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POST-AUTHORISATION SAFETY STUDY PROTOCOL
BPR-PAS-001

Zevtera 500 mg powder for concentrate for solution for infusion

Ceftobiprole medocaril

Retrospective chart review to evaluate the safety profile of ceftobiprole in patients with impaired hepatic or renal function or immunosuppression

PROTOCOL APPROVAL	
Protocol Number/ Version:	BPR-PAS-001 / Version 4.0
EU PAS Register Number:	Not registered
Date:	20 February 2018

Title Page

Title	Retrospective chart review to evaluate the safety profile of ceftobiprole in patients with impaired hepatic or renal function or immunosuppression
Protocol version identifier	BPR-PAS-001 / Version 4.0
Date of last version of protocol	20 February 2018
EU PAS Register Number	Study not registered
Active Substance	Ceftobiprole medocaril sodium ATC code: J01DI01
Medicinal Product	Zevtera 500 mg powder for concentrate for solution for infusion, and its associated names
Product Reference	Not available
Procedure number	UK/H/5304/001/DC
Joint PASS	No
Research question and objectives	**Research question:** To estimate the proportion and relative frequency of treatment-emergent adverse events in patients treated with ceftobiprole, who have at least one of the following conditions • impaired renal function • impaired hepatic function • immunosuppression The observed frequency of adverse events in patients with the above risk factors will be compared to the frequency of the adverse events in patients without these risk factors. **Objectives** The objective of this study is to further characterise the safety profile of ceftobiprole, with particular emphasis on the following groups of patients: • patients with severe renal impairment / end-stage renal disease • patients with impaired baseline hepatic function • Patients with immunosuppression, including – HIV-positive patients – immunocompromised patients (any type or aetiology) – patients with baseline neutropenia – patients with baseline myelosuppression

	The primary aim of this study is the assessment of treatment-emergent adverse events and the following adverse events of special interest: • Hyponatraemia • Hepatobiliary disorders • Renal toxicity (including potential interactions with nephrotoxic drugs) • Coombs test (DAT) positivity + clinical evidence of haemolysis • Hypersensitivity reactions, including anaphylactic reactions • Pseudomembranous colitis / *Clostridium difficile* colitis • Convulsions The secondary aim is the assessment of ceftobiprole in the naturalistic clinical setting with respect to: • Treatment duration and dosage • Safety as a result of off-label use (i.e., outside labelled indications)
Countries of study	Participating countries have not yet been identified.Centres would be chosen from countries where ceftobiprole is commercialised.

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
CD4	Cluster of differentiation 4
CLCr	Creatinine clearance
CRF	Case report form
DAT	Direct antiglobulin test
ESRD	End-stage renal disease
EEA	European Economic Area
EU	European Union
IEC	Independent Ethics Committee
GGT	Gamma glutamyl transferase
HCT	Haematocrit
HIV	Human immunodeficiency virus
INR	International normalized ratio
MAH	Marketing Authorisation Holder
N/A	Not applicable
PASS	Post-authorisation safety study
PMN	Polymorphonuclear neutrophils
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
TBD	To be determined
ULN	Upper limit of normal
WBC	White blood cell

1 RESPONSIBLE PARTIES

Principal Investigator: TBD
Coordinating Investigator TBD

2 ABSTRACT

Title

Retrospective chart review to evaluate the safety profile of ceftobiprole in patients with impaired organ function or immunosuppression.

Rationale and background

Ceftobiprole is a beta-lactam antibiotic with bactericidal activity against a broad spectrum of Gram-positive and Gram-negative bacteria, that was developed to treat patients with pneumonia both in a hospital or community setting. Clinical trials were conducted in adult immune-competent patients with normal or mild to moderate renal or hepatic function impairment. The clinical trial program completed to date has excluded patients with immune suppression and significant organ function impairment (hepatic or renal). The safety profile of ceftobiprole in these patient groups was recognized during the marketing authorization procedure as important missing information and the applicant committed to conduct a post authorization safety study.

A randomized Phase 3 study in the indication of acute bacterial skin and skin structure infections (ABSSSIs) is ongoing (NCT03137173), and a randomized Phase 3 study in the indication of *S. aureus* bacteremia is planned (NCT03138733).

This retrospective chart review is conducted to further evaluate the safety profile of ceftobiprole in patient populations with specific risk factors.

Research question and objectives

Research question

To estimate the proportion and the relative frequency of treatment-emergent adverse events (AEs) in patients treated with ceftobiprole and who have at least one of the following conditions:

- Impaired renal function
- Impaired hepatic function
- Immunosuppression

Treatment-emergent AEs are defined as events occurring after first study-drug administration, up to 28 days after the completion of treatment.

The observed frequency of adverse events in patients with the above risk factors will be compared to the frequency of the adverse events in patients without these risk factors (see Section 7.5).

Objectives

The objective of this study is to further characterise the safety profile of ceftobiprole, with particular emphasis on the following groups of patients:

- Patients with severe renal impairment /ESRD
- Patients with impaired baseline hepatic function

- Patients with immunosuppression, including
  - HIV-positive patients
  - Immunocompromised patients (any type or aetiology)
  - patients with baseline neutropenia
  - patients with baseline myelosuppression

The primary aim of this study is the assessment of treatment-emergent AEs and the following events of special interest:

- Hyponatraemia
- Hepatobiliary disorders
- Renal toxicity (including potential interactions with nephrotoxic drugs)
- Coombs test (DAT) positivity + clinical evidence of haemolysis
- Hypersensitivity reactions, including anaphylactic reactions
- Pseudomembranous colitis / *Clostridium difficile* colitis
- Convulsions

The secondary aim is the assessment of ceftobiprole in the naturalistic clinical setting with respect to:

- Treatment duration and dosage
- Safety as a result of off-label use (i.e., outside labelled indications)

Study design

This study is a non-interventional, multicentre, multinational, retrospective chart review.

Population

The study will enroll patients in whom treatment with ceftobiprole has been completed (including both on-label and off-label use) plus at least one of the following criteria (more than one may apply):

- Patients with severe renal impairment / end-stage renal disease (ESRD)
- Impaired baseline hepatic function
- Patients with immunosuppression, including
  - HIV-positive patients
  - patients with baseline neutropenia
  - patients with baseline myelosuppression
  - Immunocompromised patients (any other type or aetiology as determined by the investigator)

In addition, the study will enroll a control group of patients in whom treatment has been completed without any of the criteria listed above.

Patient charts will be selected from hospital sentinel sites. The date when the first ceftobiprole was prescribed at the site will be selected as the index date. Each site should contribute at least 5 patient charts. All consecutive patient charts of patients who meet the inclusion criteria and have received at least one dose of ceftobiprole after the index date will be selected for the chart review.

Patient observation would normally be planned for 28 days after completion of ceftobiprole therapy. If, at the time of the review of any patient medical records, an AE has not been resolved, these patients would be followed up until resolution.

The study would continue until the target number of patients has been reached. The end date of this study would be set at the date of the last patient record review, or in cases where follow-up is extended beyond this period, until the end of follow-up. Study timelines are detailed in Section 4.

Variables

The following variables will be identified from the patient charts

- Year of birth and gender
- Weight
- Indication of treatment
- Attribution to a specific population group (see inclusion criteria) and criteria to assign the patient
- Start date of ceftobiprole
- Stop date of ceftobiprole and main reason for stopping (if known)
- Prescribed dose/regimen at treatment start
- Changes in dose during treatment
- Relevant medical history (diagnosis within 1 year prior to treatment start)
- Presence of ascites and hepatic encephalopathy at baseline
- Laboratory investigations undertaken as part of routine clinical practice and management of the patient related to the outcomes of interest, e.g., serum sodium, AST, ALT, serum albumin, total bilirubin, GGT and AP, prothrombin time, INR, creatinine, haemoglobin, HCT, Coombs (DAT), *C. difficile* toxin tests prior (within 1 month) and up to 28 days after completion of treatment
- Findings of colonoscopy/sigmoidoscopy (for *C. difficile* colitis)
- Concomitant medication at baseline and up to 28 days after completion of treatment with focus on new onset use or dose modification of medications to treat hypersensitivity/anaphylaxis, convulsions, or *C. difficile* colitis
- Treatment-emergent AEs (event reports up to 28 days after completion of treatment), with focus on AEs of special interest (AESIs)
- Date and cause(s) of death (if applicable)
- Use during pregnancy (with follow-up until delivery)

Data sources

This study will use data from patient charts, which includes physician and nurse notes, admission and discharge summaries, consultancy reports, laboratory test sheets, and microbiology sheets.

Study size

The ability to detect any particular AE is dependent on the expected proportion of the event in those exposed to the drug, the background rate in those not exposed to the drug, and the total number of patients. The objectives of this observational study are focused on determining the safety profile of ceftopriole in RMP risk groups and allow the assessment of the benefit-risk

profile in these special populations, rather than testing one hypothesis (primary aim in efficacy studies) as done in randomized controlled trials.

For reliable identification of a 2–3-fold increase in the frequency of AEs of special interest obtained in the PASS study compared to the frequencies of events (observed > 5%) in the pooled ceftobiprole Phase 3 (pneumonia clinical studies and ongoing ABSSSI study), the review of 180 patient charts in patients with ceftobiprole defined RMP-risk factors overall and at least 50 patient charts in each subgroup of patients with severe renal impairment / ESRD, impaired baseline hepatic function, or immunosuppression is required. To account for missing or unevaluable data, it is planned to review 211 patient charts in order to obtain at least 180 evaluable patients with at least 50 patients in each subgroup of patients with severe renal impairment / ESRD, impaired baseline hepatic function, or immunosuppression. In addition, 180 control patients of ceftobiprole-treated patients without RMP-defined risk factors will be collected to obtain a contemporary control group (see Section 7.5). In total, approximately 422 patient charts will be reviewed to obtain 180 patients with ceftobiprole-defined RMP-risk factors ('cases'), and 180 patients without ceftobiprole-defined RMP-risk factors (controls).

Based on the 'rule of three'[1], if no AE events could be seen in a cohort of at least 180 evaluable patients, it would allow to exclude a frequency of about 2% or larger with a 95% probability.

Data analysis

Basic epidemiological and demographic data will be collected, as well as specific required outcomes. Safety data collected during the study will be summarised using descriptive statistics (number and percentage of patients with AEs overall, by System Organ Class and Preferred Term). The Safety population (defined as patients who took at least 1 dose of ceftobiprole during the programme) will be used to analyse safety data.

Data for the following patient groups would be described:

- Baseline renal dysfunction: stratified categories
- Baseline hepatic dysfunction: stratified categories
- HIV-positive
- Immunocompromised
- Baseline neutropenia
- Baseline myelosuppression
- Age groups
- Indications: label and off-label

Secondary outcomes will be presented using descriptive statistics including summary statistics on dosage and treatment duration.

Milestones

Enrollment in this study is expected to begin after the availability of sufficient patients in the participating countries, and the approval of the protocol by Ethics Committees and Competent

[1] Hanley, J. A.; A. Lippman-Hand (1983). 'If nothing goes wrong, is everything alright?'. *JAMA* 249 (13): 1743–5. doi:10.1001/jama.1983.03330370053031

Authorities. After 10% of charts have been reviewed, availability of variables and progress of the study will be reviewed and adjusted if necessary.

The study would continue until the target number of patients has been reached. The status of the PASS will be reported with the DSUR (if applicable), PSUR, and RMP updates.

3 AMENDMENTS AND UPDATES

Protocol Amendment 1 and Protocol Version 2.0 were implemented on 29 November 2017.

4 MILESTONES

Initiation of PASS data collection would start approximately 6 months prior to the availability of safety data from the ongoing ABSSSI study, which is expected in the second half of 2019.

Milestone	Planned date
Start of data collection	Q2 2019
DSUR /PSUR / RMP update	Ongoing
End of data collection	Q4 2021
Final study report	Q4 2022

5 RATIONALE AND BACKGROUND

Ceftobiprole is a newly-developed beta-lactam antibiotic with bactericidal activity against a broad spectrum of Gram-positive and Gram-negative bacteria, that was developed to treat patients with pneumonia in both hospital and community settings. Clinical trials were conducted in adult immune-competent patients with normal or mild-to-moderate impairment of renal or hepatic function.

The clinical trial program prior to marketing authorisation excluded patients with immune suppression and significant organ function impairment (hepatic or renal).

Immune suppression is a typical exclusion criterion for pre-authorisation studies in order to increase homogeneity of the study population and to avoid distortion of the treatment effect by the underlying disease. Nevertheless, pneumonia is an important health risk for these patients, who have an increased risk of acquiring pneumonia compared with the general population. Pneumonia is a major cause of morbidity and mortality in immunosuppressed patients. In patients with HIV who are infected with *S. pneumonia* the risk of pneumonia is 10–100 times greater than in non-HIV infected patents[2]. Similarly, patients who are immunosuppressed from other aetiologies (transplant recipients, extremes of age, alcoholism, asplenia etc.) experience more frequent and more severe lower respiratory tract infections,[3] including bacterial pneumonia. Treatment of this patient group poses additional difficulties, because the patients may need prolonged therapy in combination with other antibiotics, frequently take other medications, and thus may have an increased risk of AEs associated with the treatment.

[2] Ortqvist A, Hedlund J, Kalin M. Streptococcus pneumoniae: epidemiology, risk factors, and clinical features. Semin Respir Crit Care Med. Dec 2005;26(6):563–74

[3] Augenbraun MH, Pneumonia in Immnunocompromised patients Medscape 2012 Oct 12 Accessed on 12 Aug 2013.

Exclusion of patients with severe renal function impairment was introduced as a safeguard in the pre-authorisation programme based on results of PK studies of ceftobriprole. Ceftobiprole is mainly excreted by the kidneys, and studies have shown that the AUC of ceftobiprole is higher in patients with moderate and severe renal failure, thus potentially increasing the risk of treatment-emergent AEs. Nevertheless, patients with severe kidney failure and ESRD have an increased risk of infections, particularly of pneumonia. In a record linkage study, the cumulative probability of pneumonia hospitalisation was 0.09 at 1 year and 0.36 at 5 years of dialysis[4]. It is thus reasonable to assume that patients may benefit from ceftobiprole treatment provided the risk is acceptable. Although the liver plays a less important role in the metabolism of ceftobiprole, the pharmacokinetics of ceftobiprole in patients with hepatic impairment is not established, and patients were excluded from the pre-authorisation program on a precautionary principle.

The knowledge gap regarding the safety profile of ceftobiprole from these patient groups was recognized during the marketing authorisation procedure, and the applicant committed to conducting a post-authorisation safety study (PASS). This retrospective chart review is conducted to fulfil the commitment, and to further evaluate the safety profile of ceftobiprole in these patient populations.

6 RESEARCH QUESTION AND OBJECTIVES

This retrospective chart review is conducted to estimate the proportion and relative frequency of treatment-emergent AEs in patients treated with ceftobiprole who have at least one of the following conditions:

- Impaired renal function
- Impaired hepatic function
- Immunosuppression.

The objective of this study is to further characterise the safety profile of ceftobiprole, with particular emphasis on the following groups of patients:

- Patients with severe renal impairment / ESRD
- Patients with impaired baseline hepatic function
- Patients with immunosuppression, including
  - HIV-positive patients
  - patients with baseline neutropenia
  - patients with baseline myelosuppression
  - Immunocompromised patients (any other type or aetiology as determined by the investigator).

The primary aim of this study is the estimation of the proportion and relative frequency of treatment-emergent AEs. Ceftobiprole is a newly-developed cephalosporin. As with other beta-lactam antibiotics, important identified and potential risks have been classified as AESIs. Their proportion will be evaluated in the patient cohort:

[4] Slinin Y, Foley RN Collins AJ, Clinical epidemiology of pneumonia in hemodialysis patients: the USRDS waves 1, 3, and 4 study Kidney International (2006) 70, 1135–1141. doi:10.1038/sj.ki.5001714

- Hyponatraemia
- Hepatobiliary disorders
- Renal toxicity (including potential interactions with nephrotoxic drugs)
- Coombs test (DAT) positivity + clinical evidence of haemolysis
- Hypersensitivity reactions, including anaphylactic reactions
- Pseudomembranous colitis / *C. difficile* colitis
- Convulsions

The secondary aim is the assessment of ceftobiprole in the naturalistic clinical setting with respect to:

- Treatment duration and dosage
- Safety as a result of off-label use (i.e., outside labelled indications)

7 RESEARCH METHODS

7.1 Study design

This study is a observational, non-interventional, multicentre, multinational, retrospective study based on chart review. The chart review will enable the systematic collection of drug utilisation data and reporting of safety data in patients with pre-specified underlying morbidity newly initiated on ceftobiprole in the hospital setting.

The study aims to collect exposure and outcome data for a cohort of at least 180 evaluable ceftobiprole-treated patients with RMP-defined risk factors and 180 ceftobiprole-treated control patients without RMP-defined risk factors . It is currently thought that the objectives of the study can be most efficiently met by using an intensive monitoring scheme. Intensive monitoring of the patient groups of interest would be achieved by reviewing patient medical records in selected sentinel sites. The review of readily available data will reduce the time required to collect data, with no additional risk or interventions for patients. As a further advantage, it will permit the collection of data that reflect naturalistic treatment settings.

As this is a retrospective, non-interventional study based on already-collected data (chart review), participation would not have any impact on hospital admission time or clinical procedure.

Any chart for a patient for whom treatment with ceftobiprole is initiated and who meets the other inclusion criteria will be included, thus reducing selection bias at the sentinel site in the data collection process.

7.2 Setting

Patient inclusion criteria were determined based on the characteristics of patient groups excluded during the clinical trial program and therefore identified as important missing information during the marketing authorisation procedure. No other inclusion or exclusion criteria are applied.

The study will enroll patients in whom treatment with ceftobiprole has been completed (including both on-label and off-label use) plus at least one of the following criteria (more than one criterion may apply):

- Patients with severe renal impairment / ESRD (defined as calculated CLCr < 30 mL/minute or oliguria < 20 mL/hour unresponsive to fluid challenge or any form of dialysis)
- Impaired baseline hepatic function (patients with liver failure/cirrhosis Child Pugh Grade A, B, C or existing non-cirrhotic liver disease associated with total bilirubin > 2 mg/dL or alanine aminotransferase [ALT], or aspartate aminotransferase [AST] ≥ 3 times upper limit of the normal range [ULN])
- Patients with immunosuppression, i.e.,
  - HIV-positive with CD4 counts of ≤ 0.2×10^9/L (≤ 200 cells/mm^3)
  - Immunocompromised as determined by the investigator (any type or aetiology)
  - Baseline neutropenia or baseline myelosuppression, defined as presence of myelosuppression or neutropenia (absolute neutrophil count [ANC] ≤ 0.5×10^9/L [< 500 polymorphonuclear neutrophils (PMNs)/mm^3]), severe anaemia (haemoglobin < 6.5 g/dL), or severe thrombocytopenia (< 49.9×10^9/mm^3)

In addition, the study will enroll a control group of patients in whom treatment has been completed without any of the criteria listed above.

Patient charts will be selected from hospital sentinel sites. Sites will be asked to participate in this study based on records that patients with the above-specified co-morbidities are treated in the centres and availability of resources to perform the patient chart review.

The date when the first ceftobiprole was prescribed at the site will be selected as the index date. All consecutive patient charts of patients who meet the inclusion criteria and have received at least one dose of ceftobiprole after the index date will be selected for the chart review. Each site should contribute at least 5 patient charts.

Patient observation would include a baseline evaluation prior to ceftobiprole treatment initiation. The on-treatment and post-treatment observation period would normally be planned for 28 days after completion of ceftobiprole therapy. If, at the time of the review of any patient medical records, an AE has not been resolved, these patients would be followed up until resolution. For patients without documentation through Day 28 after ceftobiprole treatment completion (e.g., due to hospital discharge), the patient or their primary care provider should be contacted to assess any AEs that may have occurred up to that date.

The attribution of patients to the intended inclusion groups (hepatic function impairment, renal function impairment, immunosuppression) cannot be predicted. To ensure that each group is adequately represented, the collection of patient charts and attribution of patients will be monitored. A minimum of 58 (to achieve at least 50 evaluable) patient charts for each group is planned to ensure adequate representation of each of the three inclusion groups (hepatic function impairment, renal function impairment, immunosuppression). Inclusion groups may be closed for further enrollment if deemed necessary to ensure the minimum number of charts in another group.

The study will continue until the target number of patients has been reached. The end date of this study will be set at the date of the last patient record review or, in cases where follow-up is extended beyond this period, at the end of follow-up.

It is difficult to predict the prescription volume of ceftobiprole prescriptions, and conduct of the study may be influenced by the number of treatment courses at the sentinel sites and availability of data in patient records. Therefore, it is planned to review progress of the study after 10% of charts have been selected and adjust the study conduct if necessary.

7.3 Variables

The following variables will be identified from the patient charts:

Demographic data and baseline variables

- Year of birth and gender.
- Weight at baseline.
- Relevant medical history (diagnosis within one year prior to treatment start).
- Presence of ascites or hepatic encephalopathy at baseline.
- Laboratory investigations undertaken as part of routine clinical practice and management of the patient related to the outcomes of interest, e.g., serum sodium, AST, ALT, total bilirubin, serum albumin, GGT and AP, prothrombin time, INR, creatinine, WBC count, haemoglobin, HCT, Coombs (DAT) *C. difficile* toxin tests within 1 month prior to starting treatment (if available). Laboratory values will be selected as last value prior to treatment start (baseline) and the lowest and highest value during 1 month prior to treatment.
  Note: the minimum requirement of baseline laboratory values for a patient to be included as evaluable in the analysis is availability of WBC count, haemoglobin, creatinine, sodium, AST, ALT, and total bilirubin.
- Attribution to a specific population group (see inclusion criteria) and criteria to assign the patient (HIV test, CD4 count, ClCr, ANC, PMN, haemoglobin, platelets).
- Concomitant medication at baseline.

Exposure variables

- Indication of treatment
- Start date of ceftobiprole
- Stop date of ceftobiprole and main reason (if known)
- Prescribed dose/regimen at treatment start
- Changes in dose during treatment

Outcome variables

- Laboratory investigations undertaken as part of routine clinical practice and management of the patient related to the outcomes of interest. The following laboratory parameters will be selected from the patient charts. All available values/results will be selected, including dates when the test was performed, applicable units, and reference ranges.
  - serum sodium
  - AST
  - ALT
  - total bilirubin
  - GGT
  - AP
  - INR; prothrombin time

  - serum albumin
  - serum creatinine (CLCr derived by Cockgroft-Gault formula)
  - WBC count
  - haemoglobin
  - HCT
  - Coombs (DAT)
  - *C. difficile* toxin tests up to 28 days after completion of treatment
- Findings of colonoscopy/sigmoidoscopy (for *C. difficile* colitis)
- Concomitant medication up to 28 days after completion of treatment with focus on new onset use or dose modification of medications to treat hypersensitivity/anaphylaxis (e.g., antihistamines, corticosteroids, adrenaline), convulsions, or *C. difficile* colitis (e.g., oral vancomycin, metronidazole, fidaxomicin, rifaximin)
- Adverse event reports up to 28 days after completion of treatment, with focus on AESIs
- Date and causes of death (if applicable)
- Use during pregnancy

An AE in the context of this retrospective chart review is defined as any untoward medical occurrence documented in physician, nurse or consultancy notes for a patient administered at least one dose of ceftobiprole, regardless of whether there is a causal relationship with this treatment.

New onset use or dose modification of medications to treat hypersensitivity/anaphylaxis, convulsions, or *C. difficile* colitis will be carefully reviewed to identify AEs of special interest that were not included as separate AE terms in the medical notes.

The chart review will identify instances of lack of efficacy, overdose, abuse, off-label use, misuse, medication error, and occupational exposure to ceftobiprole, and – where available – the cause of these instances.

For the purpose of this review, AEs will be documented including the reported term, the start and stop date, and the outcome.

The following have been identified as AEs of special interest. Reviewers will receive training and instruction manuals to ensure consistent and accurate identification of these events:

- Hyponatraemia or (hyponatraemia or low/decreased sodium documented in the physician or nurse or consultancy notes)
- Hepatobiliary disorders (defined as any newly-diagnosed or worsening of a pre-existing liver disease/event or related symptom, e.g., jaundice)
- Renal AEs documented in the physician, nurse or consultancy notes
- Coombs test (DAT) positivity + clinical evidence of haemolysis (drop in haemoglobin ≥ 1 g/dL without bleeding, increase in indirect bilirubin, jaundice, increase in reticulocytes, decrease in haptoglobin)
- Hypersensitivity reactions, including anaphylactic reactions
- Pseudomembranous colitis / *C. difficile* colitis (positive *C. difficile* toxin)
- Convulsions

7.4 Data sources

This study will use data from patient charts, with the entire chart provided to the reviewer. Outcome variables will be selected from the following type of documents (depending on availability)

- admission notes
- physician and nurse notes
- consultancy reports
- discharge summaries
- laboratory test sheets.

The availability of data will be verified after 10% of patient charts have been reviewed. Thereafter a modification of the information collected from the data sources may become necessary.

7.5 Study size

The objectives of this study are focused on determining the safety profile of ceftopriole in RMP risk groups, and allowing the assessment of the benefit-risk profile in these special populations, rather than on specific hypothesis testing.

The proportion of AEs of special interest observed in the retrospective case review will be compared to:

1. The proportion of AEs of special interest from Phase 3 clinical studies (see Section 7.5.1) including:
   - The pooled pneumonia studies (CAP-3001 and BAP248/307): N=696 (ceftobiprole-treated patients) and
   - The ongoing study BPR-CS-008 in ABSSSI: estimated N=337 (ceftobiprole-treated patients)

   The expected size of the pooled clinical trial database is N=1,033 patients treated with ceftobiprole.
2. The proportion of AEs of special interest from a control group using one control patient treated with ceftobiprole without RMP-defined risk factors per one ceftobiprole treated case with at least one RMP-defined risk factor (see section 7.5.2).

7.5.1 Comparison of AEs of special interest from the clinical Phase 3 programme and the retrospective chart review

For reliable identification of a 2–3-fold increase in the frequency of AEs of special interest obtained in the PASS study compared to the frequencies of events (observed > 5%) in the pooled ceftobiprole Phase 3 (pneumonia and ABSSSI) clinical studies, the review of 176 evaluable patient charts overall (rounded to 180) and at least 46 patient charts (rounded to 50) in each subgroup of patients with severe renal impairment / ESRD, impaired baseline hepatic function, or immunosuppression is required. To account for missing or unevaluable data, it is planned to review 211patient charts in order to obtain at least 180 evaluable patients with at least 50 patient charts in each subgroup of patients with severe renal impairment / ESRD, impaired baseline hepatic function, or immunosuppression, assuming an approximately 15% drop-out rate due to non-evaluability.

Table 1 shows the number of patients required for AEs of special interest to detect an increase in the proportion of frequent AEs of special interest (i.e., occurrence > 5%) from the pooled Phase 3 studies (pneumonia and ABSSSI), if this proportion was increased by 2-fold or 3-fold in the PASS (in ceftobiprole-treated patients with RMP-defined risk factors).

A sample size of 180 patients in the group of ceftobiprole-treated cases with RMP-defined risk factors, and 1033 ceftobiprole treated patients in the pooled Phase 3 studies, would allow detection of a 2-fold increase in the proportion of PASS AEs of special interest when the AE occurs with a frequency of ≥ 5% in the pooled Phase 3 studies (using a one-sided Z-test at an alpha level of 0.05 and a power of 80%).

A sample size of 50 patients in the group of ceftobiprole-treated cases in each RMP-defined risk subgroup (patients with severe renal impairment / ESRD, impaired baseline hepatic function, or immunosuppression) and 1033 ceftobiprole-treated patients in the pooled Phase 3 studies, would allow detection of a 3-fold increase in the proportion of PASS AEs of special interest when the AE occurs with a frequency of ≥ 5% in the pooled Phase 3 studies (using a one-sided Z-test at an alpha of 0.05 and a power of > 80%).

Low-frequency events such as convulsions, pseudomembranous colitis/*C. difficile* colitis, anaphylactic reaction, or direct Coombs test positivity with evidence of haemolytic anaemia) are expected to occur rarely and will be primarily assessed by a qualitative approach.

Based on the 'rule of three'[5], if no AE events could be seen in a cohort of at least 180 evaluable patients, it would allow to exclude a frequency of about 2% or larger with a 95% probability.

Table 1 Sample size estimates for identification of safety signals for treatment-emergent adverse events of special interest

Preferred Term / Group of events	Frequency in pooled Phase 3 pneumonia clinical studies N=1033 % [95% CI]	Sample size (N) to detect 2-fold increase in proportion of AE (one-sided Z-test, α=0.05, Power >80%)	Sample size (N) to detect 3-fold increase in proportion of AE (one-sided Z-test, α=0.05, Power >80%)
Hepatic enzyme elevations	6.3 [4.9 to 8.0]	137	36
Hyponatraemia	6.0 [4.6 to 7.6]	146	38
Hypersensitivity reactions	5.5 [4.2 to 7.1]	164	43
Renal-related events	5.2 [3.9 to 6.7]	176	46

[5] Hanley, J. A.; A. Lippman-Hand (1983). 'If nothing goes wrong, is everything alright?'. *JAMA* 249 (13): 1743–5. doi:10.1001/jama.1983.03330370053031

7.5.2 Comparison of AEs of special interest from the retrospective chart review in patients with RMP-defined risk factors treated with ceftobiprole versus controls of patients without RMP-defined risk factors treated with ceftobiprole

During the data collection for the retrospective chart review, a control group of 180 patients without RMP-defined risk factors who were treated with ceftobiprole will be collected from participating clinical centres for comparison to the 180 patients with RMP-defined risk factors.

A control group describing the use of ceftobiprole in non-RMP risk groups is considered the best choice for the control group because cases describing the use of ceftobiprole in the RMP risk groups vs controls in non-risk groups would provide support for statements in sections 4.4 and 4.8 of the ceftobiprole SmPC regarding the use of ceftobiprole in RMP-defined risk groups, and would complement the comparison from the Phase 3 clinical study experience outlined in Section 7.5.1.

Furthermore, a comparison group of ceftobiprole non-RMP risk patients is best suited to minimising issues of 'matching' baseline conditions of ceftobiprole-treated patients with and without RMP-defined risk factors; a comparison with a control group of patients who received other (non-ceftobiprole) antibacterial treatments would result in more severe limitations regarding the comparability of results, considering that ceftobiprole is currently used as a last-resort drug. This would likely result in substantial heterogeneity, especially if ceftobiprole-treated patients were compared to those treated with antibacterials broadly used for first line therapy.

A sample size of 180 ceftobiprole-treated patients with RMP-defined risk factors and 180 controls of ceftobiprole-treated patients without RMP-defined risk factors would allow detection of a 2.5-fold increase in the proportion of cases versus controls when the AE of interest occurs with a frequency of ≥ 5% in the control group (using a one-sided Z-test at an alpha of 0.05 and a power of >80%).

A sample size of 50 patients in the group of ceftobiprole-treated patients in each RMP-defined risk subgroup (patients with severe renal impairment / ESRD, impaired baseline hepatic function, or immunosuppression) and 180 controls of ceftobiprole-treated controls without RMP-defined risk factors would allow detection of a 3.5-fold increase in the proportion of cases versus controls when the AE of interest occurs with a frequency of ≥ 5% in the control group (using a one-sided Z-test at an alpha of 0.05 and a power of >80%).

7.6 Data management

Data retrieval will be performed by clinically trained reviewers, who will transfer extracted data from the patient charts to the case report form (CRF). Each chart will be independently reviewed by two reviewers. If chart notes are ambiguous or illegible, the two reviewers will consult with each other and resolve the discrepancy or ambiguity by consensus. If necessary, the reviewers may consult with the responsible sponsor contact person to clarify data extraction questions.

All CRFs will be collected and data entered into the clinical database. No source data verification by the sponsor is foreseen. Data management will perform data entry and clean the data. Adverse events, medical history, indication of study treatment will be coded in MedDRA. Drugs will be coded according to the WHO Drug Dictionary.

All queries will be raised and resolved. During data entry, programmatic checking of the data will be performed, and once saved into the database more complex programmatic checks will also be performed. The database will be locked and the data released for summary and analysis after all queries have been resolved, the data analysis plan has been signed and released, and the analysis populations have been approved.

7.7 Data analysis

Raw data will be reviewed and checked for plausibility using statistical and graphical methods. Continuous parameters, especially laboratory data, will be checked for consistent use of units and recalculated as appropriate, in accordance with the Statistical Analysis Plan (SAP). Patterns of missing data will also be investigated by study centre, and important missing data will be indicated for retrieval.

Derived variables will be calculated, especially:

- Inclusion-/exclusion criteria will be checked and the allocation of each patient to the safety set will be documented
- Calendar dates will be transformed to study days, with Day 1 as the start of treatment and Day −1 as the day before.
- Variables for allocation of patients to subgroups/categories will be implemented; for each variable, allocation of patients to categories should be as complete as possible
- Laboratory data will be classified according to reference ranges

The Safety population (defined as patients who received at least one dose of ceftobiprole during the programme) will be used to analyse the safety data.

Basic epidemiological and demographic data will be presented as descriptive summary statistics.

The data will be analysed overall and by the following patient groups/categories :

- Baseline renal function
- Baseline hepatic function
- HIV-positive / CD4 counts
- Baseline neutropenia
- Baseline myelosuppression
- Age groups
- Indications: label and off-label
- Duration (latency) and dose of ceftobiprole therapy

Safety data collected during the study will be summarised using descriptive statistics (number and percentage of patients with AEs overall, by System Organ Class and Preferred Term); for continuous parameters n, arithmetic mean, standard deviation, median, Min and Max will be calculated. Incidence of AEs (including those of special interest) will be estimated, including exact two-sided 95% CIs overall and by the above subgroups. Time to first onset of most frequent treatment-emergent AEs will be analysed using Kaplan-Meier Methods.

The frequencies of AEs of special interest obtained in the PASS from the ceftobiprole-treated patients with RMP-defined risk factors will be displayed with their 95% CIs, and will be compared to the frequencies of the corresponding events in the pooled ceftobiprole pneumonia Phase 3 clinical study database and the control group of ceftobiprole-treated patients without

RMP-defined risk factors in the PASS. Risk ratios and their corresponding 95% CI will be displayed for AESIs comparing ceftobiprole-treated patients in the PASS with RMP-defined risk factors versus the patients from the pooled clinical study database and versus the ceftobiprole-treated control patients in the PASS without RMP-defined risk factors after adjustment for covariates such as age and gender.

Laboratory values for serum sodium, AST, ALT, bilirubin, GGT, AP, creatinine, haemoglobin, HCT, Coombs (DAT) *C. difficile* toxin tests, will be further analysed for differences and trend during and after treatment. Statistical summaries as indicated above will be presented by study period; changes from baseline and shift tables will be presented.

Analysis of secondary study aims will be presented using descriptive statistics including summary statistics on indication, dosage and treatment duration.

For each statistical analysis, all available data for patients in the Safety population will be included; in addition, imputation methods for missing data may be considered dependent on the pattern of missing data.

Summary tables and listings will be reviewed by the sponsor every 3 months to ensure continuous safety monitoring and signal detection process.

7.8 Quality control

Data will be extracted by two clinically trained data reviewers per chart. Reviewers will receive training on at least three sample charts and the data collection tool (CRF). After 10% of the charts have been assessed, an interim review will be performed to verify that necessary data are available in the charts.

7.9 Limitations of the research methods

This retrospective chart review is being performed to generate safety data in patient groups not exposed to ceftobiprole during the clinical study program. It is solely designed to amend existing data on safety. It may generate safety signals or hypotheses on the safety profile of ceftobiprole. Depending on the study results, further research may become necessary to test any hypotheses identified from the chart review.

Potential safety signals obtained from the PASS will undergo further medical review to assess clinical relevance. The requirement for subsequent actions will be determined in accordance with the *Guideline on good pharmacovigilance practices (GVP) – Module IX EMA/827661/2011*.

8 PROTECTION OF HUMAN SUBJECTS

The study will be submitted for review by the responsible IECs of the sites, and Competent Authorities of the participating countries.

The retrospective chart review is based on secondary data. Participation will not have any impact on hospital admission time or clinical procedures for the individual patient. No additional interventions are planned. Extracted data are anonymised, with patient identifiers restricted to year of birth and gender. The sponsor of the chart review will have no access to the personal data of the individual patients. In summary, the well-being and rights of participants is not impacted by the chart review.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events will be summarised in the final study report. Consistent with European GVP modules, adverse reaction reporting is not required for studies based on secondary use of data, such as medical chart reviews. Any new safety information generated while the study is being conducted that may affect the risk-benefit balance of the medicinal product will be reported as an Emerging Safety Issue to competent authorities of the Member States.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be produced within 12 months of the end of data collection, in addition to regular updates of the European RMP and DSUR and PSUR submissions for as long as the study continues.

The original CRFs and all data generated during the study using this study protocol will become the property of the sponsor. Any proposed publication or presentation (including a manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the sponsor for review at least 1 month prior to submission.

No single centre or groups of centres may individually publish data generated during this study using this study protocol.

11 REFERENCES

See footnotes.