was slightly above the human exposure

- Pharmacodynamic drug interactions

In *in vitro* combination studies, no antagonism was observed between ceftobiprole and doripenem, levofloxacin, colisin sulphate, amikacin, tobramycin, ciprofloxacin or gentamicin. Synergism was observed for some of the combinations in some of the investigated strains, but overall not to a relevant extent.

Pharmacokinetics

Conversion of BAL5788 to BAL9141

The prodrug BAL5788 is *in vivo* and *in vitro* rapidly converted to the active drug BAL9141 ($t_{1/2}$ in vivo is 10-201 seconds depending on the species). As a consequence, BAL5788 is generally only measurable for a short period after dosing so that little reliable information on the pharmacokinetics of BAL5788 is provided. Although one study (bap00067) suggests that BAL5788 may not always be fully and rapidly converted to BAL9141, other studies indicate that almost all BAL5788 in humans is rapidly converted to BAL9141.

Kinetics of BAL9141

BAL9141 is hardly soluble in water. Due to the rapid conversion of BAL5788 to BAL9141, the solubility of BAL9141 may be locally exceeded after injection/infusion. This is not expected at clinically relevant conditions, but could occur at higher dosage or greater infusion rate.

- Absorption and Distribution

Absorption of BAL5788 is not an issue as BAL5788 will be administered by the iv route. Cmax values highly depend on the regimen of iv dosing, e.g. iv bolus versus iv infusion, duration of infusion.
After iv administration of 14C-BAL5788, radioactivity distributed rapidly throughout rats and mice. Higher levels of BAL9141 were found in tissue cage fluid (i.e. extracellular water) compared to plasma levels. Very high levels of radioactivity were recovered in the coagulating gland. According to the applicant, this finding is not relevant as the coagulating gland has no direct equivalent in humans. However, radioactivity levels in the coagulating gland were very high both in rat and mouse (tissue/plasma ratio's up to respectively 15 and 50), indicating that probably BAL9141 concentrated in this specific tissue. As no female animal reproductive tissues were investigated and human tissues cannot be studied, it is stressed that extra attention should be paid to signs of toxicity in reproductive tissues. However, in repeat-dose toxicity studies, no toxic effects were observed on the reproductive organs. In addition, initial decline in the radioactivity in the kidney cortex was much slower than in other tissues, causing high levels of radioactivity in this tissue even 24 h after dosing. Hence, the drug may accumulate in the kidney cortex with multiple dosing.

- Metabolism (in vitro/in vivo) and Excretion

Clearance of BAL9141 was close to the glomerular filtration rate across the tested animal species. BAL9141 is probably not excreted by active transport processes in the kidney as co-medication with probenecid did not affect the pharmacokinetics of BAL9141.

BAL9141 is not metabolised extensively. BAL9141 is the predominant component found in plasma and urine. The major metabolite was the ring-opened product BAL1029. In addition, low amounts of some unknown other metabolites were observed.
Excretion was rapid and occurred mainly via the urine and a smaller fraction via faeces.BAL5788 and BAL9141 are transferred into the milk in lactating rats. However, nursing pups were not exposed systemically to BAL9141 due to the low oral absorption.

- Pharmacokinetic drug interactions

Little interactions with other drugs are anticipated based on in vitro studies. BAL9141 (0-100 μM) did not or only slightly inhibited known reactions by CYP P450 1A2, 2C19, 2D6, and 3A4. In addition, BAL9141 did not cause induction or suppression of CYP1A2, 2B6, 2C9, 2C19, or 3A4/5. Finally, considerable interactions via Pgp-transporters are not anticipated.

Toxicology

- Single dose toxicity

No single-dose toxicity studies were conducted.

- Repeat dose toxicity

In three-day pilot studies in rats, i.v. bolus administration of ≥150 mg/kg (t.i.d.) (i.e. 450 mg/kg/day) of BAL5788 led to drug precipitation in the distal parts of the nephron, which was associated with damage in the distal part of the nephron. In contrast, doses up to 250 mg/kg given via intermittent infusion (4 h, b.i.d.) (i.e. 500 mg/kg/day) were well tolerated without signs of renal damage. Administration via intermittent infusion seems therefore less toxic than via bolus injection. Three-day pilot studies in marmosets confirmed these findings.

In repeat-dose toxicity studies (up to 13 weeks in rats, dogs and marmosets), main observed effects were renal toxicity, convulsions and infusion site irritation associated with thrombus formation.

Findings in the kidney indicated the presence of drug-related material in the renal tubular system. The retention of drug-like material in the proximal tubular cells is not considered to be toxicologically relevant, since it did not cause remarkable adverse effects. The precipitation of drug-like material in the distal parts of the nephron was associated with renal tissue damage in rats and marmosets and may lead to impairment of renal function. The observed effects included dilatation, hyaline cast, and degeneration and/or necrosis of the distal tubules and collecting ducts and/or dilatation of the renal pelvis.

The renal effects were more pronounced for a bolus dose as compared to a 2h infusions and showed reversibility after cessation of dosing. Based on the NOAEL's for these kidney findings, safety margins of 2-7 based on plasma exposures and 4-34 based on urine exposures were calculated as compared to the recommended therapeutic exposure of 500 mg dose administered as a 2-h infusion.

Convulsions were observed in marmosets (and in mice, see section on Pharmacology). After 2-week administration, convulsions were observed at the high dose of 360 mg/kg/b.i.d. (10x human exposure based on Cmax). After 13-week administration, convulsions were also observed at the low dose of 50 mg/kg/day, probably due to poor condition of the animals.

Infusion site-related problems, necrosis and thrombus formation, leading to pulmonary thrombosis, were observed in rats and marmosets. In dogs, infusion site irritation was observed to a lesser extent and not dose-related. In dogs, clogging of the surgically implanted cannula resulting in an inability to dose was the primary reason of the premature sacrifice of these animals between Weeks 4 and 11. The cause of the clogging is considered to be clot formation resulting from prolonged contact between blood elements and high concentration of BAL5788 (8 mg/ml). This clog formation is not likely to be clinically relevant, in

view of the four times lower concentration of BAL5788 (2 mg/ml), the two times shorter infusion time (120 min) and the shorter duration of treatment (7-14 days) in the human situation.

In the i.v. infusion (4-h) studies in rats and marmorsets, necrosis and thrombus formation, leading to pulmonary thrombosis were also observed at the infusion site. These effects were seen at ≥125 mg/kg/day (15.6 mg/ml) in rats and at 50 mg/kg/day (6.25 mg/ml). Lower doses were not tested.

- Genotoxicity

The Ames test scored negative for genotoxicity; however, cytotoxicity was already observed at very low concentrations, which is due to the fact that ceftobiprole is an antibiotic. In a mouse lymphoma assay, large colony mutants were observed at high, cytotoxic doses. Initially, a clear cut negative result of a suitable gene mutation test was therefore lacking and the Applicant has therefore conducted a CHO hypoxanthine-guanine phosphoribosyl transferase (hgprt) mammalian cell mutagenicity assay for BAL5788. This study did not indicate genotoxic potential for BAL5788. Mouse lymphoma assays and *in vitro* chromosome aberration assays indicated clastogenicity of BAL5788, which may have been caused by the diacetyl group which is split off from BAL5788 to form BAL9141, since diacetyl also tested positive in these tests. Literature showed that diacetyl, an endogenous molecule, *in vivo* is rapidly reduced to non-mutagenic substances. BAL9141 scored negative in the *in vitro* chromosome aberration assay and positive in the mouse lymphoma assay. However, two *in vivo* assays, the mouse micronucleus test and the unscheduled DNA synthesis test were negative; therefore, overall the result for clastogenicity can be regarded negative.

- Carcinogenicity

Carcinogenicity studies were not conducted based on the intended short-term clinical duration of therapy, 7 - 10 days for the majority of patients, and because results of the genotoxicity testing showed a low potential for genotoxicity.

- Reproduction Toxicity

BAL5788 had no effects on fertility and early embryonic development in rats. BAL5788 was neither teratogenic nor embryotoxic in rats, nor teratogenic in monkeys. In monkeys at the high dose, abortions were observed which could be treatment-related; however this is not certain since also in the control group, an abortion and an embryonic death were observed. The safety margin for this effect was 4 (based on Cmax). In a pre-and postnatal toxicity study in rats, a slight increase in gestation length was observed in F0 animals at the high dose. In F1 pups, litter size and survival up to 4 days post partum were decreased at the high dose. No effects were observed in F2 pups. Juvenile toxicity was not investigated.

- Local tolerance

In local tolerance studies in rabbits, no irritation was observed after intravenous administration with retention of the drug in the vessel for 3 minutes. Local tolerance was not investigated after administration via other parenteral routes, which could occur accidentally: intraarterial, intramuscular, subcutaneous or paravenous. The applicant indicated that the local tolerance has been tested in juvenile rats (subcutaneous route) and in rabbits (intramuscular, subcutaneous and paravenous routes).

- Other toxicity studies

Studies on impurities:

Three impurities, para-nitrophenol (PNP), BAL1030 and BAL6235 showed genotoxic alerts in DEREK analysis.

PNP scored negative in tests for gene mutation potential. PNP scored positive for clastogenicity in chromosome aberration tests, also at non-cytotoxic concentrations. The tests were not completely consistent regarding the absence or presence of S9, but overall there seemed to be a positive result in this test. Negative results were obtained in the mouse lymphoma assay and the Comet assay. However, it appeared that in this mouse lymphoma assay, predominantly large colonies were scored and that it therefore cannot be regarded suitable for testing clastogenicity. The Comet assay was negative; it is however not as sensitive as the chromosome aberration assay for determining clastogenicity. In the mouse carcinogenicity study, dermal administration was applied and therefore this study does not provide suitable evidence for the absence of carcinogenicity after systemic use.

For the definitive determination of the genotoxic potential of PNP, an *in vivo* test is necessary. The applicant has conducted an *in vivo* mouse micronucleus test for PNP using intravenous administration. No evidence for genotoxic potential of PNP was observed in this study. Regarding general toxicity, this impurity can be considered qualified based on literature data.
For BAL6235, the limit was not indicated at first, but the applicant initially hinted that this would be around 1 ppm. Now, the limit is proposed at 0.25% and for this impurity the same conclusions apply as for the list of other impurities as discussed below.

For BAL1030, the applicant has now conducted an Ames test and CHO hgprt assay. No evidence for genotoxic potential was observed for BAL1030 in these studies. A test for clastogenicity has not been performed because an *in vitro* test for clastogenicity is expected to test positive, because it did for PNP. Because BAL1030 is converted into PNP, it can be concluded that BAL1030 is not likely to pose a risk for clastogenicity if the *in vivo* mouse micronucleus test testing PNP is negative. Regarding general toxicity, the same conclusions apply as for the list of other impurities.

Furthermore, there is a long list of other impurities, without genotoxic alerts of which the majority was not toxicologically qualified. The Applicant has lowered the specifications for the impurities. Impurities which now have specifications in drug substance ≤ 0.15% and in drug product ≤ 0.2% are acceptable. Among the impurities with specifications above the qualification limit, there are still quite a number which have not been tested at levels up to the proposed specification, but (sometimes far) below these levels. This goes for the general toxicity and genotoxicity studies which were submitted for the qualification of impurities (a CHO hgprt assay investigating genotoxicity of BAL5788 and impurities was submitted at day 180, in study TOX8637; this study was negative).

Antigenicity: BAL5788 showed potential for skin sensitization in the active systemic anaphylaxis test in guinea pigs. This is consistent with findings for other cephalosporins. A Maximization Test and a passive anaphylactic assay, both in guinea pigs, were negative.

Haemocompatibility: No hemolysis or precipitation in blood occurred at concentrations ≤16.62 mg/ml (blood from dogs) or ≤5 mg/ml (blood from rats, marmosets and humans). The safety margin for human therapeutic use seems large enough (Cmax is 33 µg/ml). At higher doses, adverse reactions occurred (hemolysis or precipitation).

Phototoxicity: BAL9141 absorbs light between 240 and 400 nm. An *in vitro* test in mouse fibroblasts and an *in vivo* test in rats revealed no phototoxic potential.

Ecotoxicity/environmental risk assessment

The environmental risk assessment of ceftobiprole medocaril and its metabolite ceftobiprole, followed primarily the draft of guidelines related to this issue.

Based on the provided information, the phase I environmental risk assessment for ceftobiprole medocaril/ceftobiprole is completed. Based on additional information on ecotoxicity of ceftobiprole, BAL9141 was assumed not to be readily biodegradable. This assumption is a worst-case scenario and does not have a negative impact on the actual conclusions of the environmental risk assessment.

It is concluded that ceftobiprole medocaril powder for solution for infusion is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.

Discussion on the non-clinical aspects

There is not a high safety margin to ensure the safety of BAL5788 for potential renal effects in human. In addition, the extrapolation to the human situation is complicated by the fact that the process of crystal formation and renal crystal deposition varies not only between species but also between individuals. It depends on the concentration of the compound in urine and the urinary pH and is regulated by a range of urinary inhibitors and promoters of crystal formation and agglomeration. In addition, humans have their own profile of urinary inhibitors and promoters of crystal formation. Therefore, from preclinical point of view, the risk of renal drug deposition and loss of renal function for humans upon treatment should be taken into consideration in the risk benefit evaluation and be included in the risk management plan. At the moment, it is still not possible to estimate the risk of irreversible renal damage in humans. However, crystalluria is an important risk factor for renal crystal deposition and crystal nephropathy. In the clinical situation, there are metabolic disturbances such as systemic metabolic acidosis or alkalosis or renal tubular acidosis that promote changes in urinary pH favouring crystal precipitation. In view of these findings, the applicant was requested to evaluate the solubility of BAL9141 and BAL5788 (pKA) in human urine, under these conditions. In relation to existing experience with other medicinal products that cause crystal formation in urine and crystal nephropathy, it should be discussed whether or not patients with certain metabolic disturbances are at higher risk. The applicant discussed this and proposed an appropriate precaution how to deal with patients who are at higher risk of crystal nephropathy (e.g. patients with metabolic disturbances such as systemic metabolic acidosis or alkalosis or renal tubular acidosis that promote changes in urinary pH favouring crystal precipitation). This was intended to be included in section 4.4 of the SPC and this point was to be implemented in the proposed Risk Management Plan (RMP).

The CHMP noted during the review that the occurrence of convulsions had also to be part of the proposed RMP.

It cannot be assumed that the clotting effects are irrelevant for humans. Therefore, these effects are regarded as potential adverse effects which were to be addressed in the RMP and in the intended SPC.

Studies have been performed to qualify impurities. The outcome of these studies is that adverse effects due to impurities cannot be completely excluded. However, since tested absolute amounts of the impurities were generally several times above the expected daily intake by humans, no new toxicities are expected, since no new toxicities were observed in the rat studies that were performed to qualify impurities. Impurities have been examined for genotoxic alerts and impurities with genotoxic alerts were tested negative for genotoxic potential. Because of this, and because ceftobiprole is intended for short-term use, a relevant increase of risk caused by the impurities will not be expected.

3.4 Revised clinical aspects

Introduction

GCP

The CHMP adopted a GCP inspection request in February 2009 for the inspection of the two pivotal clinical trials BAP00154 and BAP004144 997. The inspection request involved four investigator sites and the CRO, responsible for monitoring and study management. All of these sites were involved in the conduct of both trials. The inspections were conducted between June-July 2009.

Taking into account the results of the CHMP requested inspections, as summarised in the Integrated Inspection Report (IIR) issued on 15 September 2009, the inspection team concluded from the observed deviations that the conduct of the studies BAP00154 and BAP00414 was not fully compliant with GCP. The GCP inspectors recommended the exclusion of the data from 2 out of the 4 investigator sites inspected. Although no critical findings were identified during the inspection of the CRO, inadequate monitoring was observed at 2 out of the 4 investigator sites inspected.

Additional information on the GCP compliance of the sites involved in these two trials includes:

- FDA Inspections conducted between 01 October 2007 to 25 April 2008: 10 sites were inspected.
- The 42-Site Audit conducted by the independent auditor, engaged by the applicant. Their audits were conducted between 10 February 2009 to 9 April 2009:
  - 42 sites were audited: The auditors concluded that 2 sites had conducted the study inadequately. In addition the FDA's 28 Dec 2009 Complete Response action letter, provided by the applicant, raises concern about 5 additional sites based on the 42 site audit outcome (one of them being one of the sites inspected by the EU inspectors).

Considering that 11 out of the 50 sites audited or inspected (the 50 sites involve 71% of the study population) have been excluded, at the request of CHMP or of FDA or by the company, due to GCP non-compliance, the conduct of the studies must be regarded as questionable. One of the audited sites was excluded following the EU GCP inspection.

It is therefore concluded that:

- These trials cannot be considered to have been conducted in accordance with GCP as required by Annex I of Directive 2001/83/EC.
- The statement provided in the clinical overview and in the Clinical Study Report concerning GCP compliance can no longer be considered valid.

- It is recommended that the studies BAP00154 and BAP004144 are not reliable for evaluation in connection with the evaluation of the Zeftera MAA.

Pharmacokinetics

To support the application of Ceftobiprole, 15 pharmacokinetic studies were submitted (12 studies with healthy volunteers and 3 studies involving patients with complicated skin and soft tissue infection). In addition to these studies, several *in vitro* studies were submitted, to support protein binding, metabolism and the interaction potential.

Pharmacokinetic data were obtained from 255 healthy subjects, 15 subjects with impaired renal function and 86 patients with cSSTI.

- Absorption

After infusion, the pro-drug ceftibiprole medocaril is rapidly and almost completely converted into the active ceftobiprole.

Based on the preclincial results it is hypothesized that the enzyme responsible for the prodrug conversion is a paraoxonase izoenzyme named PON1. This enzyme is involved in the metabolism of number of medicinal products and it is inhibited by a couple of others. Furthermore, marked pharmacogenomic differences had been described for PON esterases. Of note the source of the plasma PON1 is the liver, so theoretically it is possible that conversion process is limited in severe hepatic impairment. A follow-up measure is planned to elucidate the specific enzymes involved in the conversion of the pro-drug into ceftobiprolol.

Ceftobiprole AUC and C_{max} values increased linear with dose after single dose administration over the dose range of 125– 1000 mg and after multiple dose administration over the dose range of 500 – 750 mg q12h and at 300 mg q12h. Steady state was achieved within 2 days, and no accumulation occurs. In line with the linear pharmacokinetics, the total daily exposure is similar in case the total daily dose was divided q12h or q8h.

- Distribution

In vitro protein binding studies indicated that ceftobiprole is bound to plasma proteins for ca. 16%. The volume of distribution was about 18 l and was consistent across the dose range of 125 – 1000 mg, between single and multiple doses, and in patients with renal impairment. Females had an about 25% lower volume of distribution compared to males, which correlated with the lower body weight.
Animal data indicated that ceftobiprole is excreted into mother milk.

- Elimination

In vitro studies using human liver hepatocytes and microsomal preparations indicate that ceftobiprole is not (or negligibly) metabolised. Preliminary data indicate that ceftobiprolol does also not induce CYP enzymes. *In vivo*, renal clearance covered >80% of the total clearance, which was indicated by the excretion of more than 80% of the dose as intact ceftobiprole in the urine. The elimination half-life of about 3 - 5 h was independent of dose and not affected by repeat administration. The total body clearance is about 85 ml/min.

- Special populations

Pharmacokinetics in patients with cSSTI were comparable with the pharmacokinetics in healthy volunteers. With regard to male and female patients, patients with an impaired liver function and elderly, the pharmacokinetics are not expected to be clinically significant altered. As can be expected from a medicinal product that is excreted completely intact into the urine, an impaired renal function resulted in a lower elimination of ceftobiprole, leading to increased exposure. Therefore a dose reduction is proposed in these circumstances.

Based on simulations of the concentration time profiles for a range of creatinine clearance values, the steady state AUC_{0-24h} ratios (assuming a CLCr of 120 ml /minute as a reference for normal renal function) were less than 2, indicating that significant accumulation is not expected in patients with renal impairment given the proposed dosing adjustments. Applying these dosing regimens indicated comparable and sufficient concentrations above the MIC target.

In contrast to the observations observed in healthy subjects, the conversion of ceftobiprolol medocaril in End Stage Renal Disease (ESRD) patients is slower, and measurable even up to 3 h. This may be due to reduced levels of plasma esterases like PON 1, as reported in literature.

In ERSD patients the plasma concentrations of ceftobiprolol are markedly increased, which is expected as ceftobiprolol is mainly excreted via the kidney. The increase in AUC at pre-dialysis phase is comparable to that observed in patients with severe renal impairment (3-4 fold), while post-dialysis the increase is more pronounced (7-fold increase). Ceftobiprolol is extracted during hemodialysis, with a clearance of about 8 l/h. Also the concentrations of the open-ring metabolite are pronounced higher (in compariosn with the concentrations observed in healthy subjects). As a result of a decreased elimination, the hepatic metabolism plays a more important role, resulting in an increased metabolism of ceftobiprolol into the open ring metabolite. Protein binding was comparable in ESRD patients and healthy subjects. Also in the protein binding assay one subject showed deviating results. In response to concern from CHMP and based on the limited available data, the applicant has updated section 4.2 of the SPC to include a warning that due to increased exposure of ceftobiprole and its metabolite, ceftobiprole should be used with caution in patients with severe renal impairment and that ceftobiprole is not recommended for use in patients on dialysis.

- Pharmacokinetic interaction studies

Based upon the *in vitro* and *in vivo* metabolism studies, indicating that ceftobiprole is not a substrate for cytochrome P450 isozymes, does not inhibit cytochrome P450 isozymes, is not a substrate of P-gp nor inducer of P-gp, and binds to plasma proteins only to a low extent, it is concluded that ceftobiprole has a low interaction potential.

As could be expected for a substance with a low distribution volume (about 18 l), the impact of body weight on exposure is limited. The submitted simulations indicate that predicted exposure levels are acceptable, and target attainment rates still sufficient.

Pharmacodynamics

- Mechanism of action

Ceftobiprole has a comparable mechanism of action as other cephalosporins by binding to essential cell wall synthesizing enzymes, the penicillin binding proteins (PBPs), in all susceptible bacteria. Of note is that Ceftobiprole displayed little or no resistance development in *in vitro* studies completed with gram-positive pathogens. Ceftobiprole is reported to have bactericidal activity against MRSS primarily due to its strong binding to the staphylococcal PBP2a, the PBP that is chiefly responsible for β-lactam resistance in methicillin-resistant staphylococci including methicillin-resistant *S. aureus* (MRSA).

- Primary and Secondary pharmacology

Dose-response studies

Dose selection of ceftobiprole for the pivotal Phase III efficacy studies was based on the estimated probability of target attainment rates for two PK/PD targets: 30% T>MIC for coverage of gram-positive pathogens and 50% T>MIC for broad spectrum coverage of both gram-positive and gram-negative pathogens, assuming an MIC of 4 μg/ml.

A population pharmacokinetic analysis of concentration data from several Phase I studies and 1 Phase II study (n=150 subjects in total) and relevant microbiology data was conducted and Monte Carlo simulations were subsequently performed to determine the probability of target attainment for several dosing regimens, including the 500 mg 3-times-daily, 2-hour infusion regimen and the 500 mg twice-daily, 1-hour infusion regimen. For both ceftobiprole 500 mg twice-daily (1-hour infusion) and 500 mg 3-times-daily (2-hour infusion) regimens, the probability of target attainment corresponding to 50% T>MIC exceeded 90% for MSSA (96.9% and 99.9% for the twice-daily and 3-times-daily regimens, respectively) and MRSA (92.6% and 98.8% for the twice-daily and 3-times-daily regimens, respectively). For gram-negative pathogens, the probability of target attainment corresponding to 50% T>MIC for ceftobiprole 500 mg 3-times-daily (2-hour infusion) was 89% or greater for both ampC-producing and non-ampC-producing bacilli.

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis was subsequently conducted to evaluate whether the clinical response of ceftobiprole as observed in Phase III studies was related to the extent of drug exposure (i.e., %T>MIC). The mITT analysis set from study BAP00414 with measured ceftobiprole concentrations (n=309 plus 3 from study BAP00154) and the baseline MIC values of the major pathogens Enterobacteriaceae, *E. faecalis*, *P. aeruginosa*, Staphylococcus, and Streptococcus species (excluding *S. pneumoniae*) were used in this analysis. Pearson's chi square test was used to test the independence of 2 variables: %T>MIC and clinical responses (i.e., clinical cure/failure and microbiological eradication/failure). A chi-square probability of 0.05 or less was justification for rejecting the null hypothesis. 84%and 81% of the patients achieved clinical or microbiological cure respectively, when the exposure to ceftobiprole was ≥30% of T>MIC. Similar results were observed using a threshold value of 50% T>MIC. Based on the p-values, it was concluded that there was a strong association between achieving the metrics of ≥30% or ≥50% T>MIC and the probability of achieving clinical or microbiological success.

CHMP finds the magnitude of cure rates (81-84%) associated with target attainment rates for two PK/PD targets rather low for broad spectrum coverage of both gram-positive and gram-negative pathogens

based on present tested population. Furthermore, ceftobiprole clinical cure rates at the test of cure (TOC) visit in patients with *S. pyogenes* infection in the pooled data was lower compared to the vancomycin based comparator regimens (84% and 90% respectively: whereas the experience in patients with cSSTI due to gram-positive pathogens other than *S. aureus* and gram-negative other than *E. coli* infections is very limited. Generally the limited data for patients with cSSTI due to specific major gram-negative pathogens suggest a lower efficacy of ceftobiprole compared to the comparator regimen. Based on the present clinical cure rates, achieving >50% T>MIC with the proposed 500 mg TID daily should be considered as a better option to cover the claimed broad spectrum efficacy against severe gram-positive and gram-negative infections of the skin and skin structure. The effectiveness of the 500 mg BID dosing in clinical (empiric) practice in the target indication may be disputable. In line with CHMP request, the 500 mg TID dosing regimen is now recommended as the standard dosing recommendation for the claimed broad-spectrum of gram-positive and gram-negative cSSTI infections in order to avoid confusion in clinical practice.

Higher doses >500 mg TID daily should also have been explored although applicant states that the choice of 500 mg TID for treating patients with cSSTI was based on a trend towards decreased tolerability at doses above 500 mg in addition to PK/PD considerations. Dose related safety did not seem to be a notable issue in the Phase III studies also when renal impairment is involved. Hence, it is regretful that the benefit of doses higher than 500 mg TID in patients with severe (community acquired or nosocomial) cSSTI (including also immunocompromised patients) has not been undertaken.

Secondary pharmacology

Two studies in healthy volunteers evaluated PK and pharmacodynamic effects on *cardiac parameters* such as ECGs, QTc intervals and safety using therapeutic and higher doses.

CSI 1001 was a randomized, double-blind, placebo- and positive-controlled, double-dummy, 4-way crossover, single-centre study. Ceftobiprole was administered at therapeutic and supratherapeutic doses of 500 and 1,000 mg (ceftobiprole equivalent), respectively, intravenously infused over a 2-hour duration every 8 hours. The study has been discontinued due to frequency of infusion-site reactions.
No conclusions could be drawn in regards to QTc prolongation due to the limited number of subjects with serial ECG data. The frequencies of nausea, vomiting and dysgeusea suggested a dose –response relation to ceftobiprole.

A second study **(CSI-1003)** has been designed with the same treatments to assess the effect of ceftobiprole on QT/QTc intervals but after single-dose administration of above mentioned doses. A total of 60 healthy adults (32 men, 28 women) were planned for enrolment, 60 subjects (32 men, 28 women) were enrolled, and 54 subjects (29 men, 25 women) completed the study. The effect of ceftobiprole on QT/QTc prolongation was similar to that of placebo. No subject had a QTcF value greater than 480 ms in any treatment at any time point. No subject had a time-matched ΔQTcF exceeding 60 ms in any treatment at any time point. There was no discernible relationship between ceftobiprole plasma concentration and QTc. Similarly, ceftobiprole had no effect on heart rate or other ECG parameters. Assay sensitivity was established using moxifloxacin as a positive control. There was no apparent relationship between ceftobiprole plasma concentration and ΔQTcF as a function of time.

Initial clinical efficacy

Three studies were conducted to support the indication of cSSTI: one Phase II proof-of-concept study **(BAP00034)** and two Phase III main studies **(BAP00154 and BAP00414).**

Table 1: Studies Supporting the Efficacy of Ceftobiprole Medocaril in cSSTI

Study	Design and Dosage	Number of Subjects Randomized/Treatment
Completed Phase 2 Efficacy and Safety Study		
BAP00034	An open-label multicenter Phase 2 study of ceftobiprole medocaril in subjects with complicated skin and skin structure infections Treatment: 30-min or 60-min i.v. infusion of ceftobiprole medocaril (750 mg ceftobiprole equivalent) b.i.d. for 7 to 14 days	N=40, one group
Completed Phase 3 Efficacy and Safety Studies		
BAP00154	Randomized (1:1), double-blind, multicenter, Phase 3 noninferiority study of ceftobiprole medocaril versus vancomycin in the treatment of complicated skin and skin structure infections Treatment: i.v. infusion of ceftobiprole medocaril (500 mg ceftobiprole equivalent) b.i.d. over 60 min, or 1000 mg vancomycin b.i.d. for 7 to 14 days	N=784 Two groups: Ceftobiprole, n=397 Vancomycin, n=387
BAP00414	Randomized (2:1), double-blind, multicenter Phase 3 noninferiority study of ceftobiprole medocaril versus vancomycin/ceftazidime in the treatment of complicated skin and skin structure infections, including diabetic foot infections Treatment: i.v. infusion of ceftobiprole medocaril (500 mg equivalents of ceftobiprole) t.i.d over 120 min plus placebo b.i.d. over 60 min, or 1000 mg vancomycin b.i.d. over 60 min plus 1000 mg ceftazidime t.i.d. over 120 min for 7 to 14 days	N=828 Two groups: Ceftobiprole, n=547 Vancomycin plus ceftazidime, n=281

- Proof of concept study

The population in the Phase II proof-of-concept study included 40 patients (≥18 years of age) with cSSTI, with or without bacteraemia, and involving either a surgical incision or site of trauma (including burns) within 30 days after the time of surgery or trauma, an abscess requiring surgical intervention (without open wound) with acute onset within 7 days before enrolment or cellulitis with acute onset within 7 days before enrolment. The study was enriched with patients at risk for infections due to MRSA such as patients with a history of intravenous drug abuse (IVDAs, 22/40 enrolled patients), 20 were hepatitis C infected. The distribution of infection types was 65% abscesses, 23% wounds, and 13% cellulitis. *S. aureus* (MSSA and MRSA) was the most frequently isolated pathogen at baseline. Patients were treated with ceftobiprole (750 mg every 12 hours as an i.v. infusion over 30 minutes or 60 minutes for 7 to 14 days). A TOC evaluation was conducted 7 to 10 days after the end of therapy and an LFU visit was conducted 28 to 35 days after the last infusion of study drug.

In this trial, clinical cures were reported for all 34 (100%) clinically evaluable subjects, including 4 subjects with cases of MRSA. Microbiological eradication was reported for 21 (91%) of 23 microbiologically evaluable subjects, including 3 of the 4 cases of MRSA. In the microbiologically evaluable analysis set, the mean time to eradication was 5.5 days overall. An improvement over time of clinical signs and symptoms was observed for all parameters after the start of therapy. At the TOC assessment, the majority of subjects in the ITT analysis set (79%) had no clinical signs and symptoms of the infection and the size of the primary site of infection was substantially reduced.

- Main studies

The designs of the two Phase III studies were consistent with the guidelines of the U.S. Food and Drug Administration (FDA) and the Committee for Proprietary Medicinal Products (CPMP), for antimicrobial drug development.

Both trials were double-blind, randomized (1:1 for **BAP00154** and 2:1 for **BAP00414**), multicentre, controlled non-inferiority studies in patients ≥18 years of age. Efficacy of ceftobiprole therapy was compared with that of a comparator in patients with cSSTIs due to suspected or proven gram-positive

infection (**BAP00154**), or patients with cSSTIs due to gram-positive, gram-negative, or mixed pathogens, including patients with diabetic foot infections (DFIs) (**BAP00414**).

METHODS

Participants

Main inclusion/exclusion criteria of pivotal studies:

The inclusion and exclusion criteria for both studies were similar. Included patients were those patients aged ≥18 years who were having a diagnosis consistent with cSSTI and required an anti-MRSA antibiotic or gram-negative infection (in study BAP00414). Patients had suspected or proven infection with gram-positive pathogen(s) (or gram-negative infection in study BAP00414) with biological fluid/tissue samples available from infected lesion at baseline for microbiological culture.

Excluded patients were among others those patients with osteomyelitis, necrotizing fasciitis, gas gangrene, critical limb ischemia, endocarditis, septic arthritis, or toxic shock syndrome or shock, ischemic wounds where vascular supply was insufficient to allow wound healing.

In study BAP00154 patients were excluded when the infections presumed at enrolment to be caused by gram-negative pathogen(s) or mixed anaerobic/aerobic infections, such as decubitus ulcers, episiotomy infection, peri-anal cellulitis, Fournier's gangrene, diabetic foot infections,, infections due to animal or human bites, wound infections after surgical procedures where there was a high probability of gram-negative pathogen(s) (e.g., if the infection extended to the oropharyngeal, gastrointestinal, urogenital or gynaecological tract).

Patients with known or suspected hypersensitivity to any study medication and with QTcB (QT interval corrected for heart rate, Bazett's correction) >450 msec at baseline and patients with severe renal or hepatic impairment were also excluded.

The differences between two trials were primarily related to the exclusion of patients with gram-negative infections and DFIs from BAP00154 and the inclusion of these patients in study BAP00414. In both studies this was based on biological fluid/tissue samples available from infected lesion at baseline for microbiological culture. Of note, the presence of osteomyelitis in DFIs is often hard to exclude clinically. So far, no data are available to address the penetration in bones for ceftobiprole, compared to that of other antimicrobial agents approved for the indication SSTI.

Treatments

In **BAP00154** the dosing regimen of ceftobiprole 500 mg administered twice daily infused over 1 hour was used to provide activity against suspected or confirmed gram-positive infections. The comparator was vancomycin (1,000 mg every 12 hours as a 60-minute infusion). Aztreonam was also included to provide activity against gram-negative organisms, pending microbiology culture results in both groups.

BAP00414 used a dosing regimen of ceftobiprole 500 mg administered 3 times daily over 2 hours to provide broad spectrum activity against gram-positive and gram-negative (including *P. aeruginosa*) organisms. The comparator was a combination of vancomycin (1,000 mg every 12 hours as a 60-minute infusion) plus ceftazidime (1,000 mg every 8 hours as a 120-minute infusion). Ceftazidime was used longer than what is generally used in clinical practice, in order to maintain the study blind.

In the light of the fact that in both pivotal studies there was a need to adapt the dose of vancomycin based on therapeutic monitoring, measures were taken to ensure that the blinding was respected throughout the course of the studies.

Vancomycin was chosen as a comparator in both studies to provide reliable activity against gram-positive pathogens, given the increasing prevalence of MRSA as a cause of cSSTI and because it is the standard of care for infections caused by methicillin-resistant pathogens. Experience suggesting that patients with bacteraemic disease treated with β-lactam antibiotics generally do better than those treated with vancomycin is important in assessing the overall acceptability of vancomycin as an anti-staphylococcal agent. The applicant justified the choice of vancomycin by the goal of the studies to select patients with risk of having an infection caused by drug resistant, and perhaps more virulent, pathogens. Furthermore, in a published similarly designed study in which vancomycin was compared with linezolid, the cure rate associated with vancomycin treatment was 90.4% (clinical outcome of Cure was observed in 394 of 436 patients). Given these observations, along with the increasing prevalence of MRSA as a cause of cSSTI, vancomycin was considered as an appropriate comparator for use in both ceftobiprole cSSTI clinical trials.

Both studies allowed the empiric use of metronidazole for the first 48 hours of the study to provide activity against anaerobic pathogens. At the investigator's discretion, study BAP00414 allowed the use of metronidazole for up to 7 days in the case of proven anaerobic infections and beyond 7 days for moderate or severe DFIs in the presence of a foul-smelling discharge and an aerobic co-pathogen sensitive to study drugs.

Outcomes/ endpoints

Definitions

Cure: A patient was considered a clinical Cure at the TOC visit if, in the opinion of the investigator, there was ***resolution of all*** signs and symptoms of the infection ***or improvement*** such that no further antimicrobial therapy was necessary.

Failure: A patient who was not assessed as a Cure at the TOC visit was considered a clinical Failure if he or she took study medication for at least 48 hours (BAP00414) or 72 hours (BAP00154) and met any of the following criteria:

- The investigator's assessment of clinical outcome at TOC was Failure (i.e., patient needed a non-study antibiotic due to a treatment-related adverse event or due to lack of efficacy);
- Patient withdrew from the treatment because of a treatment-related adverse event;
- Patient withdrew from the study due to lack of efficacy;
- Patient had an unplanned surgical incision or drainage for the primary infection more than 48 hours after study entry (in study BAP00414 only);
- Patient was missing a TOC visit assessment and the final clinical assessment before TOC was Unchanged or Worsened from baseline;
- Patient received non-study antimicrobial therapy for cSSSI infection prior to TOC.

Not Evaluable: Overall reasons for clinical non-evaluability unless the patient was an evaluable failure included the following:

- Absence of clinical assessments at TOC;
- In study BAP00154, less than 7 days of study treatment for patients assessed as cure and less than 3 days of study treatment for patients assessed as failure; in study BAP00414, less than 5 days of study treatment for patients assessed as cure and less than 2 days of study treatment for patients assessed as failure;
- Patient received less than 80% of specified study treatment;
- Concomitant treatment with a systemic antibiotic active against gram-positive (both studies) or gram-negative (study BAP00414 only) pathogens, administered for a reason other than the skin infection under investigation;
- In study BAP00154 only, administration of study therapy outside of a hospital or clinical study site unless study therapy was administered by a qualified nurse, study staff member, or infusion specialist, and the ceftobiprole lyophilisate and solution had been stored properly, as described in the protocol;
- In study BAP00154 only, gram-negative bacteria present at baseline;
- In study BAP00414 only, patients whose cultures yielded (co-)pathogens resistant to the study drug(s).

In DFI, severity of infection was defined using a classification scheme similar to the Infectious Diseases Society of America (IDSA) classification scheme and the corresponding grades of the International Working Group on the Diabetic Foot (IWGDF).

Identification of severe infection in patients with *S. aureus*-positive infection at baseline was based on: systemic inflammatory response syndrome (SIRS) criteria of sepsis, (SIRS criteria used in **BAP00154** did not include respiratory rates); patients with elevation of acute phase reactants (based on a baseline C-reactive protein level of >50 mg/L); or infection involved the tissues extending to the fascia or muscle (deep infections).

Defining the microbiology of the infections was based on aseptic biopsy or aspirations. Swabs were only to be performed if no tissue specimen or fluid for aspiration was obtained from the biopsy or aspiration. Cultures from swabs were only considered evaluable in the presence of leukocytes with absent or rare epithelial cells (<10/lpf) in the sample. Coagulase-negative staphylococci, viridans streptococci group, *Acinetobacter* species, and enterococci were not considered pathogens except when isolated in pure culture by sterile biopsy or aspiration. In cases of samples containing an invalid pathogen, negative culture, or if (in study **BAP00154**) only gram-negative bacteria could be isolated from culture, the patient could continue in the study at the investigator's discretion.

Primary efficacy endpoints

The primary efficacy endpoint the main Phase III studies was the same, clinical outcome - cure, failure, not evaluable at the TOC visit; primary objective of the studies was to demonstrate the non-inferiority of ceftobiprole compared with vancomycin based regimens with respect to the clinical cure rate.

Secondary efficacy endpoints

The secondary efficacy endpoints in the main Phase III studies were the same and included clinical relapse rate at LFU visit and microbiological eradication rate at the TOC visit, and time to clinical cure, or microbiological eradication, time to defervescence.

Microbiological outcome at the TOC visit at the patient level was derived through a combination of clinical assessment, infection site evaluation, and microbiological assessment at baseline and TOC visits. Given the timing of the TOC visit and the clinical course of an infection that when treated results in improvement or cure, material for culture was often not available in patients who were cured or substantially improved; for these patients, eradication was presumed based on clinical findings. In the analyses of microbiologic eradication, presumed eradication and eradication, as demonstrated by culture results not demonstrating a pathogen, were grouped together.

The *microbiological ITT* (mITT) analysis set included all patients in the ITT analysis set who had a valid pathogen at the primary infection site at baseline. The *microbiologically evaluable* analysis set included all patients belonging to the mITT and clinically evaluable analysis sets, excluding those with a microbiological outcome of Not Evaluable at the TOC visit.

Other efficacy analyses planned in the pivotal Phase III studies were: time to clinical cure, time to microbiological eradication, time to defervescence, duration of treatment, association between clinical outcome and microbiological outcome, and status of pathogen resistance to study drug.

The following analyses were also performed on the pooled Phase 3 data, but only for the ceftobiprole treatment group: clinical outcome summarized by pathogens and their MIC values, and the number of patients in the microbiologically evaluable analysis set with pathogens that displayed at least a 4-fold increase from baseline in their MIC values at any time during the study, summarized by pathogen.

In addition, 40 patients were to be randomly assigned in a 1:1 ratio to the 2 treatment arms for pharmacokinetic sampling in BAP00154 and 90 patients in a 2:1 ratio in study BAP00414.

Sample size

Both studies were powered at 80%. Based on these assumptions, for **BAP00154**, the protocol specified that randomization of 700 patients was needed in order to accrue 504 clinically evaluable patients, 252 in each treatment group. Likewise, for BAP00414, the protocol specified that randomization of 816 patients was needed in order to accrue 570 clinically evaluable patients with 380 in the ceftobiprole group and 190 in the vancomycin plus ceftazidime group. After the interim analysis, **BAP00154** was amended to be powered at 90%, in order to provide a more robust safety and efficacy database, with a total of 790 patients to be randomly assigned to treatment.

Randomisation

BAP00154
Patients with cSSSI were randomly assigned in a 1:1 ratio to treatment for 7 to 14 days (with possible prolongation to 28 days)

BAP00414
Subjects were randomly assigned in a 2:1 ratio to treatment for 7 to 14 days (with possible prolongation to 28 days)

Blinding (masking)

Trials were double blinded. In Phase 3 study **(BAP00414)** for blinding purposes, subjects randomized to the ceftobiprole treatment group also received a placebo matched to vancomycin every 12 hours as a 60-minute i.v. infusion.

Statistical methods

In the comparative pivotal studies the chosen non-inferiority margin of 10% was in alignment with regulatory guidances for such studies and conform previous cSSTI trials for other products. Clinical cure rates were analyzed by presenting a 2-sided 95% confidence interval for the difference of the clinical cure rate for ceftobiprole to that of the comparator at the TOC visit. For the individual studies, non-inferiority of ceftobiprole compared with comparator was concluded if the lower limit of this confidence interval was greater than or equal to -10%.

The primary efficacy analysis was performed on the clinically evaluable and the ITT analysis sets as co-primary analysis sets. The ITT analysis set included all randomized subjects whereas the clinically evaluable analysis set (which included all subjects in the ITT analysis set excluding those with a derived clinical outcome of Not Evaluable at the TOC visit). The clinically evaluable and ITT were the co-primary analysis sets.

The primary efficacy evaluation was also evaluated for key subgroups of patients to provide further insight into any potential differences between treatment with ceftobiprole and comparator regimens. Clinical relapse rate and microbiological relapse rate were analyzed by presenting a 2-sided 95% confidence interval for the difference of the rate of ceftobiprole to that of the comparator at the LFU visit. For the individual studies, non-inferiority of ceftobiprole compared with comparator was concluded if the upper limit of this interval was less than or equal to 10%.

Interim analyses

In study **BAP00154**, a pre-planned, blinded interim analysis was performed on the first 60% of the clinically evaluable subjects who had completed their test of cure (TOC) visit in order to confirm whether the original assumptions of an overall clinical cure rate of 80% and a clinical evaluability rate of 70% for the 2 treatment groups combined were still appropriate. The power of the study was changed from 80% to 90% to provide a more robust safety and efficacy database, led to the decision to increase the sample size from approximately 700 subjects to 790. Analyses of the data before and after the change showed similar results.

RESULTS

Participant flow

Disposition of patients who were randomly assigned to treatment in the 2 studies and present in different analysis sets are displayed in the following table.

Table 2: Number of patients in Each Analysis Set by Study

Analysis Set	Ceftobiprole n (%)	Comparator[b] n (%)	Total n (%)
Study BAP00154			
Intent-to-Treat	397 (100)	387 (100)	784 (100)
Clinically evaluable	282 (71)	277 (72)	559 (71)
Modified Intent-to-Treat[a]	312 (79)	301 (78)	613 (78)
Microbiologically evaluable	226 (57)	217 (56)	443 (57)
Safety	389 (98)	382 (99)	771 (98)
Study BAP00414			
Intent-to-Treat	547 (100)	281 (100)	828 (100)
Clinically evaluable	485 (89)	244 (87)	729 (88)
Microbiological Intent-to-Treat[a]	434 (79)	224 (80)	658 (79)
Microbiologically evaluable	391 (71)	199 (71)	590 (71)
Safety	543 (99)	279 (99)	822 (99)

Note: Percentages were calculated with the number of ITT patients as the denominator.

[a] Patients in the ITT set with valid pathogen identified at Baseline. This analysis set is referred to as modified ITT in BAP00154 and as microbiological ITT in BAP00414.

[b] In all tables, comparator denotes vancomycin in BAP00154 and vancomycin plus ceftazidime in BAP00414.

The reasons for clinical non-evaluability were distributed similarly between treatment groups in each study. In study **BAP00154** the most common reasons were 'gram-negative present' (9%), 'course too short' (8%), and 'self-administered medication' (7%). In study **BAP00414** the most common reason was 'missing TOC visit' (7%).

The percentage of patients who completed the study was similar between treatment groups in each study and for the pooled studies. The most common reasons for discontinuation from study BAP00154 were adverse event or intercurrent illness (4%) and refused treatment, did not cooperate, or withdrew consent (4%). The most common reasons in study BAP00414 were lost to follow-up (3%), subject withdrew consent (2%), and other (2%).

Baseline data

The demographic and baseline characteristics for the ITT analysis set were comparable between the ceftobiprole and comparator treatment groups in each study. Similar demographic and baseline characteristics were seen in the microbiologically evaluable population. In the microbiologically evaluable sets of both studies the distributions of pathogens especially the prominent pathogens (MRSA, MSSA in both studies and *E.coli* in study **BAP00414**) were similar between the ceftobiprole and control groups.

Numbers analysed

Patients were stratified by the major categories of cSSTI. Overall, the numbers of patients in each of the major categories of cSSTI were as follows in the ceftobiprole groups in the pooled pivotal studies: abscesses (354/944 [38%]), wound infection including surgical (n=88), trauma (n=128), and burns (n=33) totalled to 249/944 [26%], cellulitis (172 [18%]) and DFIs (168 [18%]).

For pooled studies, the clinically evaluable analysis set included 767 ceftobiprole-treated patients and 521 comparator-treated patients. The ITT analysis set included 944 patients in the ceftobiprole treatment group and 668 patients in the comparator group.

Outcomes and estimation

***Clinical outcome*.** In trial **BAP00154**, clinical cure rates for clinically evaluable patients at the test-of-cure (TOC) visit 7 to 14 days after the end of treatment were 93.3% (263/282) for ceftobiprole and 93.5% (277/259) for vancomycin. In the ITT analysis sets the cure rates were 77.8% and 77.5% respectively.

In trial **BAP00414**, clinical cure rates for clinically evaluable patients at the TOC visit 7 to 14 days after the end of treatment were 90.5% (439/486) in patients receiving ceftobiprole and 90.2% (439/485) in patients receiving vancomycin plus ceftazidime. In the ITT analysis sets the cure rates were 81.9% and 80.8% for ceftobiprole and vancomycin plus ceftazidime, respectively. In this trial, although not statistically significant, clinical cure rates in patients with diabetic foot infections were numerically higher in patients receiving ceftobiprole (86.2%; 125/145) compared with patients receiving vancomycin plus ceftazidime (81.8%; 63/77). The overall clinical cure rates were lower in the ITT analysis set because the assessment of outcome in this group was more conservative; patients with missing or indeterminate responses were counted as failures.

Table 3: Clinical Cure Rates at the TOC Visit by study (Clinically Evaluable and ITT Analysis Sets)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff(%)[a]	95% CI[b]
Clinically Evaluable Analysis Set								
All patients								
Study BAP00154*	282	263	93.3	277	259	93.5	-0.2	(-4.4; 3.9)
Study BAP00414	485	439	90.5	244	220	90.2	0.4	(-4.2; 4.9)
Patients without DFIs								
Study BAP00154	282	263	93.3	277	259	93.5	-0.2	(-4.4; 3.9)
Study BAP00414	340	314	92.4	167	157	94.0	-1.7	(-6.2; 2.9)
Type of infection								
Study BAP00154								
Wound	80	77	96.3	87	78	89.7	6.6	(-1.0; 14.2)
Abscess	152	142	93.4	134	129	96.3	-2.8	(-7.9; 2.2)
Cellulitis	50	44	88.0	56	52	92.9	-4.9	(-16.1; 6.4)
Study BAP00414								
Diabetic foot infection	145	125	86.2	77	63	81.8	4.4	(-5.9; 14.7)
Wound	110	102	92.7	51	48	94.1	-1.4	(-9.5; 6.7)
Abscess	144	132	91.7	80	77	96.3	-4.6	(-10.7; 1.6)
Cellulitis	86	80	93.0	36	32	88.9	4.1	(-7.5; 15.7)
Patients with only gram-positive pathogens at baseline								
Study BAP00154	226	213	94.2	217	204	94.0	0.2	(-4.1; 4.6)
Study BAP00414	267	246	92.1	131	119	90.8	1.3	(-4.6; 7.2)
Patients with gram-negative or mixed pathogens at baseline[c]								
Study BAP00414	124	109	87.9	68	61	89.7	-1.8	(-11.0; 7.4)
ITT Analysis set								
Patients without DFIs								
Study BAP00154	397	309	77.8	387	300	77.5	0.3	(-5.5; 6.1)
Study BAP00414	379	318	83.9	192	163	84.9	-1.0	(-7.3; 5.3)
Patients with DFIs								
Study BAP00414	168	130	77.4	89	64	71.9	5.5	(-5.8; 16.7)
Patients with only gram-positive pathogens at baseline								
Study BAP00154	276	225	81.5	267	219	82.0	-0.5	(-7.0; 6.0)
Study BAP00414	291	249	85.6	146	122	83.6	2.0	(-5.2; 9.2)
Patients with gram-negative or mixed pathogens at baseline[c]								
Study BAP00154	36	27	75.0	34	17	50.0	25.0	(3.0; 47.0)
Study BAP00414	143	114	79.7	78	64	82.1	-2.3	(-13.1; 8.4)

Note: n is the number of patients with a clinical outcome of Cure.
Note: The randomization between ceftobiprole to comparator was 1:1 in BAP00154 and 2:1 in BAP00414.
* In study BAP00154 the primary reason for non-evaluability was the presence of gram-negative organism at baseline for 9% of patients in each study arm.

[a] Ceftobiprole minus comparator.
[b] 2-sided 95% confidence interval is based on the Normal approximation to the difference of the 2 proportions.
[c] Only study BAP00414 included patients with gram-negative/mixed pathogens. In BAP00154, these patients were considered not clinically evaluable but were included in the Intent-to-Treat Analysis Set.

Clinical cure rates for patients with DFIs in the ceftobiprole and the vancomycin plus ceftazidime groups were 86.2% and 81.8%, respectively, in the clinically evaluable analysis set. These clinical cure rates were lower in both treatment groups compared with patients with other infection types. Diabetic foot infections are generally considered the most severe of cSSTI and difficult to treat because of poor vascularization of infected tissues as well as deficiencies in immune function.

Of note also the lower cure rates for patients with *abscess* in the ceftobiprole treatment group. Wound care was similar in both treatment groups at the primary infection site.

Overall, baseline *blood cultures* were positive in 36 subjects randomly assigned to ceftobiprole, including 11 clinically evaluable patients with *S. aureus* bacteraemia, clinical cure was observed for 10/11 of these patients.

The cure rates in patients in whom gram-positive pathogens alone were isolated from the infection site were numerically higher than those observed in patients who had polymicrobial infections due to both gram-positive and gram-negative pathogens.

In study **BAP00414**, clinical cure rates for patients with gram-negative or mixed pathogens present at baseline, ceftobiprole treatment showed numerically lower cure rates in both evaluable and ITT analysis sets and the lower 95%CI (-11 and -13) disfavoured ceftobiprole.

Overall results for all patients seem to indicate non- inferiority of ceftobiprole versus comparator regimens for the clinical cure rate at the TOC visit in each study in both the clinically evaluable and ITT analysis sets, with the lower bound of the 2-sided 95% confidence intervals for the differences in cure rates being greater than -10%.

However, based on the existing analysis of the results of primary clinical non-inferiority endpoint it could not be concluded at that stage that the two treatments in the main trials (whereas only trial BAP00414 can be considered pivotal) will exhibit clinically similar efficacy in the sought indication: Although the used definition of cure in the main trials i.e. cure plus improvement such that no further antimicrobial therapy was necessary, would be acceptable for the sought indication (see NfG for Guidance on Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections- CHMP/EWP/558/95), definitive assessment of the present results is hampered because overviews of baseline data for clinical signs and symptoms for the pivotal study BAP00414 and separate analysis included DFI patients could not be retrieved in the study report. Furthermore, separate analysis of the cure and improved rates at the TOC and LFU visits is requested. Subsequently, the applicant provided sufficient clarifications to raised issues. The additional analyses lend support to consider the provided results of both studies in the assessment of the non-inferiority of the efficacy of ceftobiprole versus the chosen comparator regimens in both studies.

Consistency of the results across subgroup analyses, particularly infection type by causative agent could not be concluded.

There was a concern that study BAP 00154 enrolled such a select group and used a particular regimen using questionable low dosage of ceftobiprole such that the findings are not representative to the general

population of patients who have cSSTI. Therefore, it was considered that this application relied primarily on a single pivotal study i.e. BAP00414 to support the indication of cSSTI. In response to this concern, the applicant argued in support of maintaining this study as pivotal for the claimed efficacy of ceftobiprole 500 mg BID regimen against gram-positive infections.

Clinical cure rates by pathogen at the TOC visit against major causative pathogens (isolated from 10 or more patients in the pooled dataset) of cSSTI observed in each study in microbiologically evaluable patients are presented for infection site isolates in composite table 5.

Applicant has also provided pooled data analysis (not shown here). Ceftobiprole clinical cure rates in the microbiologically evaluable analysis set at the TOC visit in patients with PVL-positive *S. aureus* infections were similar in ceftobiprole and comparator treated groups: 133/139 (95.7%) for PVL-positive *S. aureus* and 62/67 (92.5%) for PVL-positive MRSA in the ceftobiprole group compared with 100/109 (91.7%) and 38/45 (84.4%) in the comparator group respectively. Differences between the treatment groups were statistically significant.

Concurrent *bacteraemia* at baseline was present in 26/617 patients in the ceftobiprole and 15/416 patients in the comparator treatment group in the pooled microbiologically evaluable dataset. Clinical cure was observed for 21 (80.8%) and 12 (80.0%) patients with bacteraemia respectively. As requested by the CHMP, applicant has detailed the results obtained for bacteraemic patients per study. (See table below).

Table 4: Clinical Cure Rates at the TOC Visit by Study for Bacteraemic Subjects in Studies BAP00154 and BAP00414

(Studies BAP00154 and BAP00414: Microbiologically Evaluable and Microbiological Intent-to-Treat Analysis Set)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff[a] (%)	95% CI[b]
Study BAP00154								
Microbiologically Evaluable	13	10	76.9	7	7	100.0	-23.1	(-46.0; -0.2)
Modified Intent-to-Treat	20	11	55.0	11	8	72.7	-17.7	(-51.9; 16.4)
Study BAP00414								
Microbiologically Evaluable	13	11	84.6	8	5	62.5	22.1	(-16.7; 61.0)
Microbiological Intent-to-Treat	16	13	81.3	11	6	54.5	26.7	(-8.4; 61.8)

[a] Ceftobiprole minus comparator; comparator denotes vancomycin in BAP00154 and vancomycin/ceftazidime in BAP00414.
[b] 2-sided 95% CI is based on the Normal approximation to the difference of the 2 proportions.
q17_rclin_bact_t1.rtf generated by q17_rclin_bact.sas.

Applicant's conclusion that similar clinical cure and microbiological eradication rates between the ceftobiprole- and comparator-treated patients with bacteraemia were observed in the pooled data could not be endorsed. Numerically, the comparator was favoured to ceftobiprole in study BAP00154; vice versa ceftobiprole was favoured to the comparator in study BAP00414. The seemingly inconsistent performance of the comparator was probably caused by the very limited number of cases involved in the comparisons. Applicant was requested to reflect the limited experience in section 4.4 of SPC and SPC has been adjusted accordingly.

In **BAP00154**, clinical cure rates for ceftobiprole treated patients in the microbiologically evaluable analysis set for patients with infection involving *S. aureus* were 91.8% and 96.0% for MRSA and MSSA respectively. These results were comparable with those observed for the comparator (with 90% and 96% for MRSA and MSSA, respectively). The corresponding cure rates in study **BAP00414** in the ceftobiprole

treated patients were 89.7% and 93.8% for MRSA and MSSA, respectively. This compared with 86% and 93% for MRSA and MRSS, respectively of the patients on the control regimen.

Table 5: Clinical Cure Rates at the TOC Visit by study and by Infection Site Pathogens (Microbiologically Evaluable Analysis Set)

Study BAP00154				
	------ Ceftobiprole ------ (N=226)		------- Comparator ------- (N=217)	
Main Heading Infection Specified Term	Total n	Category, n (%) Cure	Total n	Category, n (%) Cure
Gram-positive				
Staphylococcus, coagulase-positive				
Staphylococcus aureus/MSSA	126	121 (96)	112	108 (96)
Staphylococcus aureus/MRSA	61	56 (92)	60	54 (90)
Staphylococcus aureus/unk[a]	4	3	3	3
Streptococcus, beta-hemolytic				
Streptococcus pyogenes	11	8 (73)	17	15 (88)
Streptococcus agalactiae	3	3	1	1
Staphylococcus, coagulase-negative				
Staphylococcus epidermidis	8	8	9	8
Enterococcus				
Enterococcus faecalis	5	5	3	3
Study BAP00414				
	------ Ceftobiprole ------ (N=391)		------- Comparator ------- (N=199)	
Gram-positive				
Staphylococcus, coagulase-positive				
Staphylococcus aureus/MSSA	160	150 (94)	90	84 (93)
Staphylococcus aureus/MRSA	87	78 (90)	36	31 (86)
Staphylococcus aureus/unk[a]	0	0	2	2 (100)
Streptococcus, beta-hemolytic				
Streptococcus pyogenes	20	18 (90)	12	11 (92)
Streptococcus agalactiae	16	14 (88)	4	3
Staphylococcus, coagulase-negative				
Staphylococcus epidermidis	12	10 (83)	3	3
Enterococcus				
Enterococcus faecalis	6	4	2	1
Gram-negative				
Enterobacteriaceae				
Escherichia coli	37	33 (89)	26	24 (92)
Enterobacter cloacae	12	10 (83)	10	9 (90)
Proteus mirabilis	12	9 (75)	10	9 (90)
Klebsiella pneumoniae	11	9 (82)	3	3
Pseudomonas				
Pseudomonas aeruginosa	30	26 (87)	9	9

[a] *Staphylococcus aureus* isolates with unknown susceptibility to methicillin due to the unavailability of central laboratory data.

Overall, the pathogens isolated from the primary infection site at baseline in both treatment groups in both studies were predominantly gram-positive organisms and primarily *S. aureus* (both MSSA and MRSA). A broader representation of pathogens including larger numbers of other gram-positive pathogens and gram-negative pathogens which would be more consistent with the known aetiology of severe cSSTI would have been expected in the light of the claimed broad spectrum coverage for ceftobiprole.

Applicant was requested to discuss how *colonisation* was excluded from testing in all MRSA cases (with particular attention to Non-EU countries such as Russia, Ukraine, Serbia and Montenegro, Mexico, Swaziland, and Thailand). The methods to detect the phenotype resistances for all MRSAs (disk and/or MIC, used cut-off values) and whether all MRSA cases were confirmed by central lab were also to be discussed. As requested, applicant gave sufficient explanation of the raised issues.

There was a trend for lower clinical cure rates at the TOC visit in ceftobiprole treated patients with *S. pyogenes* infection in the individual studies compared to the vancomycin based comparator regimens. Furthermore, numbers of patients with cSSTI due to the gram-positive aerobes *S. agalactiae* and *E. faecalis* are too limited to allow appropriate conclusions.

In response to major CHMP question, the applicant maintained that experience in patients with cSSTI due to gram-positive pathogens other than staphylococci is sufficient based on a pooled analysis to underline this conclusion. In the latter analysis beta-haemolytic Streptococci were the main relevant isolate, the clinical cure rate in the microbiologically evaluable population was 56/63 (89%) in the ceftobiprole group vs. 50/54 (93%) in the control group. For the most frequent isolates in this group the clinical cure rates were as follows: *Streptococcus pyogenes* 26/31 (84%) and 26/29 (90%) for ceftobiprole and control group resp.; for *Streptococcus agalactiae* 17/19 (89%) and 4/5 (80%) for ceftobiprole and control group respectively.

The small numbers and seemingly non-consistent performance of the comparator illustrate the non robustness of the pooled comparative data. This is further underlined by the examined data from individual studies, as examination by the applicant, indicated that the difference in clinical cure rates for *S. pyogenes* between the ceftobiprole and comparator groups in the pooled analysis in the microbiologically evaluable analysis set was primarily due to the results observed in Study BAP00154 (clinical cure rates for subjects with *S. pyogenes* of 73% and 88% for ceftobiprole and comparator, respectively) rather than in study BAP00414 (clinical cure rates for subjects with *S. pyogenes* were 90% and 92% for ceftobiprole and comparator, respectively). Inconsistent findings across studies are at least partially explained by the small numbers involved. This situation is not in support of the hypothesized adequacy of ceftobiprole 500 mg BID for the treatment of confirmed gram-positive infections at large or infections due to streptococci such as *S. pyogenes* in particular.

In response to CHMP question, applicant provided additional *in vitro* data with respect to minimal numbers tested and concluded that *S. aureus*, *S. epidermidis*, *S. agalactiae* and *S. pyogenes* should also be included in the SPC in Section 5.1, with inclusion of an asterisk denoting clinical efficacy. Utmost, based on the available results in the ceftobiprole groups in the microbiologically evaluable analysis set and the *in vitro* data plus the improved dosing recommendation (500 mg t.i.d.), the CHMP concluded that only *Streptococcus pyogenes* had to be added to *S. aureus* as species for which sufficient data had been obtained and to reflect this in section 5.1 of the intended SPC..

Experience in patients with cSSTI due to relevant gram-negative pathogens other than *E. coli* is very limited. The predominating gram-negative infections were due to *E. coli* and *P. aeruginosa*. Comparison of efficacy of ceftobiprole against *P. aeruginosa* is difficult due to the limited number of patients in whom *P. aeruginosa* was isolated in particular in the control groups. Data on the gram-negative pathogens by infection type from Study BAP00414 for the mITT show the very low numbers of pathogens other than *E.coli* and the unbalanced distribution over the two treatment groups and types of infection (partly due to the 2:1 randomisation).

Furthermore, numerically lower clinical cure rates in the ceftobiprole group were observed for most frequently isolated Enterobacteriaceae other than *E.coli* in the microbiologically evaluable analysis set in Study BAP00414. For patients infected with Enterobacteriaceae in Studies BAP00154 and BAP00414, clinical cure rates by highest MIC were assessed in the mITT analysis set. The mITT analysis set was chosen for this analysis because of the exclusion of gram-negative pathogens in the microbiologically evaluable analysis set in Study BAP00154. The pooling of results from both studies in this mITT analysis can be questioned due to the different dosage regimens used and differences in design and populations between studies.

The numbers of patients infected with Enterobacteriaceae with a ceftobiprole MIC 0.25-16 mg/L remain very small to decide on a breakpoint or efficacy against the whole family of Enterobacteriaceae.

Clinical cure rates among patients across infection types with gram-negative monomicrobial and polymicrobial infections performed in the clinically evaluable and ITT analysis sets suggested also lower cure rates in the ceftobiprole treated patients with monomicrobial gram-negative wound and abscess infections and in polymicrobial cases in DFI patients. More experience in gram-negative infections other than *E. coli* is warranted in order to allow robust conclusions on comparable clinical efficacy with studied comparator regimen.

Applicant was requested to discuss the evidence that *P. aeruginosa* was the pathogen (not colonizer) in these infections. As requested, the applicant gave sufficient clarification, although not entirely satisfactory, the bits of evidence can be accepted.

Patients in whom *P. aeruginosa* was isolated as a single pathogen, the cure rate was 75% (9 of 12 patients) in the ceftobiprole group, whereas this was 78% (28 of 36 patients) in patients in whom this pathogen was isolated either as a single pathogen, or in the presence of other pathogens. In the control 9/9 patients were cured. Generally the limited data for patients with cSSTI due to specific major gram-negative pathogens other than *E.coli* suggest a lower efficacy of ceftobiprole compared to the comparator regimen and this is of concern which makes the sought indication for this group of patients questionable. In response to CHMP question, the applicant provided additional *in vitro* data and gave an analysis of available results and concluded that the clinical experience with *E. cloacae*, *K. pneumoniae*, and *P. mirabilis*, together with the clinical experience with the family Enterobacteriaceae as a whole was sufficient; and therefore, *E. coli*, *E. cloacae*, *K. pneumoniae*, and *P. mirabilis* should also be included in the SPC in Section 5.1, with inclusion of an asterisk denoting clinical efficacy. CHMP is of the opinion that the provided data remain non-robust to draw this conclusion from the only pivotal study BAP00414 for such infections (as described above).

The efficacy results of ceftobiprole against *Pseudomonas* infections are certainly not convincing although the total number of cases evaluated were > 20 (35 in this case). The present results even with the improved dosage recommendation 500 mg t.i.d. are not reassuring.

More experience in gram-negative infections other than *E. coli* is warranted in order to allow robust conclusions on comparable clinical efficacy with studied comparator regimen.

Microbiological outcome. No differences in the overall microbiologic eradication rates between treatment groups were evident. See table below.

Table 6: Microbiological Eradication Rates at the TOC Visit by Study
(Microbiologically Evaluable and Microbiological Intent-to-Treat Analysis Sets)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff(%)[a]	95% CI[b]
Study BAP00154								
Microbiologically evaluable	226	213	94.2	217	203	93.5	0.7	(-3.8; 5.2)
Persistence / presumed persistence		12	5		9	4		
Superinfection		0			2	1		
Modified ITT[c]	312	213	68.3	301	203	67.4	0.8	(-6.6; 8.2)
Study BAP00414								
Microbiologically evaluable	391	344	88.0	199	177	88.9	-1.0	(-6.4; 4.5)
Persistence / presumed persistence		38	10		20	10		
Superinfection		6	2		2	1		
Microbiological ITTt[c]	434	344	79.3	224	177	79.0	0.2	(-6.3; 6.8)

Note: n is the number of patients with a microbiological outcome of Eradication or Presumed Eradication.
[a] Ceftobiprole minus comparator.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Subjects in the ITT set with valid pathogen identified at Baseline. This analysis set is referred to as modified ITT in BAP00154 and as microbiological ITT in BAP00414.

By definition, there was 100% association with a patient's clinical outcome for the microbiological outcomes Presumed Eradication, Presumed Persistence, Colonization, and Superinfection.

Follow-up results

In the assessment of outcome at LFU measured as sustained clinical cure and microbiologic eradication through to the LFU visit - including patients who dropped out of the LFU relapse assessment because of their unfavourable clinical and microbiologic outcome at TOC - in the clinically evaluable analysis set, the sustained clinical cure rate of 87.9% and 84.5% at LFU for ceftobiprole in studies BAP00154 and BAP00414 respectively compared with 87.0% and 84.8% for comparator-treated patients.

Efficacy by susceptibility to ceftobiprole

In the 2 Phase III cSSTI studies, ceftobiprole MICs were ≤2 μg/mL against the majority of bacteria isolated at baseline. A small number of pathogens had ceftobiprole MICs ≥16 □g/mL (19 of 635 isolates from microbiologically evaluable, ceftobiprole-treated patients). Only 17 gram-negative isolates (3 *K. pneumoniae*, 1 *P. mirabilis* and 13 *P aeruginosa*) had a ceftobiprole MIC >4 μg/mL. In study BAP00414 only 3/6 patients with infections due to *P aeruginosa* isolates with a ceftobiprole MIC ≥8 □g/mL were cured, similarly only 5/9 patients with *P. aeruginosa* isolated from specimens in addition to having gram-negative rods were cured.

For patients with gram-negative infections at baseline (other than those caused by *P. aeruginosa*), in the ceftobiprole treatment group, clinical cure was observed for 65 (85.5%) of the 76 patients with MIC ≤4 □g/mL and for 12 (60.0%) of the 20 patients with MIC ≥8 □g/mL. A clear relationship between favourable clinical outcomes and isolation of bacteria at baseline with a ceftobiprole MIC >4 μg/mL was not evident in this analysis. However, the number of gram-negative isolates with MIC >4 μg/mL is very limited. Applicant was requested to clarify the number of ESBL producing Gram-negative bacteria which were isolated from mixed cSSTIs. As requested, the applicant gave sufficient clarification (this pertained to 4/129 patients in the ceftobiprole group).

Emergence of resistance.

To evaluate the emergence of ceftobiprole resistance in a clinical setting, patient isolates from the ceftobiprole clinical trials BAP00154 and BAP00414 were examined for a 4-fold or greater increase in ceftobiprole MIC between the screening and post treatment isolates. Six patients from the BAP00414 fit the inclusion criteria and β-lactamase mediated resistance mechanisms were characterized in these isolates. All ceftobiprole-treated patients were assessed as clinical cures with the exception of the *C.*

braakii pair. The potential for the emergence of resistance after clinical use of ceftobiprole cannot be denied. The very low frequency noted in the present clinical database should be interpreted with caution due to the controlled trial conditions and rather limited database. In the RMP the potential for developing antimicrobial resistance is considered as a specific issue that needs to be followed and evaluated. This is reflected in the present RMP.

Ancillary analyses

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

Table 7: Clinical Cure Rates at the TOC Visit by Baseline Infection Characteristics in the Pooled Studies
(Studies BAP00154 and BAP00414: Clinically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---					
	N	n	%	N	n	%	Diff (%)[a]	95% CI[b]	p-value[c]
Clinically evaluable									
All subjects	767	702	91.5	521	479	91.9	-0.4	(-3.5; 2.6)	
By depth of infection									
Subcutaneous tissue	502	469	93.4	345	321	93.0	0.4	(-3.1; 3.8)	0.779
Fascial plane	180	159	88.3	121	110	90.9	-2.6	(-9.5; 4.4)	
Muscle	84	73	86.9	55	48	87.3	-0.4	(-11.8; 11.0)	
By SIRS[d]									
Yes	146	130	89.0	103	92	89.3	-0.3	(-8.1; 7.5)	0.936
No	621	572	92.1	418	387	92.6	-0.5	(-3.8; 2.8)	
By surgical debridement[e]									
Present	296	270	91.2	194	184	94.8	-3.6	(-8.1; 0.9)	0.097
Absent	471	432	91.7	327	295	90.2	1.5	(-2.6; 5.6)	
By on study surgical debridement[f]									
Present	85	52	61.2	48	31	64.6	-3.4	(-20.4; 13.6)	0.559
Absent	682	650	95.3	473	448	94.7	0.6	(-2.0; 3.2)	
By C-reactive protein									
≤50 mg/L	438	410	93.6	269	259	96.3	-2.7	(-5.9; 0.5)	0.286
>50 mg/L	302	267	88.4	230	205	89.1	-0.7	(-6.1; 4.7)	
By C-reactive protein 2									
≤100 mg/L	549	515	93.8	345	331	95.9	-2.1	(-5.0; 0.8)	0.476
>100 mg/L	191	162	84.8	154	133	86.4	-1.5	(-9.0; 5.9)	
By severity of diabetic foot infection[g]									
Mild (Grade 2)	42	41	97.6	17	17	100.0	-2.4	(-7.0; 2.2)	0.600
Moderate (Grade 3)	86	72	83.7	46	38	82.6	1.1	(-12.3; 14.6)	
Severe (Grade 4)	17	12	70.6	13	7	53.8	16.7	(-17.9; 51.4)	

Note: n is the number of subjects with a clinical outcome of Cure.
[a] Ceftobiprole minus comparator.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Breslow-Day's test was used to test the homogeneity of treatment differences across strata.
[d] Systemic Inflammatory Response Syndrome (SIRS).
[e] Includes surgical debridement procedures that occurred up to 48 hours after baseline.
[f] On study surgical debridement is any surgical debridement procedure that occurred more than 48 hours after baseline.

- Subgroup analyses

Subgroup analyses were performed by age, gender, race, region, and pre-study antibiotics in study BAP00154 and study BAP00414.

Table 8: Clinical Cure Rates at the TOC Visit by Subgroup in the Pooled Studies
(Studies BAP00154 and BAP00414: Clinically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---					
	N	n	%	N	n	%	Diff(%)[a]	95% CI[b]	p-value[c]
Clinically evaluable									
All subjects	767	702	91.5	521	479	91.9	-0.4	(-3.5; 2.6)	
By region 1									
U.S.	214	185	86.4	158	138	87.3	-0.9	(-7.8; 6.0)	0.991
Europe[d]	415	394	94.9	283	269	95.1	-0.1	(-3.4; 3.2)	
Other[e]	138	123	89.1	80	72	90.0	-0.9	(-9.2; 7.5)	
By region 2									
U.S.	214	185	86.4	158	138	87.3	-0.9	(-7.8; 6.0)	0.996
Non-U.S.	553	517	93.5	363	341	93.9	-0.4	(-3.7; 2.8)	
By infection type									
Diabetic foot infection[f]	145	125	86.2	77	63	81.8	4.4	(-5.9; 14.7)	0.183
Wound	190	179	94.2	138	126	91.3	2.9	(-2.8; 8.7)	
Abscess	296	274	92.6	214	206	96.3	-3.7	(-7.6; 0.2)	
Cellulitis	136	124	91.2	92	84	91.3	-0.1	(-7.6; 7.3)	
By age group 1									
<65 years	594	544	91.6	420	387	92.1	-0.6	(-4.0; 2.8)	0.834
≥65 years	173	158	91.3	101	92	91.1	0.2	(-6.7; 7.2)	
By age group 2									
<75 years	719	660	91.8	494	456	92.3	-0.5	(-3.6; 2.6)	0.714
≥75 years	48	42	87.5	27	23	85.2	2.3	(-14.0; 18.7)	
By sex									
Male	451	410	90.9	339	314	92.6	-1.7	(-5.6; 2.1)	0.284
Female	316	292	92.4	182	165	90.7	1.7	(-3.4; 6.9)	
By race									
White	591	542	91.7	404	377	93.3	-1.6	(-4.9; 1.7)	0.300
Black	43	38	88.4	28	25	89.3	-0.9	(-15.8; 14.0)	
Other[g]	133	122	91.7	89	77	86.5	5.2	(-3.3; 13.7)	
By prestudy antibiotics[h]									
No antibiotics	432	409	94.7	307	292	95.1	-0.4	(-3.6; 2.8)	0.968
Using ≤24 hours	192	167	87.0	112	97	86.6	0.4	(-7.5; 8.3)	
Using >24 hours	143	126	88.1	102	90	88.2	-0.1	(-8.3; 8.1)	

Note: n is the number of subjects with a clinical outcome of Cure.
[a] Ceftobiprole minus comparator.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Breslow-Day's test was used to test the homogeneity of treatment differences across strata.
[d] For both studies, Europe includes Bulgaria, Hungary, Latvia, Lithuania, Romania, Russia, and Ukraine; for study BAP00154, it also includes Germany, Italy, Serbia and Montenegro; for study BAP00414, it also includes Czech Republic and Estonia.
[e] For both studies, other region includes Argentina, India, Israel, and South Africa; for study BAP00154, it also includes Mexico, Swaziland, and Thailand; for study BAP00414, it also includes Canada, Chile, Costa Rica, Democratic People's Republic of Korea, and Taiwan.
[f] Only study BAP00414 included subjects with diabetic foot infection.
[g] Other race includes Hispanic, Asian and mixed-race subjects.
[h] In study BAP00414, the window for prestudy antibiotics was limited to 72 hours prior to baseline; in BAP00154, there was no time window.

Very small numbers of patients in study BAP00154 in the clinically evaluable dataset received protocol allowed initial aztreonam and metronidazole to cover for eventual gram-negative and anaerobic infections respectively. The cure rates remained comparable in both treatment groups when these patients were not included in the analysis.

Cure rates were numerically lower in the US (although this was not so apparent from the microbiological eradication results in the microbiologically evaluable analysis set). Furthermore, in the U.S. in the larger study BAP00414, patients treated with ceftobiprole had a lower clinical cure rate than those treated with the comparator regimen, 81.0% and 90.4% respectively. This difference could not be explained by baseline severity of infection or the presence of resistant organisms.

The majority of patients in the ceftobiprole and comparator groups in both studies had either no antibiotic therapy or less than 24 hours of antibiotic therapy prior to enrolment. The cure rates were similar between treatment groups by duration of pre-study antibiotic use.

In the small number clinically evaluable patients who received dose reduction due to renal impairment; clinical cures were observed for 21/28 (75%) patients in the ceftobiprole treatment group and 13/17 (76%) patients in the comparator-treatment group.

The percentage of patients who had surgical debridement was similar across treatment groups. Clinical cure rates in patients who had surgical debridement as part of their therapy were comparable to those of patients who did not undergo this adjunctive therapy.

Clinical cure rates in both treatment groups were observed to be numerically lower in patients with more serious infections (i.e., deeper infections, presence of SIRS, C-reactive protein level >50 mg/L or >100 mg/L, and moderate or severe diabetic foot infections).

The number of patients with severe diabetic foot infections is very limited. Furthermore, the applicant was requested to clarify the number of infections that were of nosocomial origin and to discuss these separately. In addition, in study report of study BAP00154 analyses of results for the effect of debridement, presence of SIRS, C-reactive protein level >50 mg/L or >100 mg/L are not mentioned although these are included in the pooled analysis of efficacy in the pivotal studies. The applicant was requested to provide subgroup analyses for both studies by comorbidity strata of diabetes, perivascular disease, injection drug use; and primary diagnoses including major abscesses, infected ulcers, complicated erysipelas and causes of infection including spontaneous, bites or others. The requested analyses were provided by the applicant.

CHMP commented to the fact that only 18% of patients included in phase III trials suffered diabetic foot infection (without osteomyelitis). Hence, this limited experience could not justify a specific notion relating this subgroup, as part of the intended indication.

Time to cure or defervescence
Median time to clinical or microbiological cure was 8 days for ceftobiprole and control regimens in study BAP00414 whereas this was 8 days and 5 days for clinical or microbiological cures respectively for both treatment groups in study BAP00154. Median time to defervescence was 4 days for ceftobiprole and control regimens in both studies.

- Clinical studies in special populations

Paediatric experience

There are currently no data available on the efficacy of ceftobiprole in children. The applicant submitted a paediatric investigational plan (PIP) and this plan is agreed by the Paediatric Committee (PDCO).

- Supportive study

In the open Phase II trial **(BAP00034)** a small number of patients (n=40) with CSSSI (wound 9 cases, abscess 26 cases, cellulitis 5 cases) due to gram-positive pathogens was treated with ceftobiprole (750 mg every 12 hours as an i.v. infusion over 30 minutes or 60 minutes for 7 to 14 days). The most frequently occurring prior treatments involved surgical and medical procedures (53% of patients) with abscess drainage (43%) the most common procedure. 36 (90%) patients completed the minimum scheduled study therapy of 7 days (14 infusions) according to the protocol (1 withdrew due to AE polyarthritis after receiving 13 infusions due an AE; and 3 withdrew after 13 infusions due to improvement). In 4 cases concomitant antibiotics were given before the TOC assessment, leading to exclusion of efficacy data from the CE and/or ME analysis populations.

Seventeen patients were excluded from the microbiologically evaluable population due to no pathogen at baseline (10 patients), swab at baseline with no leucocytes (2 patients), coactive treatment (4 patients) and no gram-positive pathogen at baseline (1 patient). Microbiological eradication was reported for 21/ 23 (91%) microbiologically evaluable patients, including 3 of the 4 cases of MRSA; with 1 MRSA and 1 MSSA case were failures. Times to microbiological success varied between 3-21 days (maximum 7 days for wound and 21 days for abscess).

Overall, this study has an exploratory character with serious limitations in design, spectrum of cSSSI studied and deviating dosing of ceftobiprole used. Hence, it does not contribute appropriate data for the efficacy evaluation of the sought indication at the recommended dose.

- **Initial discussion on clinical efficacy (which supported the adoption of the positive opinion on 20 November 2008)**

Ceftobiprole performed favourably at the recommended doses in the primary efficacy analysis in the overall cure rates for the clinically evaluable analysis sets. The clinical cure rates in the co-primary ITT analysis set were consistent with those of the clinically evaluable analysis set. Both studies BAP00154 and BAP00414 enrolled subjects with gram-positive infections. The results of both studies are consistent in the clinically evaluable and ITT analysis sets for patients with the major only gram-positive pathogens MSSA and MRSA present at baseline. In study BAP00414, clinical cure rates for patients with diabetic foot infections in the ceftobiprole and the vancomycin plus ceftazidime groups were 86.2% and 81.8%, respectively, in the clinically evaluable analysis set, and 77.4% and 71.9%, respectively, in the ITT analysis set. The number of patients with a clinical relapse at the LFU visit was low (<2.5%) for both treatment groups in each study and for the pooled studies. Relapse was not associated with the presence of resistant infections at baseline or the development of resistant infections. The applicant acknowledged that pooled analyses were exploratory. Pooling of the individual studies for efficacy analysis is performed to assess the consistency of treatment effects and trends across subgroups. Similar observations were made for across study safety comparisons.

For the assessment of non-inferiority of ceftobiprole to comparator regimens, the CHMP requested the Applicant to provide overviews of baseline data for clinical signs and symptoms for the pivotal study BAP00414 and separate analysis included DFI patients from this study. Furthermore, separate analysis of the cure and improved rates at the TOC and LFU visits was requested. The provided additional analyses in response to CHMP request lend support to consider the provided results of both studies in the assessment of the non-inferiority of the efficacy of ceftobiprole versus the chosen comparator regimens in both studies.

- Some relevant groups of patients excluded from clinical studies: Infection related to a foreign body (e.g. catheter etc.); endocarditis; osteomyelitis; septic arthritis; necrotizing fasciitis; superinfected eczema or neoplasia; critical limb ischemia; immunocompromised patients. In others there is only limited experience (e.g bacteraemic patients, major infected burn wounds). Further to discussion within CHMP, the limited experience in phase III trials with patients suffering DFI did not justify a separate notion in the proposed indication

- The applicant argued not to evaluate the potential benefit of higher doses based on present systemic exposure data for unbound (plasma) ceftobiprole in patients (with %T>MIC of 77%) and dose dependent safety considerations.

- The potential for the emergence of resistance after clinical use of ceftobiprole cannot be denied. The very low frequency noted in the present clinical database should be interpreted with caution due to the limited database

Revised Clinical Efficacy

Following the notification about GCP deficiencies, the overall data integrity for studies BAP00154 and BAP00414 was questioned by the CHMP. The Applicant provided additional sensitivity analysis, in which 11 sites with questioned reliability were excluded. The exclusion criteria took into account findings from the EU and FDA inspections (7 sites with observations), as well as findings from the 42-site audit conducted by a 3rd party on behalf of the applicant (further 4 sites with observations).

The overall ITT dataset included 1612 patients (ITT). Exclusion of the 11 sites reduced the evaluable patient population to 657 patients. The results of this additional analysis are shown in the following table.

Table 3S11: Clinical Cure Rates at the TOC Visit by Study and in the Pooled Studies Excluding 11 Sites (Studies BAP00154 and BAP00414: Intent-to-Treat and Clinically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Clinically Evaluable Analysis Set								
All subjects								
Study BAP00154	244	226	92.6	221	211	95.5	-2.9	(-7.1; 1.4)
Study BAP00414	413	371	89.8	209	186	89.0	0.8	(-4.3; 6.0)
Subjects without diabetic foot infections								
Study BAP00154	244	226	92.6	221	211	95.5	-2.9	(-7.1; 1.4)
Study BAP00414	297	274	92.3	149	140	94.0	-1.7	(-6.6; 3.2)
Type of Infection								
Study BAP00154								
Wound	76	73	96.1	70	65	92.9	3.2	(-4.3; 10.6)
Abscess	124	114	91.9	107	104	97.2	-5.3	(-11.0; 0.5)
Cellulitis	44	39	88.6	44	42	95.5	-6.8	(-18.0; 4.4)
Study BAP00414								
Diabetic Foot Infection	116	97	83.6	60	46	76.7	7.0	(-5.7; 19.6)
Wound	102	95	93.1	45	42	93.3	-0.2	(-9.0; 8.6)
Abscess	122	112	91.8	73	70	95.9	-4.1	(-10.8; 2.6)
Cellulitis	73	67	91.8	31	28	90.3	1.5	(-10.7; 13.6)
Subjects with gram-positive pathogen at baseline								
Study BAP00154	191	179	93.7	174	166	95.4	-1.7	(-6.3; 3.0)
Study BAP00414	227	208	91.6	116	104	89.7	2.0	(-4.6; 8.6)
Subjects with gram-negative or mixed pathogens at baseline[c]								
Study BAP00414	106	92	86.8	58	51	87.9	-1.1	(-11.7; 9.4)
Intent-to-Treat Analysis Set								
All subjects								
Study BAP00154	330	263	79.7	308	238	77.3	2.4	(-4.0; 8.8)
Study BAP00414	467	379	81.2	240	192	80.0	1.2	(-5.0; 7.3)
Subjects without diabetic foot infections								
Study BAP00154	330	263	79.7	308	238	77.3	2.4	(-4.0; 8.8)
Study BAP00414	332	278	83.7	171	145	84.8	-1.1	(-7.7; 5.6)
Subjects with gram-positive pathogen at baseline								
Study BAP00154	227	186	81.9	210	174	82.9	-0.9	(-8.1; 6.2)
Study BAP00414	248	211	85.1	128	106	82.8	2.3	(-5.6; 10.2)
Subjects with gram-negative or mixed pathogens at baseline[c]								
Study BAP00154	29	25	86.2	29	13	44.8	41.4	(19.4; 63.4)
Study BAP00414	124	96	77.4	65	54	83.1	-5.7	(-17.4; 6.1)

Note: n is the number of subjects with a clinical outcome of Cure.
Note: The randomization between ceftobiprole to comparator was 1:1 in BAP00154 and 2:1 in BAP00414.
[a] Ceftobiprole minus comparator.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Only study BAP00414 included subjects with gram-negative/mixed pathogens. In BAP00154, these subjects were considered not clinically evaluable.

The results of the sensitivity analysis excluding the 11 sites showed similar primary and secondary efficacy results as the data presented in the original MA.

After an oral explanation on 20 January 2010, the company provided additional sensitivity analysis for those sites inspected and not excluded by FDA and European Medicines Agency. The number of subjects in the subgroup analysis including only 9 sites (SG9 in the forest plot) that were inspected by either the FDA or EU inspectors and that were not identified as unverifiable or unreliable involved 476 (29.5%) of the original 1612 subjects.

Results of analysis in this subgroup were consistent with the results of the analysis of the complete dataset (S0 in the forest plot), with the lower bound of the 2 sided 95% confidence intervals for the differences in cure rates being greater than -10%, except for the clinically evaluable analysis set in BAP00414 where the lower bound was -11.5%. See the table below. Review of cure rates in the complete dataset (S0) compared to the SG9 analysis suggests this result is primarily due to an observed increase in the cure rate for the comparator SG9 group (90.2% for S0 compared to 95.7% for SG9) rather than a meaningful decrease in the cure rate of the ceftobiprole treatment group. In addition, as this confidence interval includes zero, superiority of the comparator is not implied.

Table 3SG9: Clinical Cure Rates at the TOC Visit by Study and in the Pooled Studies on Subgroup of 9 Investigators
(Studies BAP00154 and BAP00414: Intent-to-Treat and Clinically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Clinically Evaluable Analysis Set								
All subjects								
Study BAP00154	79	77	97.5	87	82	94.3	3.2	(-2.8; 9.2)
Study BAP00414	143	130	90.9	70	67	95.7	-4.8	(-11.5; 1.9)
Subjects without diabetic foot infections								
Study BAP00154	79	77	97.5	87	82	94.3	3.2	(-2.8; 9.2)
Study BAP00414	120	110	91.7	61	58	95.1	-3.4	(-10.8; 3.9)
Type of Infection								
Study BAP00154								
Wound	24	24	100.0	25	23	92.0	8.0	(-2.6; 18.6)
Abscess	47	45	95.7	46	43	93.5	2.3	(-6.9; 11.4)
Cellulitis	8	8	100.0	16	16	100.0	0.0	(0.0; 0.0)
Study BAP00414								
Diabetic Foot Infection	23	20	87.0	9	9	100.0	-13.0	(-26.8; 0.7)
Wound	41	38	92.7	19	17	89.5	3.2	(-12.7; 19.1)
Abscess	70	65	92.9	35	34	97.1	-4.3	(-12.5; 3.9)
Cellulitis	9	7	77.8	7	7	100.0	-22.2	(-49.4; 4.9)
Subjects with gram-positive pathogen at baseline								
Study BAP00154	56	55	98.2	68	64	94.1	4.1	(-2.5; 10.7)
Study BAP00414	98	91	92.9	48	45	93.8	-0.9	(-9.4; 7.6)
Subjects with gram-negative or mixed pathogens at baseline[c]								
Study BAP00414	25	24	96.0	16	16	100.0	-4.0	(-11.7; 3.7)
Intent-to-Treat Analysis Set								
All subjects								
Study BAP00154	118	101	85.6	115	96	83.5	2.1	(-7.2; 11.4)
Study BAP00414	160	132	82.5	83	68	81.9	0.6	(-9.6; 10.7)
Subjects without diabetic foot infections								
Study BAP00154	118	101	85.6	115	96	83.5	2.1	(-7.2; 11.4)
Study BAP00414	133	111	83.5	71	59	83.1	0.4	(-10.4; 11.1)
Subjects with gram-positive pathogen at baseline								
Study BAP00154	74	62	83.8	80	67	83.8	0.0	(-11.6; 11.7)
Study BAP00414	108	92	85.2	54	46	85.2	0.0	(-11.6; 11.6)
Subjects with gram-negative or mixed pathogens at baseline[c]								
Study BAP00154	12	12	100.0	6	5	83.3	16.7	(-13.2; 46.5)
Study BAP00414	27	24	88.9	18	16	88.9	0.0	(-18.7; 18.7)

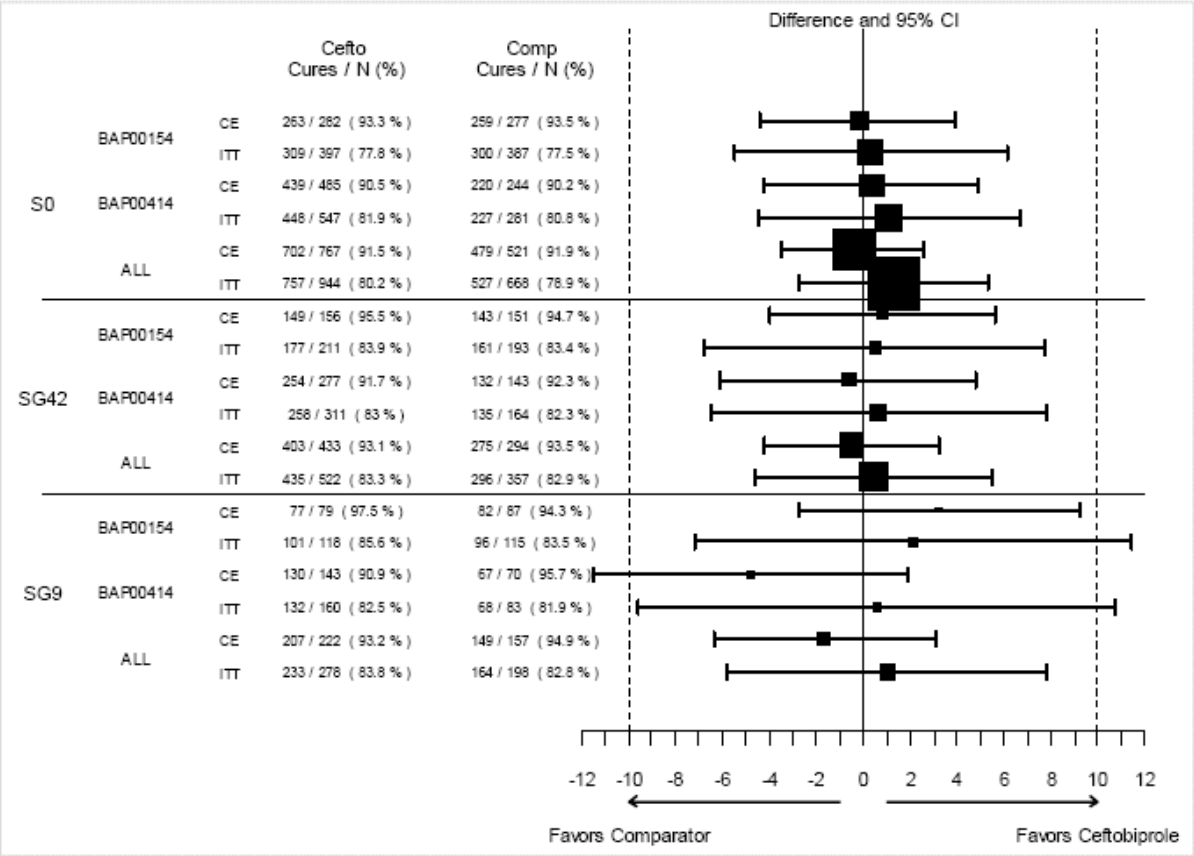
Subgroup analysis of those investigators inspected and not excluded by FDA (7 out of 10 investigators) and European Medicines Agency (2 out of 4 investigators).
Note: n is the number of subjects with a clinical outcome of Cure.
Note: The randomization between ceftobiprole to comparator was 1:1 in BAP00154 and 2:1 in BAP00414.
[a] Ceftobiprole minus comparator.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Only study BAP00414 included subjects with gram-negative/mixed pathogens. In BAP00154, these subjects were considered not clinically evaluable.

In addition, the company provided similar sensitivity analysis including 42 sites- (SG42, including above mentioned 9 sites) that were inspected by either the FDA or EU inspectors or were audited by an independent QA auditor and that were not identified as unverifiable or unreliable involved 879 (54.5%) of the original 1612 subjects. Results of analysis in this subgroup were consistent with the results of the analysis of the complete dataset.

To illustrate the above mentioned conclusions a forest plot showing the primary endpoint in each study alone and in the pooled studies for both subgroups (SG9 and SG42) in comparison to the complete

dataset is shown in Figure 1. In this plot, the point estimate of the difference in cure rates at the test-of-cure (TOC) visit is represented by the black box at the centre of the 95% confidence interval. The size of the box is proportional to the overall sample size.

Figure1: Forest Plot of the Primary Efficacy Analysis for S0, SG9, and SG42



The clinical cure rate by pathogen is displayed in the table below for the SG9 analysis.

Table 5SG9: Clinical Cure Rates at the TOC Visit by Study and by Infection Site Pathogens on Subgroup of 9 Investigators
(Study BAP00154 and BAP00414: Microbiologically Evaluable Analysis Set)

	Study BAP00154			
	------ Ceftobiprole ------ (N=56)		------- Comparator ------- (N=68)	
Main heading Infection specified term	Total n	Category, n (%) Cure	Total n	Category, n (%) Cure
Gram-positive				
Staphylococcus, coagulase-positive				
Staphylococcus aureus/MSSA	27	27 (100)	30	28 (93)
Staphylococcus aureus/MRSA	17	16 (94)	26	25 (96)
Staphylococcus aureus/unk[a]	0	0	2	2 (100)
Streptococcus, beta-hemolytic				
Streptococcus pyogenes	3	3 (100)	1	1 (100)
Streptococcus agalactiae	0	0	0	0
Staphylococcus, coagulase-negative				
Staphylococcus epidermidis	1	1 (100)	2	2 (100)
Enterococcus				
Enterococcus faecalis	2	2 (100)	2	2 (100)
	Study BAP00414			
	------ Ceftobiprole ------ (N=123)		------- Comparator ------- (N=64)	
Gram-positive				
Staphylococcus, coagulase-positive				
Staphylococcus aureus/MSSA	61	58 (95)	25	25 (100)
Staphylococcus aureus/MRSA	34	29 (85)	18	15 (83)
Staphylococcus aureus/unk[a]	0	0	1	1 (100)
Streptococcus, beta-hemolytic				
Streptococcus pyogenes	4	4 (100)	2	2 (100)
Streptococcus agalactiae	4	2 (50)	0	0
Staphylococcus, coagulase-negative				
Staphylococcus epidermidis	6	6 (100)	3	3 (100)
Enterococcus				
Enterococcus faecalis	2	2 (100)	1	1 (100)
Gram-negative[b]				
Enterobacteriaceae				
Escherichia coli	4	4 (100)	4	4 (100)
Enterobacter cloacae	2	2 (100)	3	3 (100)
Klebsiella pneumoniae	3	2 (67)	0	0
Proteus mirabilis	2	2 (100)	1	1 (100)
Pseudomonas				
Pseudomonas aeruginosa	7	7 (100)	2	2 (100)

Subgroup analysis of those investigators inspected and not excluded by FDA (7 out of 10 investigators) and European Medicines Agency (2 out of 4 investigators).

[a] *Staphylococcus aureus* isolates with unknown susceptibility to methicillin due to unavailability of central laboratory data.

[b] Only study BAP00414 included subjects with gram-negative pathogen.

- **Revised discussion on clinical efficacy**

Although the provided sensitivity analyses seem to be in line with the conclusion of non-inferiority, this needs to be interpreted with caution. Indeed, the decreased number of patients involved in this analysis compromise the robustness of the conclusion, especially in the relevant subgroups (by pathogen or cSSTI specific diagnoses) with limited data within the total clinically evaluable patient populations in both treatment arms of these pivotal studies. Nevertheless, for the leading diagnoses such as wound, abscesses and diabetic foot the results appear in agreement with the original conclusion although the confidence interval becomes larger in study BAP00414; the same applies for the leading pathogen *S.*

aureus (MRSA and MSSA). For *E. coli* the numbers are too limited to draw clear conclusions on efficacy, but not unfavourable for ceftobiprole as well as for the comparator regimen.

The overall poor data control of these trials, as evidenced by the various GCP findings at multiple inspected and audited sites, indicates a lack of rigour in the available data set. Such poor control favours a non-inferiority result, as potential differences in results may become non detectable. It should be appreciated that in trials intended to show a difference between treatments there is a strong imperative to use a good trial design and minimise trial errors because many trial imperfections increase the likelihood of failing to show a difference between treatments when one exists.

As each round of inspection or audit has led to the exclusion of additional sites, the overall conduct of the trial is questionable and it can no longer be concluded that the conduct of the trial did not undermine its ability to distinguish effective treatments from less effective treatments.

Therefore, the CHMP did not consider the additionally performed sensitivity analyses sufficient to support the efficacy demonstration of this marketing authorisation application.

Clinical safety

- Patient exposure

Table 9: Main Datasets for Safety Analysis

Dataset	Contributing Studies	N
Phase I	10*	234 healthy volunteers
Phase II	BAP00034 in which	40 patients with cSSSI
Phase III	Studies BAP00154 and BAP00414	1,593** patients with cSSSI

* Data in subjects with normal renal function. Data from the renally-impaired subjects in the Phase I study BAP00018 are not included in the integrated safety analysis, they are presented in the clinical study. Data from Studies NP16104 and CSI-1001 were not integrated; Likewise Study NP16104 was an exploratory study in 3 healthy male volunteers, and Study CSI-1001 (20 subjects) was discontinued due to an unexpected number of infusion site reactions that appeared to be secondary to procedures being followed to maintain i.v. catheters and administer study drug.
** including ceftobiprole and comparator treated patients

The safety data for the Phase I studies were integrated and analysed separately.

Safety data from the pivotal Phase III studies were integrated and analyzed separately, although these studies had different patient populations (only Study BAP00414 included subjects with DFIs), randomization ratios (1:1 in Study BAP00154 and 2:1 in Study BAP00414), and dosing regimens (500 mg of ceftobiprole or 1,000 mg of vancomycin by a 60-minute i.v. infusion twice daily in Study BAP00154 and 500 mg of ceftobiprole three times daily and placebo twice daily [matched to the vancomycin infusion] or 1,000 mg of vancomycin b.i.d. and 1,000 mg of ceftazidime three times daily by a 120-minute i.v. infusion).

Table 10: Exposure to recommended ceftobiprole dose (IV) in phase III studies

Study	Dose	N
BAP00154	500 mg of ceftobiprole over a 1-hour infusion BID	389
BAP00414	500 mg of ceftobiprole over a 2-hour infusion TID	543

A total of 757 (81.2%) patients received 7 to 14 days of ceftobiprole. Eighteen (1.9%) patients in the ceftobiprole treatment group received more than 14 days of treatment; none of the patients received ceftobiprole for >21 days.

- Adverse events

Phase III studies

In the pooled analysis of the pivotal studies similar safety percentages of patients who received ceftobiprole and patients who received the comparators had at least 1 adverse event and had treatment-related adverse events.

Table 11: Summary of Treatment-Emergent Adverse Events
(Pooled Phase III Studies BAP00154 and BAP00414: Safety Analysis Set)

	Ceftobiprole (n=932) n (%)	Comparator (n=661) n (%)	Ceftobiprole Minus Comparator Diff (%)[b] 95% CI[c]
Without AE	425 (45.6)	309 (46.7)	-0.4 (-5.4, 4.7)
At least one AE	507 (54.4)	352 (53.3)	0.4 (-4.7, 5.4)
Treatment-related AEs[a]	345 (37.0)	215 (32.5)	4.1 (-0.6, 8.9)
Death	3 (0.3)	4 (0.6)	-0.3 (-1.0, 0.3)
Serious AEs	63 (6.8)	47 (7.1)	-0.6 (-3.2, 2.0)
Treatment-related serious AEs[a]	16 (1.7)	15 (2.3)	-0.6 (-1.9, 0.8)
AE leading to discontinuation	43 (4.6)	38 (5.7)	-1.2 (-3.4, 1.1)
Treatment-related AEs[a] leading to discontinuation	35 (3.8)	27 (4.1)	-0.3 (-2.3, 1.6)

AE=adverse event.
[a] Any patient with missing relationship, remotely, possibly, or probably related were counted as related.
[b] A Cochran-Mantel-Haenszel weighted average of the differences in the individual studies.
[c] 2-sided 95% confidence interval was based on the Cochran-Mantel-Haenszel weighted variances from the individual studies.

Nausea (9.1%), vomiting (4.8%) and diarrhoea(4.8%) , dysgeusia (5.6%) , headache (4.5%), dizziness (2.7%) , phlebitis (1.9%)and hyponatraemia (1.1%) were reported at higher rates by patients who received ceftobiprole than patients in the comparator group in the pooled analysis of Treatment-related adverse events presents most frequently reported (in 1% or more patients).

Drug-related adverse reactions with >5% incidence reported by ceftobiprole treated patients were nausea, infusion site reactions, headache, diarrhoea, vomiting and dysgeusia, see the following table.

Table 12: Adverse Drug Reaction by Preferred Terms
(Pooled Phase 3 Studies BAP00154 and BAP00414: Safety Analysis Set)

	Ceftobiprole (N=932) n (%)	Comparator (N=661) n (%)
Total No. Patients with ADR	345 (37.0)	206 (31.2)
Nausea	113 (12.1)	49 (7.4)
Infusion site reactions	70 (7.5)	42 (6.4)
Headache	68 (7.3)	39 (5.9)
Diarrhoea	67 (7.2)	35 (5.3)
Vomiting	61 (6.5)	27 (4.1)
Dysgeusia	52 (5.6)	7 (1.1)
Rash[a]	41 (4.4)	21 (3.2)
Dizziness	32 (3.4)	12 (1.8)

Pruritus[b]	30 (3.2)	50 (7.6)
Hepatic enzymes increased[c]	28 (3.0)	20 (3.0)
Dyspepsia	22 (2.4)	6 (0.9)
Yeast infections[d]	16 (1.7)	12 (1.8)
Hypersensitivity reactions[e]	11 (1.2)	18 (2.7)
Hyponatraemia	11 (1.2)	0
Clostridium difficile colitis[f]	2 (0.2)	2 (0.3)
Anaphylactic reaction	1 (0.1)	1 (0.2)

ADR=adverse drug reaction.
[a] Rash includes rash, maculo-papular, generalised, papular, macular.
[b] Pruritus includes pruritus, pruritus generalised.
[c] Hepatic enzymes increased includes alanine aminotransferase increased, alanine aminotransferase abnormal, aspartate aminotransferase increased, aspartate aminotransferase abnormal, liver function test abnormal, transaminase increased.
[d] Yeast infection includes fungal infection, vulvovaginal mycotic infections, vaginal mycosis, oral candidiasis, skin candida, fungal rash, oral fungal infection, vulvovaginitis.
[e] Hypersensitivity reactions include urticaria, drug eruption, rash pruritic, hypersensitivity, drug hypersensitivity.
[f] *Clostridium difficile* colitis includes *Clostridium difficile* colitis, clostridial infection, colitis.

In the individual study reports no overview tables of "drug-related" adverse reactions were encountered or consistently reported across studies. This holds also drug-related SAEs and AEs leading to discontinuations, clinical lab findings. Therefore these overviews per individual study based on causal relationship were presented to better assess the impact of the difference in dosing of ceftobiprole in the sought indication. Phlebitis and thrombophlebitis occurred in the testing of both regimens of ceftobiprole (500 mg BID or TID) and in similar frequencies as in the comparator arms and as such the applicant agreed to enlist these AEs in section 4.8 of the proposed SPC. Furthermore, *anaphylactic shock* was to be added to the proposed SPC based on the observation of this ADR in a recently completed clinical study with ceftobiprole for another indication (pneumonia). As requested, the Applicant agreed to monitor infusion site reactions, including phlebitis and thrombophlebitis, as part of the routine post-marketing surveillance, and updated the sections of the intended RMP accordingly

Phase I-II studies

In the 10 Phase I studies, nausea, vomiting, headache, and abnormal taste sensation (dysgeusia) were the most common adverse events reported in 234 healthy subjects with normal renal function exposed to 500mg to 1000mg of ceftobiprole. CSI studies 1001 and 1003 indicated a dose response relation with regard to nausea, vomiting, headache, and dysgeusia. No SAEs were reported.

These AEs were also observed in the small open single Phase II study BAP00034 in which 40 patients (that included 22 i.v. drug abusers) with cSSSIs suspected or documented to be due to gram-positive bacteria were treated with ceftobiprole 750 mg BID , for 7 to 14 days. However, insomnia (23%), eosinophilia (18%), elevated blood triglycerides (18%), hypomagnesemia (15%), and anxiety (13%) was also frequently observed in the latter study which can be at least partly be expected based on the drug abuse history of the patients.

Five SAEs were reported, with hypersensitivity (leading to discontinuation) being suspected of relation to the drug. No deaths were reported in these studies.

Special safety topics

Non-clinical studies identified renal toxicity, seizures and infusion site associated events with potential relevance for human use. These and other selected AEs are discussed below.

Renal toxicity
The incidence of renal-related AEs was lower in the ceftobiprole treated group (2.3%) than in the group of vancomycin based comparator regimens (3.8%): e.g. elevation of serum creatinine – defined as increase in serum creatinine >0.5 mg/dl from baseline and a concentration >1.2 mg/dl- (1% and 1.4% in respective groups), acute renal failure (0.1% and 0.5% in respective groups), renal impairment (0.1% and 0.9% in respective groups). It seems thus that the non-clinical renal toxicity signal has no significant bearing on clinical safety of ceftobiprole, however, due to the rather limited clinical experience with a potentially acceptable clinical dosage of ceftobiprole, it cannot be excluded at this stage that the observed deposition of drug-like material and crystal nephropathy in animal models has no bearing on the safety of ceftobiprole in seriously ill frail patients.

In the light of the outstanding non-clinical issue and rather limited safety experience, the applicant proposed an appropriate precaution how to deal with patients who are at higher risk of crystal nephropathy (e.g. patients with metabolic disturbances such as systemic metabolic acidosis or alkalosis or renal tubular acidosis that promote changes in urinary pH favouring crystal precipitation). Furthermore, this point was proposed to be implemented in the intended RMP.

Seizures
Seizures were reported as SAE in 3 cases in the ceftobiprole group and none of the patients in the comparator group. All 3 of these patients were in Study BAP00414 and had an underlying medical condition predisposing them to seizure activity:

- Case 140971 (history includes epilepsy, old post-traumatic haemorrhage), AE not drug related.
- Case 141076 (history includes cerebrovascular accident and intracerebral bleed), on Day 3 of ceftobiprole treatment he developed tonic-clonic grand mal seizures, which resolved in 2 days with antiepileptic medications. The investigator considered the grand mal seizure life-threatening and remotely related to the ceftobiprole. The patient received ceftobiprole treatment for a total of 10 days.
- Case 140381 had a history of diabetes mellitus; on Day 4 of ceftobiprole treatment he developed generalized tonic-clonic seizures and severe hyponatremia (112 mmol/L). The hyponatremia resolved in 8 days, whereas, the convulsions resolved in 31 days. The investigator considered the grand mal seizure life-threatening and possibly related to ceftobiprole. The patient discontinued treatment due to the adverse events on Day 4. Seizure is a recognized complication of severe hyponatremia.

Two additional cases treated with ceftobiprole with a history of epilepsy had AEs of tonic-clonic movements (case 140808) or epilepsy (case 2336; 10 days after discontinuation of ceftobiprole) that were reported as not serious and were considered to be unrelated to ceftobiprole by the investigator.

Applicant reported that since submission of the original MAA for cSSTI, the safety data from 2 recently completed Phase 3 trials for another indication were reviewed.

Infusion-associated adverse events
The incidence of infusion site-related AEs was (7.5%) in patients who received ceftobiprole compared with (6.4%) in patients who received the comparators. Phlebitis was the most commonly reported term for 2.6% of the patients who received ceftobiprole (compared with 1.7% for patients who received the comparators); thrombophlebitis occurred at a rate of 0.6% and 0.5% respectively.

Patients in Europe had a lower incidence of infusion site-related AEs than patients in the U.S. and in other regions in both treatment groups (2.6% compared with 11.0% and 15.2% in the ceftobiprole group, and 3.7% compared with 8.7% and 9.3% in the comparator group, respectively).

Overall, infusion site reaction rates in both treatment groups were higher in Study BAP00414 (8.8%) compared with Study BAP00154 (5.4%). This was most likely related to the larger number of infusions (5 infusions per day versus 2 infusions per day) in the study design of BAP00414. Within studies, similar rates of infusion site reactions were observed between ceftobiprole and the comparator. Phlebitis was reported for 4% of the patients who received ceftobiprole in BAP00414. (compared with 3% for patients who received the comparators); thrombophlebitis occurred at a rate of 1% (<1% in the comparator group). In study BAP00154 phlebitis and thrombophlebitis rates in the ceftobiprole group were 1% for each respectively (the same in the comparator group).

Other special adverse events

- Nausea: The majority of cases of nausea were mild, self-limiting, and not treatment limiting (only 5/113 nausea cases led to discontinuation, similar to the rate in the comparator group). It occurred in a higher percentage of patients who received ceftobiprole every 12 hours over a 60-minute infusion compared with patients who received ceftobiprole every 8 hours over a 120-minute infusion. Ceftobiprole-treated patients with nausea had a mean duration of 4.4 days of nausea compared with a mean duration of 5.2 days for comparator-treated patients with nausea.

- Vomiting: This followed a similar pattern as for nausea. Of the 61 patients treated with ceftobiprole who reported vomiting, 62.3% were mild and 27.9% were moderate in severity. Ceftobiprole-treated patients with vomiting had a mean duration of 2.8 days of nausea compared with a mean duration of 4.2 days for comparator-treated patients with vomiting.

- Dysgeusia: The majority (84.6%) of cases of dysgeusia were mild (15.4% were moderate and none were severe). The incidence of dysgeusia was lower in ceftobiprole-treated subjects who received the drug over longer infusion duration (4.1% in Study BAP000414 compared with 7.7% in Study BAP00154.
  The incidence of nausea, vomiting and dysgeusia varied by age, race, and region. Phase I studies CSI studies 1001 and 1003 indicated also that there is a dose response relation with regard to these ADRs.

- Hypersensitivity (pruritus, pruritus generalized, urticaria, drug eruption, rash pruritic, angioneurotic oedema, hypersensitivity, anaphylactic reaction, and drug hypersensitivity): The incidence of hypersensitivity was lower in the ceftobiprole treated group (4.4%; and 0.5% discontinued) than in the group of vancomycin based comparator regimens(10.6%; and 2.3% discontinued) . Similar pattern was noted for pruritus and generalised pruritus.
  1 case of probably drug-related anaphylaxis occurred in each of these groups.
  U.S. patients had a higher incidence of hypersensitivity than non-U.S. patients in both treatment groups (8.4% compared with 2.5% for the ceftobiprole group and 14.4% compared with 8.6% for the comparator group, respectively.

- Hyponatraemia:
  There were no AEs of hyponatraemia in either treatment group in study BAP00154 using the 500 mg BID dosing regimen of ceftobiprole (a total of 500 mL of free water was infused as part of patient's study drug regimen) or the vancomycin comparator.

Because of suspected unexpected serious adverse reaction (SUSAR) reports of hyponatraemia from both the BAP00414 and trial BAP00307, a newsletter was distributed to all sites on 2 July 2006, stating: "In subjects at risk for hyponatremia, placebo solutions may contain sodium. In addition, vancomycin may be mixed with solutions containing sodium chloride as specified in the protocol". Hyponatraemia as AE was reported for 11(1.2%) ceftobiprole-treated group and none of the comparator-treated group in Study BAP00414. 3/11 cases were symptomatic: they were elderly patients with serious underlying condition.

After the occurrence of the SUSAR reports, hyponatraemia was reported as an adverse event in 1 (<1%) of 153 patients randomized to ceftobiprole since that time compared with 10 (3%) of 394 patients prior to this intervention.

Hepatic-related AEs
The number of patients with the *adverse drug reaction term* of increased hepatic enzymes (including alanine aminotransferase increased, alanine aminotransferase abnormal, aspartate aminotransferase increased, aspartate aminotransferase abnormal, liver function test abnormal, transaminase increased) was 28 (3.0%; none were discontinued) for ceftobiprole-treated patients and 20 (3.0% ; 1 case was discontinued) for comparator-treated patients.

A single case in the ceftobiprole group had a serious adverse event of liver function test abnormal: case had serious underlying condition and increased liver transaminases prior to enrolment. High levels of alkaline phosphatase (992 U/L), bilirubin (95 µmol/L), GGT (914 U/L), and low levels of albumin (13 g/L) were reported at the TOC visit (Day 21). Laboratory tests further deteriorated following surgical debridement, 3 days after ceftobiprole discontinuation. The investigator considered this adverse event severe and possibly related to ceftobiprole.
Phase I data did not suggest ceftobiprole induced hepatic related AEs. In conclusion, hepatic safety deserves normal PMS monitoring.

- Serious adverse event/deaths/other significant events

Serious adverse events (SAE) summarised in the pooled Phase III data occurred at similar rates for the ceftobiprole and comparator treatment groups. Hyponatraemia (0.3%, 3 patients) and hypersensitivity (0.2%, 2 patients) were the only treatment-related SAEs that occurred in 2 or more of the 932 patients who received ceftobiprole. In the comparator group hypersensitivity, pruritus, and rash (0.3%, 2 patients each) were the only treatment-related SAEs that occurred in 2 or more of the 661 patients.

In the pooled Phase III data, 3 deaths were reported in the ceftobiprole groups versus 4 in the comparator group. None of these deaths were considered by the investigator to be related to study medication. One patient in each treatment group died while on treatment; the remaining patients died 2 to 25 days after their last dose of study medication.

- Laboratory findings

There were no clinically significant changes post-baseline in clinical laboratory values, vital signs, or physical examinations. The incidence of markedly abnormal test results for individual haematology and chemistry values within a given treatment group was low and ceftobiprole data compared to the comparator gave no reason for concern, with the exception of above mentioned hyponatraemia in study BAP00414.

- Safety in special populations

In Phase 1 Study BAP000018 , 3 *renally-impaired* subjects reported 5 adverse events: syncope (severe), nausea (mild), and dizziness (moderate) in 1 subject with severe renal impairment (CL_{CR} <30 mL/minute), fatigue (moderate) in 1 subject with mild impairment (CL_{CR} 51 to 80 mL/minute), and arthritis (moderate) in 1 subject with moderate impairment (CL_{CR} 30 to 50 mL/minute). The arthritis was considered to be unrelated to ceftobiprole, and the other events were considered to be remotely related to ceftobiprole.

A higher percentage of *patients with hepatic impairment* who received ceftobiprole had chest pain, dizziness, dyspnea, and headache (10.0%, 6.7%, 6.7%, and 20.0%, respectively) compared with patients with normal hepatic function (1.0%, 3.4%, 1.3%, and 7.0%, respectively) in the pooled Phase 3 studies. Hepatobiliary adverse reactions are reflected in section 4.8 of the SPC.

Pregnant or *lactating* patients were excluded from the studies; therefore, no data are available in pregnant or lactating women.

No studies have been performed to determine a specific antidote to ceftobiprole. In cases of *overdose,* general symptomatic treatment should be taken as appropriate.

Drug abuse information for ceftobiprole is not available.

Information on the effects of ceftobiprole on the *ability to drive or operate machinery* or impairment of mental ability is not available.

- Safety related to drug-drug interactions and other interactions

Based on the pharmacokinetic properties of ceftobiprole, the potential for ceftobiprole to interact with other agents and the potential for other agents to interact with ceftobiprole is considered low. As such, clinical drug-drug interaction studies have not been performed.

- Discontinuation due to adverse events

The incidence of patients who discontinued because of drug related adverse reactions was low (2.6% and 3.2% in ceftobiprole- and comparator-treated patients respectively, for the pooled pivotal Phase III data). Drug related adverse reactions that resulted in discontinuation of more than 1 ceftobiprole-treated patient were: rash (0.6%), nausea (0.5%), vomiting (0.4%), hypersensitivity reactions (0.3%), and hyponatraemia (0.3%).

- Post marketing experience

No post-marketing experience had been available at time of Marketing Authorisation Application in EU.

- Initial discussion on clinical safety (which supported the adoption of the opinion on 20 November 2008)

The safety database for the sought indication is rather limited especially if one considers the data for the two dosing recommendations separately. Only 543 patients used the potentially acceptable 500 mg TID regimen (study BAP00414). In the main clinical trials, the most common drug-related treatment

emergent adverse reactions were nausea, infusion site reactions, vomiting, diarrhoea, and dysgeusia. The latter three seem to be slightly affected by the dose level used, however, generally these were mild to moderate in nature with the present dose (500 mg TID) recommended for marketing.

Some concerns remain:

- Based on the rather limited experience with BID and TID dosing regimens separately, infusion site-related AEs including phlebitis and thrombophlebitis was an issue. Applicant agreed to monitor and discuss these AEs in routine PMS. The SPC is improved to reflect the occurrence of these adverse drug reactions.

- In the response to raised concern on whether very high ceftobiprole concentrations are associated with any increased risk of iatrogenic convulsive disorders in studied patients or any seriously ill frail patients or other patients with convulsive disorders or receiving epileptogenic concomitant therapy, applicant agreed on adding seizures to section 4.8 of the SPC, based on safety data from 2 recently completed Phase 3 trials for another indication. In addition, information regarding treating patients with pre-existing CNS/seizure disorders has been added to Section 4.4 of SPC.

- Hyponatraemia, is labelled in SPC, section 4.8. Although not studied in the clinical trials, ceftobiprole can be infused in normal saline or Lactated Ringer's injection solution, which would be unlikely to contribute to the development of hyponatraemia since extra free water would not be administered. Section 6.3 of the SPC has been modified to clarify the stability of the diluted infusion solution for sodium chloride, dextrose, and Lactated Ringer's infection solution Hyponatraemia is discussed as an important identified risk in the RMP.

- In the light of the outstanding non-clinical issue and rather limited safety experience on renal toxicity, the applicant proposed an appropriate precaution how to deal with patients who are at higher risk of crystal nephropathy (e.g. patients with metabolic disturbances such as systemic metabolic acidosis or alkalosis or renal tubular acidosis that promote changes in urinary pH favouring crystal precipitation). Furthermore, this point is implemented in the RMP.

- C.*difficile* colitis is listed as a drug-related adverse reaction. Since cephalosporines are known to cause *C.difficile* colitis and in view of the rather limited experience with ceftobiprole, the occurrence and incidence of this type of colitis is of concern. *C. difficile* colitis will be monitored as part of the routine post-marketing surveillance, as is reflected in the RMP

- In the RMP the potential for developing antimicrobial resistance should be considered as a specific issue that needs to be followed and evaluated. The protocols of 2 surveillance studies are due, in order to monitor the development of resistance as a separate FUM:

    - The BSAC Bacteraemia Resistance Surveillance Programme
    - JMI European Surveillance programme.

- **Revised discussion on clinical safety**

The GCP non-compliance observed in the conduct of the two pivotal clinical trials do not allow the conclusion that the currently available safety database for ceftobiprole is comprehensive and truly reflecting all potentially adverse events due to treatment with the compound. The potential of missing important safety information on the product renders the initially concluded positive safety profile invalid

and does no longer allow the CHMP to assess all potential risks associated with the use of the medicinal product.

3.5 Revised overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of ceftobiprole was adequately established. In general, satisfactory chemical and pharmaceutical documentation had been submitted for marketing authorisation. There were no major deviations from EU and ICH requirements.

Non-clinical pharmacology and toxicology

Non-clinical studies identified renal toxicity, seizures and infusion site associated events. In a pre- and postnatal development study in rats, litter size and survival up to four days postpartum were decreased at maternally toxic doses.

Efficacy

Although the provided sensitivity analyses seem to be in line with the conclusion of non-inferiority, this needs to be interpreted with caution. Indeed, the decreased number of patients involved in this analysis compromise the robustness of the conclusion, especially in the relevant subgroups (by pathogen or cSSTI specific diagnoses) with limited data within the total clinically evaluable patient populations in both treatment arms of these pivotal studies. Nevertheless, for the leading diagnoses such as wound, abscesses and diabetic foot the results appear in agreement with the original conclusion although the confidence interval becomes larger in study BAP00414; the same applies for the leading pathogen *S. aureus* (MRSA and MSSA). For *E. coli* the numbers are too limited to draw clear conclusions on efficacy, but not unfavourable for ceftobiprole as well as for the comparator regimen.

The overall poor data control of these trials, as evidenced by the various GCP findings at multiple inspected and audited sites, indicates a lack of rigour in the conduct of the pivotal trials. Such poor control favours a non-inferiority result, as potential differences in results may become non detectable. It should be appreciated that in trials intended to show a difference between treatments there is a strong imperative to use a good trial design and minimise trial errors because many trial imperfections increase the likelihood of failing to show a difference between treatments when one exists.

As each round of inspection or audit has led to the exclusion of additional sites, the overall conduct of the trial is questionable and it can no longer be concluded that the conduct of the trial did not undermine its ability to distinguish effective treatments from less effective treatments.

Therefore, the CHMP did not consider the additionally performed sensitivity analyses sufficient to support the efficacy demonstration of this marketing authorisation application.

Safety

The GCP non-compliance observed in the conduct of the two pivotal clinical trials does not allow the conclusion that the currently available safety database for ceftobiprole is comprehensive and truly reflects

all potentially adverse events due to treatment with the compound. The potential of missing important safety information on the product renders the initially concluded positive safety profile invalid and does no longer allow the CHMP to assess all potential risks associated with the use of the medicinal product.

Risk-benefit assessment

Based on the findings of the EU GCP inspections requested, the CHMP has concluded that the two pivotal trials BAP00154 and BAP00414 were not conducted in compliance with GCP. These findings are also corroborated by the findings of GCP inspections concluded previously by the US Food and Drug Administration. The GCP audits conducted on behalf of the sponsor showed numerous findings but the auditors still accepted data that was not considered acceptable by the EU inspectors. Each round of inspection or audit has led to the exclusion of additional sites. The nature of the findings is such that the conduct of the trial and its results cannot be relied on to support the claimed non-inferiority of ceftobiprole. Also, the uncertainties around the quality of data collection do not sufficiently re-assure the CHMP that the safety profile of ceftobiprole is sufficiently characterised.

Therefore, the CHMP is unable to establish a positive risk/benefit balance for ceftobiprole.

Recommendation

The pivotal clinical studies BAP00154 and BAP00414 were not conducted in accordance with GCP as required by Annex I of Directive 2001/83/EC as amended and the nature of the findings is such that the conduct of the studies and their results cannot be relied on to recommend the granting of a marketing authorisation.

The therapeutic efficacy and clinical safety have been insufficiently substantiated by the applicant *as per* article 12(2) of Regulation (EC) No 726/2004 and article 26(1)(b) of Directive 2001/83/EC as amended.

The risk/benefit balance is not considered to be favourable *as per* article 26(1)(a) of Directive 2001/83/EC as amended.

The CHMP has recommended by majority the refusal of the granting of the Marketing Authorisation for Zeftera in accordance with article 9(1)(a) of Regulation (EC) No 726/2004.

3.6 Re-examination of the CHMP opinion of 18 February 2010

Following the CHMP Opinion concluding that the benefit risk of Zeftera, indicated in adults for the treatment of complicated skin and soft tissue infections, was not considered favourable, the Applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant / CHMP position

The Applicant has acknowledged concerns raised related to the conduct of two phase 3 trials submitted in the Marketing Authorisation Application and understands that this concern raises uncertainty about the body of evidence that is aimed at establishing the efficacy and safety of ceftobiprole. It is with this understanding that the Applicant requested that the application for ceftobiprole be re examined with regard to two major factors:

1) Ceftobiprole is a unique antibacterial agent that has the potential to offer considerable advantages over currently available therapies.

2) The Applicant assessed in more detail the impact of observed GCP deviations on trial conduct and if these deviations are of such nature that the ability of the study to distinguish between an effective and ineffective treatment (the "assay sensitivity") is lost. Focus was put on:

   a. microbiological response, which may be considered a more objective endpoint,

   b. detailed analysis of factors which are indicated in CHMP/ICH/364/96 (ICH E-10), as important factors for appropriate trial conduct in non-inferiority studies to be "*fully evaluated after the active control non- inferiority trial is completed.*"

   c. In addition to this analysis the Applicant considered the results of two conservative analyses which in its view clearly demonstrates the robustness of the overall trial results

1) Ceftobiprole is a unique antibacterial agent that has the potential to offer considerable advantages over currently available therapies.

These advantages were identified during the course of the molecule's development and include its unique *in vitro* spectrum of antibacterial activity and its demonstrated effectiveness in treating infections in a variety of animal models. The unique microbiological and preclinical profiles compare very favourably to currently available agents and support the activity demonstrated in the cSSTI clinical trials. In considering its development as an addition to the antibacterial armamentarium, ceftobiprole's advantages observed in the clinical trials suggest trends in improved clinical and microbiological outcomes, especially in severely ill patients. These factors identify the potential for this new agent to offer a clear benefit to patients.

Data from both pre-clinical and clinical sources support the potential advantages that ceftobiprole has over other agents. Ceftobiprole's uniqueness is evident in three major ways:

- its broad-spectrum of antibacterial activity that includes activity against MRSA, which has emerged as a leading cause of serious skin infections;
- its bactericidal mode of action, in contrast to the bacteriostatic mode of action of most other agents and
- a safety profile consistent with other cephalosporins; an antibiotic drug class that is widely appreciated to be the safest available.

Ceftobiprole's gram-positive activity is comparable to that of conventional penicillins and cephalosporins but in addition also includes problematic MDR pathogens such as MRSA, PRSP, VISA and VRSA. Ceftobiprole's activity against gram-negative organisms is similar to that of third- and fourth- generation cephalosporins such as ceftazidime and cefepime. No other approved agent for cSSTI has the spectrum of antibacterial activity that includes activity against all the leading causes of these infections.

Using an agent that is consistently bactericidal is especially important in treating serious staphylococcal disease. Among the current clinically available agents for cSSTI with activity against MRSA, gycopeptides, linezolide, daptomycin or tigecycline, none of these exert a corresponding combination of broad-spectrum activity and bactericidal action.

In the course of describing the basis for these potential advantages, the Applicant has now further identified specific groups of patients with serious skin infections who may especially benefit from the immediate availability of this new drug.

Patients who may especially benefit include:

- Patients with the most serious skin infections in whom empiric monotherapy would be preferred over combination therapies given the inherent advantages of monotherapy over combination therapy (e.g., combination therapy may have higher potential for drug-drug interactions and higher incidence of adverse events associated with multiple infusions);
- Immuno-suppressed and neutropenic patients in whom bactericidal therapy would be preferred. This includes patients with cSSTI who have impaired host defence, specifically as it relates to the role of leukocyte function and opsonophagocytosis in controlling and resolving staphylococcal disease;
- Patients with wound infections that are at considerable risk for polymicrobial, gram-negative bacterial and staphylococcal infections with isolates having reduced susceptibility to glycopeptides;
- Patients whose primary infection is complicated by MRSA bacteremic disease, especially those at risk for prolonged bacteremia and metastatic infection due to staphylococci.

➢ <u>Patients with severe skin infections</u>

Several subgroup analyses performed as part of Study BAP00414 (a study that enrolled the entire spectrum of patients with cSSTI disease) showed trends suggesting that ceftobiprole therapy results in better clinical outcomes than those observed in the comparator arm of ceftazidime plus vancomycin in patients with the most severe disease. The most compelling trend in this regard occurred in patients with severe (grade 4) diabetic foot infection (DFI). In this subgroup the clinical cure rate was 16.7% higher in ceftobiprole-treated patients (70.6% [12/17] versus 53.8% [7/13]). Although this experience was small, it was observed in the setting of sequentially higher cure rates in ceftobiprole-treated patients with DFI as the severity of their infection increased from grade 2 to grade 4. Taken together, this experience did suggest that the 4.4% higher overall cure rate in ceftobiprole-treated patients with DFI (86.2% [125/145] versus 81.8% [63/77]) was contributed to by a better outcome in the most severely infected patients.

No validated measure of severity, other than those applied in diabetic patients with foot infection, were available for use in the analyses of subgroups in the patients enrolled in the trial. However, 3 subgroups proposed to represent the most severely diseased patients were analyzed. These included patients with 1) Panton Valentine Leukocidin (PVL)-positive MRSA infections, 2) marked elevation of C-reactive protein (CRP) (>50mg/dL) and 3) involvement of deep tissues.

Table 13: Clinical Cure Rates at the TOC Visit in Subjects With *S. aureus* Infection at Baseline (Study BAP00414: Microbiologically Evaluable and Microbiological Intent-to-Treat Analysis

	Ceftobiprole			Vancomycin/ Ceftazidime			Ceftobiprole Minus Vancomycin/ Ceftazidime	
	N	n	%	N	n	%	Difference (%)	95% CI[a]
Microbiologically Evaluable								
All *S. aureus*	247	228	92.3	128	117	91.4	0.9	(-5.0; 6.8)
All MRSA	87	78	89.7	36	31	86.1	3.5	(-9.4; 16.5)
All MSSA	160	150	93.8	90	84	93.3	0.4	(-6.0; 6.8)
PVL-positive *S. aureus*	65	62	95.4	38	33	86.8	8.5	(-3.4; 20.4)
PVL-positive MRSA	38	35	92.1	19	16	84.2	7.9	(-10.6; 26.4)
Microbiological Intent-to-Treat								
All *S. aureus*	269	230	85.5	143	120	83.9	1.6	(-5.8; 8.9)
All MRSA	93	78	83.9	40	33	82.5	1.4	(-12.6; 15.3)
All MSSA	176	152	86.4	101	85	84.2	2.2	(-6.5; 10.9)
PVL-positive *S. aureus*	69	62	89.9	43	33	76.7	13.1	(-1.4; 27.6)
PVL-positive MRSA	42	35	83.3	21	16	76.2	7.1	(-14.3; 28.6)

Note: n is the number of subjects with a clinical outcome of Cure.

Table 14: The Clinical Cure Rate of Subjects With *S. aureus* Infection at Baseline Who Had Elevated CRP or Deep Infections (Study BAP00414: Clinically Evaluable Analysis Set)

	Ceftobiprole		Vancomycin/Ceftazidime	
	Total n	Category, n (%) Cure	Total n	Category, n (%) Cure
CRP > 50 mg/L				
All *S. aureus*	87	79 (91)	55	47 (85)
MRSA	27	23 (85)	14	11 (79)
Deep Infections				
All *S. aureus*	88	79 (90)	50	44 (88)
MRSA	28	24 (86)	16	13 (81)

Taken together, observations in patients identified having the most severe cSSTI infections consistently show trends favouring ceftobiprole. These observations align with expectations of this drug as a bactericidal, β-lactam with broad-spectrum, as well as potent anti-staphylococcal, activity. Recognition that these effects were observed with monotherapy of ceftobiprole compared to combination therapy of ceftazidime plus vancomycin should also be considered in the severely infected patient.

- Immunocompromised patients

The observation that neutropenic patients do substantially better after receiving β-lactams compared to other classes of agents has served as a cornerstone for much of the guidance that has been given in managing immunocompromised patients who develop infections. Many of the same tenets that serve as the basis for recommendations to use β-lactams in cancer patients with infections can be applied to patients with other immunocompromising conditions. The ceftobiprole skin infection trials did not include

patients with severe immunocompromising conditions and included too few patients with underlying immunocompromising conditions to establish meaningful conclusions even about trends in clinical cure. However, the body of work that includes *in vitro* studies demonstrating ceftobiprole's consistent bactericidal activity against a broad spectrum of pathogens and the comparison of this activity to other β-lactams that have been widely used in treating seriously ill immunocompromised patients, supports the conclusion that ceftobiprole could prove to be a unique life-saving therapy in many of these patients. Staphylococci have consistently been identified as a leading or lead cause of serious infection in immunocompromised patients. Ceftobiprole's bactericidal activity against staphylococci, including drug resistant isolates such as glycopeptide-resistant and –intermediate susceptible isolates, make it an especially attractive choice in treating patients who are likely to be at highest risk to these infections

- Wound infections

In a recently conducted review that assessed the antibiotic effect on cSSTI, it was concluded that the effect of antibiotic therapy on outcome was the greatest for infections associated with wounds compared to abscess and cellulitis/erysipelas. The importance of staphylococci as a cause of wound-related infections, including an increasing frequency of drug-resistant strains, the frequency of polymicrobial infection in this clinical setting is highly dependent on using appropriate antibiotics as initial therapy, which would make ceftobiprole a much needed new agent in treating patients suffering from wound infections. In addition to ceftobiprole's anti-staphylococcal activity, its broad spectrum activity includes most of the clinically important gram-negative bacteria that can be found in polymicrobial wound infections.

Table 15: Clinical Cure Rates at the TOC Visit for Subjects With Wounds in the Pooled Studies
(Studies BAP00154 and BAP00414: Clinically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff(%)[a]	95% CI[b]
Clinically evaluable								
All subjects	767	702	91.5	521	479	91.9	-0.4	(-3.5; 2.6)
By infection type								
Wound	190	179	94.2	138	126	91.3	2.9	(-2.8; 8.7)

- Patients with bacteraemic disease

The preference for using β-lactams in treating patients with staphylococcal bacteremia has been argued based on several clinical observations. These observations have demonstrated more rapid and durable clearance of bacteria from the bloodstream of patients treated with β-lactams compared to vancomycin. These clinical observations are entirely consistent with those made under more controlled conditions with laboratory models of bacteremic infection. As expected there were few patients with bacteremia in the pivotal studies. Although not significant, cure rates in these patients were numerically higher in the ceftoboprole group, most marked in study 414, including patients with mixed infections.

Table 16: Clinical Cure Rates at the TOC Visit by Bacteremia at Baseline in the Pooled Studies
(Studies BAP00154 and BAP00414: Microbiologically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---					
	N	n	%	N	n	%	Diff(%)[a]	95% CI[b]	p-value[c]
Microbiologically evaluable									
All subjects	617	568	92.1	416	384	92.3	-0.2	(-3.6; 3.1)	
By bacteremia									
Yes	26	21	80.8	15	12	80.0	0.8	(-24.5; 26.1)	0.925
No	591	547	92.6	401	372	92.8	-0.2	(-3.5; 3.1)	

Table 17: Clinical Cure Rates at the TOC Visit by Bacteremia at Baseline in Study BAP00414
(Study BAP00414: Microbiologically Evaluable Analysis Set)

	Ceftobiprole			Vancomycin/ Ceftazidime			Ceftobiprole Minus Vancomycin/Ceftazidime		
	N	n	%	N	n	%	Difference (%)	95% CI[a]	p-value[b]
Microbiologically Evaluable									
All subjects	391	355	90.8	199	180	90.5	0.3	(-4.6; 5.3)	
By bacteremia									
Yes	13	11	84.6	8	5	62.5	22.1	(-16.7; 61.0)	
No	378	344	91.0	191	175	91.6	-0.6	(-5.5; 4.3)	0.240

- Patient populations that may benefit for safety reasons

Cephalosporins have been used in clinical practice for a half-century and they are widely appreciated to be among the safest antibiotics used. The safety profile of ceftobiprole that can be constructed to date suggests that it will share much of the tolerability and safety characteristics of other agents in its class.

Due to its availability only as a parenteral agent and its preferred dosing (every 8 hours), it is expected that ceftobiprole will be used in patients with serious infections. Many of these patients will have underlying co-morbidities and conditions that would make ceftobiprole preferred over currently available agents. Based on medical review of the contraindications and warning and precautions sections of the SmPC for each product concerning common or specific adverse events reported for other drugs with a cSSTI indication, the following list has been constructed to identify specific conditions that could make ceftobiprole preferred over these available agents:

- Thrombocytopenia (linezolid and teicoplanin)
- Depression requiring monoamine oxidase inhibitor therapy (linezolid)
- Muscle disorders or injury that would make CPK monitoring difficult (daptomycin)
- Pre-existing or drug-induced ototoxicity (vancomycin and teicoplanin)
- History of red man/red-neck syndrome (vancomycin)
- Difficult venous access (quinupristin-dalfopristin)
- Pancreatitis (tigecycline)
- Nausea and vomiting (tigecycline)

In conclusion, according to the Applicant, Ceftobiprole possesses important attributes that make it a significant addition to the antibiotic therapy options compared with currently marketed products licensed for treatment of cSSTI. The reasons for concluding that ceftobiprole offers this improvement are as follows:

- Ceftobiprole would be the first agent licensed for use in cSSTI that is reliably bactericidal against a broad spectrum of gram-positive and gram negative pathogens, including MRSA and Enterobacteriaceae. This strongly complements the agents available in treating specific patient populations where bactericidal agents are desired;
- Ceftobiprole would be the only β-lactam agent shown to be effective in treating patients with cSSTI due to MRSA;
- Ceftobiprole belongs to a class of agents that have been safely used to treat patients with cSSTI for numerous decades, and is safe and well tolerated. Ceftobiprole is likely to offer a safety advantage over currently available antibacterial agents that are approved for use in treating patients with cSSTI, especially in patients with MRSA infections given the inherent advantages of monotherapy over combination therapy (e.g., combination therapy may have higher potential for drug-drug interactions and higher incidence of adverse events associated with multiple infusions).

CHMP comments:

Ceftobiprole would be a potentially highly attractive new treatment option in many ways, especially considering the bactericidal mode of action and the *in vivo* and *in vitro* activity against the MRSA and a range of other MDR pathogens. There is also Gram-negative coverage, although the reliable clinical trial data are available mainly for *E.coli*. The main value of the product may prove to be its safety profile. The current safety database is, however, limited and eroded by the GCP concerns. Nevertheless, the overall safety profile of cephalosporins is well known to be favourable.

The Applicant argues that due to the broad antimicrobial spectrum, the bactericidal activity and safety profile of ceftobiprole, this agent would be particularly valuable for the treatment of seriously ill patients with severe cSSTIs. Although there was no validated measure of severity except for diabetic patients with foot infection, four subgroups were identified, proposed to represent the most severely diseased patients. These included patients with 1) Panton Valentine Leukocidin (PVL)-positive MRSA infections, 2) marked elevation of C-reactive protein (CRP) (>50mg/dL), 3) involvement of deep tissues and 4) patients with bacteraemia. In all these subgroups, the outcome of ceftobiprole treated patients were consistently numerically superior (not significant) to patients treated in the comparator group. The discussion of ceftobiprole's usefulness in immunocompromised patients must be considered as theoretical and mainly based on speculations supported by previous experience with other medicines of the cephalosporin class, as ceftobiprole skin infection trials did not include patients with severe immunosuppression. However, it is well acknowledged by clinicians that bactericidal agents are strongly preferred when treating this patient population.

Although reassuring and in line with clinical practice to treat serious infections with beta-lactam agents if caused by susceptible pathogens, numbers in each subgroup are low and these analyses are not considered robust enough to specify any specific subgroup in section 4.1 of the SmPC, that would particularly benefit from ceftobiprole treatment.

2) Impact of observed GCP deviations on trial conduct and if these deviations are of such nature that the ability of the study to distinguish between an effective and ineffective treatment (the "assay sensitivity") is lost.

- *Microbiological outcomes*

According to the draft CHMP guidance for anti-infectives (February 2010) were it states: "*the microbiological response is objective and is the preferred primary efficacy variable whenever this is appropriate to the indication"*.

Therefore the applicant wishes to highlight microbiological outcome data from both studies that provide further evidence of the robustness of the observed efficacy rates for ceftobiprole. For the pooled studies, the microbiological eradication rates for the ceftobiprole and comparator groups in the microbiologically evaluable analysis set were 90.3% and 91.3%, respectively, with a 2-sided 95% confidence interval for the difference of -4.6% to 2.5%. For the microbiologically evaluable analysis set in the pooled studies, 96% of subjects in both treatment groups who had a microbiological outcome of Eradication at the TOC visit also had a clinical outcome of Cure. Analyses per pathogen also indicate non-inferiority between the treatment groups. The applicant concludes that the microbiological outcome data, because of their objectiveness, provide further reassurance concerning the overall efficacy rates observed for ceftobiprole in both trials. Furthermore the correlation demonstrated between clinical and microbiological outcome provides evidence that no bias towards overestimating ceftobiprole's effect occurred, which supports the conclusions that the trials had sufficient assay sensitivity.

- *Assessing assay sensitivity: ICH E10*

Trial integrity and as a consequence the lack of assay sensitivity in the non-inferiority studies was a major concern of the CHMP. Therefore in the view of the Applicant, a thorough analysis of important factors as suggested by ICH E-10 should be considered before concluding about inadequate assay sensitivity. The Applicant therefore asked the CHMP to re-examine whether the studies are lacking assay sensitivity such that the ability to distinguish between an effective and ineffective treatment has been lost.

According to ICH E-10, the presence of assay sensitivity in a non-inferiority or equivalence trial can be deduced from 2 determinations:

1) Historical evidence of sensitivity to drug effects, i.e., that similarly designed trials in the past regularly distinguished effective treatments from less effective or ineffective treatments, and
2) Appropriate trial conduct, i.e., that the conduct of the trial did not undermine its ability to distinguish effective treatments from less effective or ineffective treatments.

Regarding point 1, the Applicant has performed an extensive review of previous cSSTI trials that used vancomycin as a comparator. This analysis involved 5 antibacterial agents (quinopristin/dalfopristin, linezolid, tigecycline, daptomycin and telavancin) and 10 Phase 3 studies. It shows that the efficacy rates in the vancomycin arm in the ceftobiprole trials is similar compared to historical information, providing strong evidence that both ceftobipirole studies had assay sensitivity.

Regarding point 2, the Applicant reviewed the studies for the presence of factors that might obscure differences between treatments:

1. Poor compliance with therapy
2. Poor responsiveness of the enrolled study population to drug effects
3. Use of concomitant non-protocol medication or other treatment that interferes with the test drug or that reduces the extent of the potential response
4. An enrolled population that tends to improve spontaneously, leaving no room for further drug-induced improvement
5. Poorly applied diagnostic criteria (patients lacking the disease to be studied)
6. Biased assessment of endpoint because of knowledge that all patients are receiving a potentially active drug,
7. Extent of, and reasons for, dropouts (could adversely affect assay sensitivity).

The Applicant addressed each of these 7 factors defined in ICH E-10, as a means to assess potential impact of identified GCP citations, relative to the impact on assay sensitivity and the ability to distinguish a safe and effective treatment from a less effective treatment.

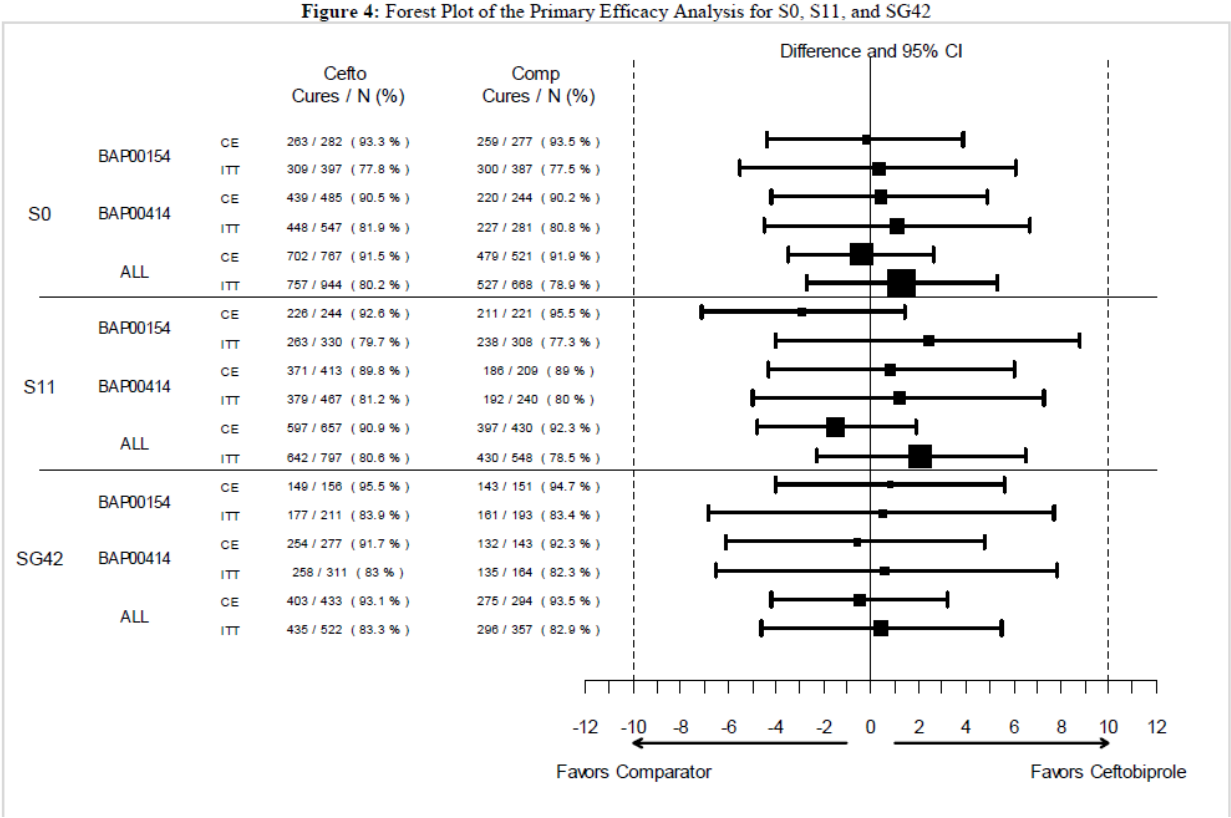
- *Sensitivity analyses*

Two conservative assessments of the reliability of the overall study results were: 1) a sensitivity analysis excluding 11 sites (S11) that were inspected or audited and identified as unreliable or unverifiable by the FDA, European Medicines Agency, or Independent auditor and 2) a subgroup analysis including only the 42 sites (SG42) that were not identified as unverifiable or unreliable by the FDA, European Medicines Agency, or Independent Auditor.

Both analyses were consistent with the results of the analysis of the complete dataset. The Applicant asserts that these analyses demonstrate that the overall study results did not depend on results from sites which have not been audited.

A forest plot showing the primary endpoint in each study alone and in the pooled studies for the S11 and SG42 in comparison to the complete dataset is shown below. The size of the box is proportional to the overall sample size. As shown in the figure, **non-inferiority (as defined by a lower bound of the confidence interval greater than or equal to the pre-specified -10%) is supported by all of these analyses.**

Figure 4: Forest Plot of the Primary Efficacy Analysis for S0, S11, and SG42



Subgroup analyses

For DFI subjects in Study BAP00414, in the complete dataset, the clinical cure rates in the clinically evaluable analysis set were 86.2% for ceftobiprole compared with 81.8% for comparator (data shown previously in Table 3, page 27). In the subgroup analysis including only the 42 sites, the clinical cure rates in the clinically evaluable analysis set were 90.0% for ceftobiprole compared with 88.2% for comparator (Table 18). Therefore, for DFI subjects, the results of the subgroup analysis including the 42 sites are consistent with the results of the analysis of the complete dataset.

Table 18: Clinical Cure Rates at the TOC Visit by Study and in the Pooled Studies Including 42 Sites (Studies BAP00154 and BAP00414: Intent-to-Treat and Clinically Evaluable Analysis Set)

	-- Ceftobiprole --			--- Comparator ---				
	N	n	%	N	n	%	Diff[a](%)	95% CI[b]
Clinically Evaluable Analysis Set								
All subjects								
Study BAP00154	156	149	95.5	151	143	94.7	0.8	(-4.0; 5.6)
Study BAP00414	277	254	91.7	143	132	92.3	-0.6	(-6.1; 4.8)
Subjects without diabetic foot infections								
Study BAP00154	156	149	95.5	151	143	94.7	0.8	(-4.0; 5.6)
Study BAP00414	217	200	92.2	109	102	93.6	-1.4	(-7.2; 4.4)
Type of Infection								
Study BAP00154								
Wound	46	46	100.0	42	38	90.5	9.5	(0.6; 18.4)
Abscess	86	81	94.2	78	75	96.2	-2.0	(-8.5; 4.6)
Cellulitis	24	22	91.7	31	30	96.8	-5.1	(-17.8; 7.6)
Study BAP00414								
Diabetic Foot Infection	60	54	90.0	34	30	88.2	1.8	(-11.5; 15.0)
Wound	73	69	94.5	35	33	94.3	0.2	(-9.1; 9.5)
Abscess	96	88	91.7	55	52	94.5	-2.9	(-11.0; 5.3)
Cellulitis	48	43	89.6	19	17	89.5	0.1	(-16.2; 16.4)
Subjects with gram-positive pathogen at baseline								
Study BAP00154	121	115	95.0	123	116	94.3	0.7	(-4.9; 6.4)
Study BAP00414	172	161	93.6	90	84	93.3	0.3	(-6.0; 6.6)
Subjects with gram-negative or mixed pathogens at baseline[c]								
Study BAP00414	55	51	92.7	33	30	90.9	1.8	(-10.2; 13.8)
Intent-to-Treat Analysis Set								
All subjects								
Study BAP00154	211	177	83.9	193	161	83.4	0.5	(-6.8; 7.7)
Study BAP00414	311	258	83.0	164	135	82.3	0.6	(-6.5; 7.8)
Subjects without diabetic foot infections								
Study BAP00154	211	177	83.9	193	161	83.4	0.5	(-6.8; 7.7)
Study BAP00414	241	202	83.8	124	104	83.9	-0.1	(-8.0; 7.9)
Subjects with gram-positive pathogen at baseline								
Study BAP00154	147	122	83.0	141	120	85.1	-2.1	(-10.6; 6.3)
Study BAP00414	186	163	87.6	99	85	85.9	1.8	(-6.6; 10.1)
Subjects with gram-negative or mixed pathogens at baseline[c]								
Study BAP00154	19	16	84.2	13	8	61.5	22.7	(-8.4; 53.8)
Study BAP00414	65	52	80.0	37	32	86.5	-6.5	(-21.2; 8.2)

Note: n is the number of subjects with a clinical outcome of Cure.
Note: The randomization between ceftobiprole to comparator was 1:1 in BAP00154 and 2:1 in BAP00414.
[a] Ceftobiprole minus comparator.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Only study BAP00414 included subjects with gram-negative/mixed pathogens. In BAP00154, these subjects were considered not clinically evaluable.

Clinical safety

Acknowledging that 5 (1 in the ceftobipirole treatment group and 4 in the comparator treatment group) of 7 subjects that died in the complete dataset are absent from the SG42, overall there was no meaningful difference between the incidence of treatment-emergent adverse events, serious adverse events, deaths, treatment-related serious adverse events, adverse events leading to discontinuation, and treatment-related adverse events leading to discontinuation between subjects who received ceftobiprole and subjects who received the comparators in both analyses. In addition consistent with the relative size

of the SG42 compared to the complete dataset (54.5%), the number of reported events is approximately one-half that in the complete dataset. This suggests that underreporting of adverse events did not occur at "unqualified" sites. The trends of ADRs were similar in the complete dataset and the SG42

MAA's conclusions for the subgroup analyses including the 42 sites

The results of the subgroup analysis including only the 42 sites inspected or audited and not identified as unreliable or unverifiable by the FDA, European Medicines Agency, or Independent auditor showed similar positive primary and secondary efficacy results, and similar profiles of overall adverse events, adverse drug reactions, deaths, serious adverse events, and adverse events leading to discontinuation, with no clinically important differences from the data presented in the original marketing application.

In conclusion, the efficacy and safety experience in the 2 randomised, double-blind, controlled, Phase 3 studies (BAP00154 and BAP00414) supports the conclusion that ceftobipirole monotherapy is an effective treatment for patients with cSSTI, including DFI, and is well tolerated with an acceptable safety profile that is comparable to other cephalosporins. The results of the subgroup analysis including the 42 sites support the original efficacy and safety conclusions as presented in the initial MAA.

CHMP comments:

The sensitivity analyses and the microbiological outcomes data have been assessed before and the results above have been given to illustrate the Applicants grounds. No new findings became apparent from the sensitivity analyses around safety.

The analyses, including the clinical safety, seem consistent. Non-inferiority was reached in the primary efficacy endpoint in both subsets (S11 and SG42). Subgroup analyses in the SG42 data set according to diabetic foot ulcer or not, type of infection, and cure per pathogen also indicate consistency with the results of the complete data set. The lower bound of the 95% confidence interval was lower than the pre-specified -10% in some of the subgroup analyses, which is expected due to the limited number of patients in the subgroup analysis including the 42 sites (54.5 % of the total data set).

However, the main remaining problem is the question of which data (including the safety data) can be trusted, as several inspection/audit rounds produced different results, increasing the number of unreliable sites. The overall picture of the studies is that compliance at the different study sites was variable and trial management was not optimal.

The Applicant's inventory of the historical data on assay sensitivity in studies of other medicinal products in this indication is not directly relevant for the issue of GCP violation in the studies under question. The 7 factors discussed by the Applicant based on the CHMP/ICH/364/96 are of importance, but do not exclude the bias caused by the issues around the study conduct or possibly incorrect recording/reporting of the study

4. OVERALL CONCLUSION ON GROUNDS FOR RE-EXAMINATION

Efficacy aspects

The conclusion reached at time of revised opinion (Feb 2010) remains valid.

While there have been clear problems associated with the conduct and monitoring of the two pivotal studies, all sensitivity analyses, including the analysis of all those centres deemed to be satisfactory by European and FDA inspectors, remain consistent with the results of the analysis of the complete dataset and continue to support the overall efficacy and safety conclusions for ceftobiprole in the original MAA, which were the basis for the positive opinion raised by CHMP November 2008. Non-inferiority for ceftobiprole vs. the comparator in the primary endpoint, clinical cure at the TOC visit, is supported for both pivotal studies for CE and ITT populations, also when only "cleared" sites (SG42) were included in the analyses.

However, as each round of inspection or audit has led to the exclusion of additional sites, the overall conduct of the trial remains questionable and it can no longer be concluded that the conduct of the trial did not undermine its ability to distinguish effective treatments from less effective treatments. The Applicant's inventory of the historical data on assay sensitivity in studies of other medicinal products in this indication is not directly relevant for the issue of GCP violation in the studies under question. The 7 factors discussed by the Applicant based on the CHMP/ICH/364/96 are of importance, but do not exclude the bias caused by the issues around the study conduct or possibly incorrect recording/reporting of the study

Potential benefit or superior role in comparison to other available agents in seriously ill patients with severe cSSTIs is not enough justified due to lack of robust clinical data available for these patients.

Therefore, the CHMP did not consider the performed sensitivity analyses and the additionally supportive (partially theoretical) considerations as sufficient to support the efficacy demonstration of this marketing authorisation application.

Safety aspects

There were no new safety signals identified in this analysis compared to the data presented in the original marketing application. Nevertheless, the conclusion reached at time of revised opinion (Feb 2010) remains valid.

Considering the systematic nature of the GCP findings, it is difficult to conclude that the data from the pivotal studies can be relied upon**.** The potential of missing important safety information on the product renders the initially concluded positive safety profile invalid and does no longer allow the CHMP to assess all potential risks associated with the use of the medicinal product.

SAG Expert Group meeting

The SAG acknowledged that more novel agents are urgently required to treat bacterial infections. There is e.g. a clear need for safer medicines to treat infections caused by multidrug resistant bacteria (gram-positive as well as gram-negative pathogens). In that sense, ceftobiprole, as a broad-range bactericidal agent belonging to a well know antibiotic class, might be a promising addition to the armamentarium.

The experts asserted that both pivotal non-inferiority trials followed a usual design, acceptable for investigation of cSSTI. As noted, the conduct of both trials was imperfect, affecting a substantial proportion of study participants. However, as supported by the methodology experts, taken account of the high power of the studies, non-inferiority could still be demonstrated for each trial, in the most conservative (sensitivity) analysis. Nevertheless, concern was raised that having in mind the number and range of identified issues, there may be other unidentified issues in the trials conduct, which could still compromise these findings. Because of this, the SAG remained divided in its opinion.

Benefit/risk assessment

The conclusion reached at time of revised opinion (Feb 2010) remains valid.

The CHMP re-iterated that the main outstanding problem remains the question of which data (including the safety data) can be trusted, as several inspection/audit rounds showed an increasingly number of unreliable sites. The overall picture of the studies is that compliance at the different study sites was variable and trial management was not optimal.

CHMP conclusion on benefit/risk

Having considered the grounds for the re-examination from the Applicant, the discussion during the SAG Expert Group meeting and the CHMP members' discussion during the oral explanation, the CHMP is unable to establish a positive risk/benefit balance for ceftobiprole in the claimed indication.

Recommendation

The pivotal clinical studies BAP00154 and BAP00414 were not conducted in accordance with GCP as required by Annex I of Directive 2001/83/EC as amended and the nature of the findings is such that the conduct of the studies and their results cannot be relied on to recommend the granting of a marketing authorisation.

The therapeutic efficacy and clinical safety have been insufficiently substantiated by the applicant *as per* article 12(1) of Regulation (EC) No 726/2004 and article 26(1)(b) of Directive 2001/83/EC as amended.

The CHMP has recommended by majority the refusal of the granting of the Marketing Authorisation for Zeftera in accordance with article 9(1)(a) of Regulation (EC) No 726/2004.