EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 February 2020
EMA/136096/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fetcroja

International non-proprietary name: cefiderocol

Procedure No. EMEA/H/C/004829/0000

Note

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

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AmpC	Class C ampicillinase
ARC	augmented renal clearance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AVI	avibactam
BAL	bronchoalveolar lavage
BAT	best available therapy
BCRP	breast cancer resistance protein
CarbNS	carbapenem-nonsusceptible
CAZ	ceftazidime
CFU	colony-forming units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval(s)
C_{max}	maximum plasma concentration
CMA	critical material attributes
(C)PP	(critical) process parameter
CQA	critical quality attributes
CrCl	creatinine clearance
CRE	carbapenem-resistant Enterobacteriaceae
CR Micro-ITT	Carbapenem-Resistant Microbiological Intent-to-treat
CRRT	Continuous renal replacement therapy
CSR	clinical study report
C_{trough}	trough plasm concentration
cUTI	complicated urinary tract infection
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous haemodialysis
CVVHDF	continuous venovenous hemodiafiltration
CYP	cytochrome P450
DDI	drug-drug interaction

ddQTcF	the time-matched placebo- and baseline adjusted QTcF
DSC	Differential Scanning Calorimetry
DSMB	Data Safety Monitoring Board
EA	Early Assessment (visit)
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram/electrocardiography
EEA	European Economic Area
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	End of Treatment (visit)
ESBL	extended spectrum β-lactamase
ESRD	end-stage renal disease
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FMEA	failure mode effect analysis
$fT_{>MIC}$	time above the MIC of free cefiderocol concentrations
FU	Follow-up (visit)
GABA	gamma-aminobutyric acid
GC	gas Chromatography
GCP	Good Clinical Practice
GES	Guiana extended spectrum
HAP	hospital-acquired pneumonia
HCAP	healthcare-associated pneumonia
HD	haemodialysis
HF	hemofiltration
HPLC	high performance liquid chromatography
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
IMP	imipenemase
INR	international normalised ratio

IPC	In-process control
IPM/CS	imipenem/cilastatin
IR	infrared
ITT	intent-to-treat
IV	intravenous(ly)
KPC	*K. pneumoniae* carbapenemase
LDPE	low-density polyethylene
MAA	marketing authorisation application
MATE	multidrug and toxin extrusion
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MIC_{90}	minimum inhibitory concentration at which 90% of isolates are inhibited
Micro-ITT	Microbiological Intent-to-Treat
NDA	new drug application
NDM	New Delhi metallo-β-lactamase
NMR	Nuclear Magnetic Resonance
NOR	normal operating range
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OXA	oxacillinase
PAR	proven acceptable range
PBP3	penicillin-binding protein-3
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PDA	photo diode array
PDE	Permitted Daily Exposure
PER	*Pseudomonas* extended resistant β-lactamase
P-gp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)

PTA	probability of target attainment
q6h	every 6 hours
q8h	every 8 hours
QbD	Quality by Design
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTTP	quality target product profile
RBC	red blood cell
RMP	risk management plan
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TEAE	treatment-emergent adverse event
TOC	Test of Cure (visit)
UTI	urinary tract infection
UV	ultraviolet
VAP	ventilator-associated pneumonia
VIM	Verona integron metallo-β-lactamase
WHO	World Health Organisation
XDR	extensively drug-resistant
XR(P)D	X-Ray (Powder) Diffraction
$\%fT_{>MIC}$	% of the time above the MIC of free concentrations

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shionogi B.V. submitted on 7 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Fetcroja, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 May 2017.

The applicant applied for the following indication:

Fetcroja is indicated for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options (see sections 4.2, 4.4 and 5.1).

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

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P0266/2018 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance cefiderocol contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

Scientific advice

The Applicant received Scientific Advice on the development of cefiderocol to treat infections due to aerobic Gram-negative pathogens in patients with limited treatment options from the CHMP on 15 December 2016 (EMEA/H/SA/3435/1/2016/PED/III) and 18 May 2017 (EMEA/H/SA/3435/2/2017/I and EMEA/H/SA/3435/1/FU/1/2017/II).

The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- Rationale for the designation of the proposed starting materials for the commercial manufacture of the Drug Substance
- The design of the juvenile rat studies to support administration in a paediatric population from premature infants
- The Modelling & simulation approach used to provide age- and weight-based dosing recommendations for cefiderocol in children from birth and above
- The design of the single dose PK, safety and tolerability studies in children from birth and above
- The extrapolation of efficacy from adults to children based on modelling and simulation to demonstrate similar probability of target attainment (PTA) in paediatric subjects compared to adults
- Acceptability of the limited clinical data package (consisting of interim report from the CREDIBLE-CR study, the final APEKs-cUTI trial results, data from six Phase 1 studies and PK/PD) to support a conditional MAA in adults

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	7 March 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	13 December 2018
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	28 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	28 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2019

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 June 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 October 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 November 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 February 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	n/a
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 Fetcroja on	27 February 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Fetcroja is proposed by the Applicant to be indicated for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options.

2.1.2. Epidemiology

The number of infections caused by multidrug-resistant (MDR) bacteria continues to increase and limits the utility of existing antibacterial agents. Data from the US Centre for Disease Control and Prevention (CDC) report more than 2 million cases of infection with resistant bacteria and at least 23,000 associated deaths in the United States every year (CDC 2013). The European Centre for Disease Prevention and Control (ECDC) estimate that nearly 700,000 infections and 33,000 deaths in the EU and European Economic Area (EEA) in 2015 are a consequence of MDR bacterial infection (Cassini et al. 2019). The burden had increased since 2007, was highest among infants and the elderly and was highest in Italy and Greece. Carbapenem-resistance (CR) in *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter* spp. contributed significantly to the number of estimated deaths (in total approximately 9,000 deaths) whereas the numbers of deaths estimated to be caused by

infections caused by CR *Escherichia coli* was lower (~100) reflecting the lower incidence of CR in this species. In 2013 to 2014, the *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillinase-48 (OXA-48) was the most widely disseminated carbapenemases across Europe (Grundmann et al. 2017). Metallo-beta-lactamases such as New-Delhi metallo-betalactamase (NDM) and Verona integron-encoded metallo-β-lactamase (VIM) were detected to a lesser extent.

2.1.3. Aetiology and pathogenesis

Multi drug resistant (MDR) Gram-negative organisms such as CR *P. aeruginosa, Acinetobacter* spp. and Enterobacteriaceae are important pathogens in complicated urinary tract infections (cUTI) including pyelonephritis, complicated intra-abdominal infections (cIAI) and hospital-acquired including ventilator-associated pneumonia (HAP/VAP) i.e. infections that are commonplace but can also be the cause of other types of infections such as wound and surgical site infections. Complicated UTIs are UTIs complicated by involvement of the upper urinary tract (pyelonephritis) or by underlying functional or anatomic abnormalities of the urinary tract. Common uropathogens causing cUTI are *E. coli*, other Enterobacteriaceae and *P. aeruginosa*. Complicated IAI is defined as the extension of an IAI beyond the organ of origin, causing peritonitis or abscess formation. Complicated IAIs are usually polymicrobial in nature and the major pathogens involved are usual residents of the gastrointestinal tract, including Enterobacteriaceae, streptococci, and certain anaerobes (particularly *Bacteroides fragilis*) but *P. aeruginosa* is also commonly encountered. HAP and VAP are by definition infections in hospitalised (or recently hospitalised) patients. Colonisation of the respiratory tract with a variety of Gram-positive and Gram-negative bacteria may lead to infection. Among the most commonly encountered pathogens in HAP/VAP are *Staphylococcus aureus*, Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*.

2.1.4. Clinical presentation, diagnosis

Infections typically caused by Gram-negative organisms (cUTI, cIAI and HAP/VAP) are diagnosed based on clinical presentations and radiologic imaging in addition to microbiological investigations to characterise the pathogens causing the infections.

2.1.5. Management

Beta-lactam antibacterial agents are commonly used to manage infections when they involve Gram-negative pathogens. Increasing resistance to beta-lactams, including the carbapenems, has led to some organisms being effectively untreatable or treatable only with resource to colistin with or without other agents to which they remain at least partly susceptible. Treatment emergent nephrotoxicity is of concern for colistin. Fosfomycin is active against beta-lactamase producing bacterial strains. However, clinical data on the treatment of MDR bacterial infections with fosfomycin are limited. Tigecycline is another option for the treatment of beta-lactam-resistant Gram-negative infections. However, tigecycline is not active against *Pseudomonas* spp. Moreover, safety concerns of an increased risk of death with tigecycline have limited its use. Newer beta-lactam/beta-lactamase (BL/BLI) combinations such as ceftolozane/tazobactam (TOL/TAZ), ceftazidime/avibactam (CAZ/AVI) and meropenem/vaborbactam (MEM/VAB) are possible options for the treatment of some carbapenem resistant Gram-negative organisms but none of them are universal or active against class B (metallo-beta-lactamase) producers. Overall, there is still a high unmet medical need for additional antibacterial agents addressing carbapenem resistance in Gram-negative organisms.

About the product

Fetcroja (cefiderocol) is a novel cephalosporin that like other β-lactam antibacterial agents inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins. Cefiderocol uptake differs from other β-lactams in that cefiderocol binds to ferric iron via its catechol moiety forming a chelating complex which allows cefiderocol to be actively transported into the periplasmic space through siderophore uptake systems.

Fetcroja is proposed by the Applicant to be indicated for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options.

The proposed posology in patients with normal renal function is 2 g q8h administered intravenously over 3 hours. Dosage adjustments are recommended in patients with renal impairment and in patients having augmented renal clearance.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the potential of cefiderocol to address an unmet medical need, as available data at that time point seemed to support activity of the product against Enterobacteriaceae and P. aeruginosa expressing Ambler Class B and/or D enzymes.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as it was clear at D90 that the number of outstanding issues could not have been reasonably addressed within an accelerated procedure.

2.2. Quality aspects

2.2.1. Introduction

The finished product Fetcroja is presented as powder for concentrate for solution for infusion containing 1 g of cefiderocol. The product contains the salt cefiderocol sulfate tosylate.

Other ingredients are: sucrose, sodium chloride, and sodium hydroxide.

The product is available in a 14 mL vial (Type I clear glass vial) with chlorobutyl elastomeric stopper and aluminum seal with a plastic flip-off cap, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of cefiderocol sulfate tosylate is tris[(6*R*,7*R*)-7-[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate] tetrakis(4-methylbenzenesulfonate) monosulfate hydrate corresponding to the molecular formula $3{\cdot}C_{30}H_{34}ClN_7O_{10}S_2{\cdot}4C_7H_8O_3S{\cdot}H_2SO_4{\cdot}xH_2O$. The active substance has a relative molecular mass of 3043.50 g/mol (anhydrous) and the following structure:

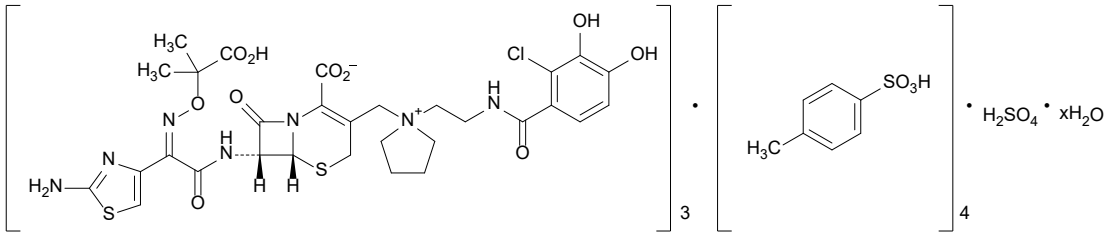


Figure Q.1: active substance structure

The chemical structure of cefiderocol sulfate tosylate, comprising 3 molecules of cefiderocol, 4 molecules of *p*- toluenesulfonic acid, and 1 molecule of sulfuric acid, has been confirmed by elemental analysis, mass spectrometry, IR, ^{1}H and ^{13}C NMR spectra and UV spectroscopy and X-ray powder diffraction (XRPD).

A crystalline form, a pseudo-polymorph and an amorphous form have been identified. The solid-state properties of the active substance were measured by DSC and XRPD and confirm that the crystalline form has been manufactured throughout clinical development and commercial scale batches.

Cefiderocol is a crystalline, light-sensitive, hygroscopic powder which is sensitive towards hydrolysis and slightly soluble in water.

Cefiderocol has two chiral centres and is isolated as a single enantiomer (*R*,*R*).

Manufacture, characterisation and process controls

Cefiderocol tosilate sulfate is synthesized using well defined starting materials with acceptable specifications. The proposed starting materials were defined following the recommendations provided during a scientific advice

For each stage, process schematic (structures, formulae, molecular weights and internal material codes), general process description and simple process narrative and lists of all materials and their stoichiometry, where relevant, are provided. Process parameters (PP), critical process parameters (CPPs,) in-process controls IPCs and their limits and overall yields are clearly defined in the narrative. During the assessment, the applicant provided a comprehensive approach to defining CPPs, including an assessment of the impact on all active substance critical quality attributes (CQAs) Adequate IPCs have been identified for each step. The specifications and control methods for intermediate products, starting materials and reagents have been presented. In the initial application, numerous proven acceptable ranges (PARs) were proposed for the manufacturing process. A major objection was raised due to the lack of supporting data. As a result, the PARs were replaced with normal operating ranges (NORs) in all synthetic steps. The NORs are based on operational variability seen in historical batches. The NORs proposed are accepted.

The risk for mutagenic impurities in the active substance has been assessed. The control strategy ensures that impurities identified as potential mutagenic are kept below the TTCwhich is acceptable. The summary of control strategies for each solvent used in the process is presented and accepted. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. All batches of cefiderocol tosilate sulfate have been manufactured by the same route, however, some process improvements were made throughout development. These have been adequately presented and justified. In the development phase, regulatory starting material was re-designated to intermediate and two new staring materials were designated. Due to this, the GMP synthesis was extended further back.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double low-density polyethylene (LDPE) bags sealed with plastic band ties. The bags are placed into stainless steel drums sealed with a steel lid. The LDPE bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, identification (UV and IR), assay of free base (HPLC), sulfuric acid and p-toluene sulfonic acid (HPLC), related substances (HPLC), residual solvent (GC), water (Ph. Eur.), sulphated ash (Ph. Eur.), endotoxins (Ph. Eur.) and microbial examination (Ph. Eur.).

The acceptance limit for the assay has been set based on the theoretical content of Cefiderocolfree base inCefiderocol tosilate sulfate and an evaluation of the representative batch data, stability results and analytical variation This has been justified by confirming that the mass balance is consistently almost 100% for representative batches ofCefiderocol tosilate sulfate. Stability data at long-term storage condition showed no significant change in assay.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

There are several potential mutagenic compounds identified related to the manufacture ofCefiderocol tosilate sulfate. Some of these are controlled by specifications in starting materials or intermediates (option 3, ICH M7); they have all be shown to be at levels less than 30% of the TTC in an intermediate orCefiderocol tosilate sulfate. Additionally, purging studies have been performed supporting the proposed specification levels

One solvent is controlled by the specificationBased on batch analysis data, supporting the absence of other potential residual solvents manufacturing the proposed control of residual solvents is accepted.

Batch data confirms that the only crystalline form identified for cefiderocol tosilate sulfate is synthesised by the proposed route. Additionally, the active substance is dissolved before it is lyophilised; hence, the absence of a test for the identity of the crystalline form and for particle size is justified.

A specification for optical rotation in the active substance is deemed not required since the only stereoisomer likely to form, is detected by the related substances method and controlled in the active substance specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data () of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from ommercial scale batches of active substance stored in the intended commercial packaging for up to 24 months under long term conditions (−20ºC ± 5ºC) and for up to 6 months under accelerated conditions (5ºC ± 3ºC) according to the ICH guidelines were provided. Due to the redefinition of the starting materials late during development, the batches were not manufactured fully

at the proposed commercial manufacturing site; however, they were manufactured at commercial scale using essentially the proposed manufacturing process. The post approval stability protocol states that the long term and accelerated stability study will be repeated with the first three production batches manufactured by the commercial GMP manufacturing process at the commercial scale and site. This is considered as acceptable. The available provided data are considered representative.

Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions, for up to 4 weeks, and forced degradation studies for up to 4 weeks in the dry state and in the solution phase were also provided. A temperature cycling study to assure the quality of the active substance in repeated freeze-thaw cycles, to simulate storage between use for manufacture of separate batches of the finished product, was performed.

The following parameters were tested: description, related substances, water, assay, sulfuric acid, p-toluenesulfonic acid, identification (IR), bacterial endotoxins, crystalline form (primary stability batches only), microbiological examination. The analytical methods used were the same as for release and were stability indicating. XRPD was used to determine the crystalline form. At long term conditions, a slight increase in the amounts of related substances were observed for the three primary stability batches. However, all tested parameters were within the specifications.

Under accelerated conditions, degradation products increased one specified impurity was out of specification at 3 months and unspecified impurities were out of specification at 6 months. The total related substances content for all batches increased at 6 months. Assay values were slightly lower at 6 months for the primary stability batches; however, in supporting data from process validation batches, they remained unchanged. No significant changes were observed forseveral parameters. The observed out of specification results indicate that the active substance is not stable under accelerated conditions.

Under stress conditions, there was an increase of the same related substances observed following storage at the accelerated stability study condition. A slight decrease in assay was also observed under stress conditions. The levels of one specified impurity and ‘any unspecified impurity’ increased at 4 weeks, respectively. Total related substances increased at 4 weeks. The assay decreased (as cefiderocol on an anhydrous basis) at 4 weeks. No significant changes were observed several parameters.

Under photostability testing, related substances increased and the assay decreased from an initial value (as free base on an anhydrous basis). Two specified impurities impurities increased as well. A slight colour change was observed. No significant changes were observed for the other test items). Based on the photostability studies, although the active substance is sensitive to light, no special handling instructions are needed during the manufacture of the active substance or the subsequent use in the finished product manufacture.

Under solid state stress conditions, a slight colour change was observed with time at all storage conditions. A large increase in related substances, especiallyone specified impurity, was observed due to hydrolysis ofcefiderocol tosilate sulfate. Under solution phase forced degradation storage conditions, no significant changes were observed for clarity, colour of solution and pH. As for related substances, an increase of one specified impurity was observed at all storage conditions due to hydrolysis of cefiderocol tosilate sulfate. Other related substances which increased significantly under each storage condition have been described.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable under long term conditions. The stability results justify the proposed retest period at the following conditions: “Keep the sealed LDPE bags in the stainless steel drum and store in a freezer below −15°C”.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Fetcroja (cefiderocol) 1 g powder for concentrate for solution for infusionl, is a sterile, white to off-white, lyophilised cake or powder containing 1 g of Cefiderocol packaged in a single-use, 14 mL Type I clear glass vial. The qualitative composition of cefiderocol powder for concentrate for solution for infusion has been provided.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Sterile filtration (aseptic processing) has been selected as the sterilisation method. This is in accordance with the decision tree for sterilisation choices for non-aqueous liquid, semi-solid or dry powder products in CPMP/QWP/054/98 and is considered acceptable.

The manufacturing process for cefiderocol finished product consists of the following unit operations: bulk solution preparation, sterile filtration, aseptic vial filling, lyophilisation and sealing. The operating units remained unchanged during the pharmaceutical development of the product.

The formulation and manufacturing development have been evaluated through the use of risk assessment, The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development and scale up studies. The potential critical material attributes (CMAs) and CPPs and the impact of their variability on finished product quality were further studied via experiments designed to understand the process and control the risks to acceptable levels. A second risk assessment was conducted, after the experimental studies, to confirm the CMAs and CPPs and to determine the operating ranges of material attributes of input materials. The process parameters were also investigated for each of the following process steps: bulk solution preparation, vial filling and lyophilisation. As a result, effective control strategies were developed to minimize the risks to acceptable levels.

Cefiderocol 1 g powder for concentrate for solution for infusion, is supplied as a sterile, lyophilised cake or powder, which must be reconstituted and subsequently diluted, under aseptic conditions, prior to intravenous infusion. To achieve the recommended dosage of 2 g cefiderocol per dose, two vials containing 1 g of cefiderocol are each reconstituted with 10 mL of commercially available 0.9% sodium chloride injection or 5% dextrose injection, taken from an infusion bag containing 100 mL. The final volume of each reconstituted solution in the vial will be approximately 11.2 mL. The resulting solution from each vial is transferred back into the same infusion bag within 60 minutes to achieve a final volume of at least 100 mL and dosing concentration of 20 mg/mL.

A study performed to determine extractable content using a 10 mL syringe with a 21 gauge needle confirmed that the extractable content is adequate. Parenteral finished product solutions should preferably have a pH in the physiological range. However, the tolerated pH range is broader for larger volumes given intravenously. Hence, in view of the solubility of the active substance, the pH range of 5.2 to 5.8 for the reconstituted solution is considered acceptable. The osmotic value of the infusion solution (572 mOsm) is in the physiological range, to avoid irritation at the site of injection. The compatibility of the finished product with 0.9% sodium chloride injection or 5% dextrose injection was demonstrated in the infusion bag, in the reconstituted vial, and in a representative infusion set; this is considered acceptable.

The primary packaging is Type I clear glass vial chlorobutyl elastomeric stopper, and aluminum seal with a plastic flip-off cap. The material complies with Ph.Eur. and EC requirements. The vials are packaged in

an outer (secondary) cardboard carton to protect from light. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: bulk solution preparation by compounding the excipients and active substance; sterile filtrationaseptic vial filling, lyophilisation and sealing. The process is considered a non-standard manufacturing process as it involves sterile filtration and aseptic. Major steps of the manufacturing process have been validated by a number of studies. The specification results complied with the release specification criteria. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual assessment), identification (HPLC/PDA), assay (HPLC), clarity and colour of the solution (visual assessment), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), particulate contamination (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), pH (potentiometry), water (Ph. Eur.) and reconstitution time (visual assessment).

During the review of the application it was confirmed that none of the identified degradation products are mutagenic. Additionally, the proposed limits for degradation above the ICH qualification threshold have been supported by batch and toxicological data.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on batches manufactured at pilot scale (representative of the commercial process) were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

The potential risk of nitrosamines was assessed. The risk of the presence of nitrosamine in the finished product is considered negligible.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented, as described in the active substance section.

Batch analysis results are provided for full scale process validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from primary pilot scale batches of finished product stored for up to 36 months under long term conditions (5 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same tests as the release specification, with the exclusion of identity and uniformity of dosage units; this is acceptable as they are not affected by stability

No significant changes were observed in any of the monitored parameters in the stability program. However, increasing trends in the content of degradation products were observed. In addition, a slight

decrease in assay, when stored under the accelerated storage condition for 6 months was observed. However, all the results were within the proposed specification limits.

Primary stability studies at accelerated and long-term storage conditions were conducted with vials in an inverted orientation and confirm absence of leachables from the rubber stoppers in the finished product impurity profiles.

In addition, one batch of the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and onebatch was exposed to temperature cycling. The content of degradation products increased. No significant change was observed in any other test attributes. In the control samples covered with aluminium foil, no significant change was observed in any test attributes. The results of the photostability testing indicate that the finished product is susceptible to decomposition when exposed to light; therefore, light-protective packaging and a precautionary labelling statement are required, as reflected in the SmPC. The data provided show that temperature cycling and repeated freeze-thaw does not have an adverse impact on the finished product.

When the finished product was stored under the solid state forced degradation storage conditions of high temperature and humiditythe major degradation product was a specified impurity. In solution, the finished product was labile to all forced degradation storage conditions (acidic, alkaline and oxidative).

Based on available stability data, the proposed shelf-life of 3 years and the proposed storage conditions "Store in a refrigerator (2 to 8°C). Store in the original carton in order to protect from light" as stated in the SmPC (section 6.3) are acceptable.

In-use solution stability study, samples taken from the primary stability batches, which are stored in the long-term stability study were used to assess the impact of aged samples on in-use stability. The in-use solution stability studies of the reconstituted product in the vial and in the infusion polyolefin bags containing 0.9% sodium chloride injection or 5% dextrose injection stored at 25°C/60%RH under fluorescent light for 6 hours (simulating administration conditions), or at 5°C protected from light for 24 hours followed by subsequent storage at 25°C /60% RH for 6 hours under fluorescent light, did not meet the shelf life acceptance criterion and the unspecified degradation product increased above the qualification threshold. However, the levels of degradation products observed in the in-use stability studies (considering both infusion bag and reconstituted vial) have been qualified based on toxicology data. No significant changes were observed in any of the other parameters studied. Additionally, the results of microbial challenge testing for reconstituted solutions, stored under the same conditions described above, support the recommended in-use shelf-life and storage conditions for the reconstituted solutions of the finished product stored in infusion bags.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The choice of the pharmaceutical form and sterilization method has been adequately justified based on the instability of the active substance in solution and its susceptibility to light and heat. The applicant resolved a major objection by replacing the proposed PARs with NORs, the control strategy was also further substantiated during the review. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary and secondary pharmacodynamic studies

The Applicant has conducted in vitro and in vivo studies to address the primary pharmacodynamics of cefiderocol, which have been presented and assessed in conjunction with the clinical data (see clinical aspects). A standard secondary pharmacology screen for the ability of cefiderocol to bind a panel of receptors, ion channels, transporters and enzymes was performed using a single concentration 100 μM. The concentration tested is relatively low and is only 1.3-fold the unbound C_{max} level seen with the proposed clinical dose. No significant effects were seen at the measured levels, with the highest level of inhibition seen with cathepsin G at 24%. The applicant has indicated, based on these findings, that cefiderocol would not cause adverse effects through the receptors, channels, transports or enzymes evaluated in this study. However, this statement was not fully supported by CHMP, considering the low concentration tested and the applicant was asked to justify the concentration of cefiderocol used for the secondary pharmacology screen, also in the context of the convulsions seen in the repeat dose toxicity studies in rats**.** In its response, the Applicant maintained the position that 100 μM was a sufficiently high concentration for the secondary pharmacology screen as this was 1.3-fold of the maximum unbound concentration in human plasma. However, the reported clinical Cmax is a geometric mean and some patients will have Cmax levels greater than the 100 μmol/L which was used in the secondary pharmacology screen. CHMP was therefore unable to conclude whether the concentration was adequate to evaluate the secondary effects.

The Applicant further suggested that while the cefiderocol sodium drug product did not show inhibitory effect against GABA receptor at 100 μmol/L, the mechanism of proconvulsive effects of cefiderocol is still likely to be related to the inhibition of γ-aminobutyric acid (GABA) receptor binding, which is generally assumed as a mechanism of the convulsion induced by the known β-lactam antibiotics. Indeed, as evidenced from the estimated brain exposure in the rats in the repeat dose studies in which convulsions were observed, it appears unlikely that an inhibitory effect on the GABA receptor is the mechanism behind the observed convulsions. However, CHMP acknowledged that the screen did not show any significant signal for inhibition of specific binding to the measured targeted molecules. Whilst using a higher concentration of the drug in the secondary pharmacology screen would seem to have been more appropriate, taking into account the absence of secondary pharmacology targets identified in the already conducted screen and the clinical safety profile to date, CHMP agreed that the issue did not need to be further pursued.

Safety pharmacology programme

In a functional GLP compliant observational study in rats, prone positions were observed in single animals at 500 mg/kg and 1000 mg/kg, indicative of sedative effects. In the 1000 mg/kg group, one animal showed decreased motor activity and decreased mean rectal temperature (-1° C). These minor findings suggest that cefiderocol may exhibit some inhibitory effects on CNS at high exposures, since all these findings were normalized within 0.5 hours in parallel with a decrease in plasma concentration of cefiderocol. No TK analysis was performed and hence not possible to estimate any exposure margins. However, no related findings such as sedation or hypothermia were noted in the repeat toxicity rat studies (with same doses - see toxicology 3.2.3). Moreover, these CNS adverse effects were not reported in the clinical studies (CTD 2.7.4.2), and hence is not considered as a potential risk in humans.

Effects of cefiderocol on respiratory function were investigated in a GLP compliant study in male SD rats (250 – 1000 mg/kg) and it was concluded that cefiderocol did not induce any effects on respiratory parameters.

Cardiovascular effects of cefiderocol were evaluated in vitro and in vivo. In vitro it was concluded that cefiderocol exert minor effects on the myocardial potential in papillary muscles isolated from guinea pigs at 1.5 mg/mL. Increases (< + 10%) in action potential duration at 90 and 30% of repolarization (APD90 and APD30) were observed. The study conducted in HEK293 cells stably expressing hERG channels, indicate a dose related suppression of hERG, being 12 % at the highest dose (1.5 mg/mL) and hence an IC50 > 1.5 mg/mL. From the in vitro studies it can be concluded that cefiderocol has minor effects on the myocardial action potential and hERG at 1.5 mg/mL, which is 27-fold the free Cmax value in humans (56 ug/mL).

In monkeys administered with 100 mg/kg and 300 mg/kg no effects on any CV parameters were observed, whereas after administration of 1000 mg/kg the blood pressure increased in all treated monkeys. An increase in both systolic (+32 mmHg) and diastolic (+21 mmHg) pressures was noted and both returned to baseline values after 4 hours. Moreover, at 1000 mg/kg prolongations of QT intervals and QTc were identified. The QTc increase reached a max 0.5 h directly after administration (+34%) which returned to vehicle levels 2 hours post dosing. The serum cefiderocol concentrations (Cmax) at 1000 mg/kg give an exposure margins of 24-fold, whereas 300 mg where no QTs prolongations were observed corresponds to an exposure margin of 8-fold. The prolongation of QTc have also been observed in repeat toxicity studies of monkeys (see toxicology assessment). A thorough QT/QTc study conducted in humans (a sub-population in study R2116), no clinically changes in cardiovascular functions (including QT-prolongation) were seen when supra-therapeutic dosing (4g), corresponding to Cmax of 183 ug/mL was administered, and conclusively QT prolongation is considered not to be of any clinical concern.

Other clinically observations throughout the monkey telemetry study include vomiting, stretching and chromaturia. The latter was found in all four monkeys at all doses.

Follow up studies (CNS)

Convulsions were observed in the 3 months repeat toxicity study in rats (S-649266-TF-224-L), and two animals died due to the convulsions. Considering these adverse findings, the Applicant conducted two follow up safety in vivo studies in mice and rats, respectively. In mice, the proconvulsive effects of cefiderocol was compared to four reference substances i.e. cefazolin (CEZ), cefepime (CFPM), ceftazidime (CAZ) and imipenem (IMP), all B-lactam antibiotics. The results showed that the potency of the proconvulsive effect was weaker for cefiderocol than that of IPM, and similar to those of CEZ and CFPM and stronger than CAZ. In the rat study EEG analysis and behaviour observations were done to assess the convulsive effect of cefiderocol and the combination of IPM and cilastatin (CS). Single

dosing of 500 mg/kg and 750 mg/kg caused no EEG signs and no convulsions whereas in the IPM/CS treated rats (dose of 400/400 mg/kg) spike and slow wave complexes were found, together with convulsions in 3 of 6 animals.

According to TK determination in the 3 months toxicity study, the NOAEL (no convulsions) corresponds to an exposure margin of 11-fold (based on C0 of 1280 ug/mL in males). It is known that B-lactam antibiotics cause convulsions in experimental animals and also occasionally reported as an adverse reaction in clinical use. The convulsive potential of B-lactam antibiotics is believed to be related to an inhibitory effect against GABA receptors at high doses. But no binding to GABA receptors were detected in the secondary pharmacodynamic in vitro study using doses up to 100 umol/L (75.2 ug/mL) which is in same concentration range as in humans (Cmax of unbound cefiderocol 55 ug/mL), indicating that supra-therapeutic exposure is needed. In SmPC 4.4 a warning for convulsion is present (in line with all classes of cephalosporins). CHMP agreed that from a non-clinical point of new no further action is considered necessary.

2.3.2. Pharmacokinetics

Methods of analysis

Cefiderocol was quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma of rat, monkey and mouse. From a regulatory perspective, the validation of the analytical methods used in the pivotal toxicity studies should be of GLP-standard, which appears not to be the case for cefiderocol (a signed GLP-statement in the bioanalytical validation reports are missing). The only TK study of cefiderocol conducted with a GLP compliant analysis is the juvenile toxicity study. The Applicant was asked by CHMP to justify the reliability of these bioanalytical assays with respect to deviation from the GLP requirements and to discuss the potential impact on the resulting TK/PK analysis. In its response, the Applicant clarified that while the bioanalytical studies were not performed according to GLP standards, they were still performed with procedures used in GLP facilities with enclosed statements. Even though the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) states that all the bioassays should be conducted with GLP validated methods, CHMP agreed that the high-quality standards of the bioanalytical methods used here can be considered adequate for the non-clinical analyses. The issue was therefore not further pursued.

Absorption

After single intravenous dose of cefiderocol a dose-linearity was found in both rats and monkeys at the doses tested i.e. 10 to 100 mg/kg. The same PK was also seen in humans at doses 100 mg to 4000 mg. The total clearance following single intravenous dose of cefiderocol was higher in rats (522 ml/hr/kg) than in monkeys (153 mL/hr/kg). The half-life of cefiderocol in rats, monkeys and humans are 0.4, 1.2 and 2-3 hours, respectively.

Distribution

Binding to plasma proteins were studied in vitro and the protein binding ratio was higher in humans (60 %) than in rodents (mice 39%, and rats 52 %), monkey being the species with most similar protein binding grade as humans (62 %). In humans, Cefiderocol binds predominantly to HAS. Notably, at the highest concentration tested (1000 ug/mL) the albumins may be saturated since the bound fraction constitute 40 % of cefiderocol in humans. The same trend is observed in rats, mice and monkeys, i.e. lower percentage of bound cefiderocol at higher doses.

Tissue distribution of 14C-cefiderocol derived radioactivity was investigated using QWBA in both albino and pigmented rats administered i.v with a single dose. Two different radio-labelled preparations of cefiderocol were used for the single dose studies, either labelled at the thiazole ring or at the catechol

moiety. This strategy was used in order to monitor both cefiderocol degradation products ATAA and PCBA. Both the thiazine and catechol radio-labelled variants were rapidly and widely distributed in the whole body with similar distribution patterns. Regardless of radiolabelled position, the radioactivity was higher in kidneys than in plasma being highest in the kidney cortex and medulla. After 120 h both thiazine- and catechol derived radioactivity remained detectable in the kidneys, whereas thiazole derived radioactivity remained detectible also at 336 h post-dose.

Because the elimination of radioactivity from thiazole-14C cefiderocol was slower than catechol-14C-cefiderocol, the former was used in the 14 days repeat-dose distribution study. Radioactivity was observed in all tissues and reached a steady state within 14 days in many of the tissues. But a few tissues including kidneys cortex, adrenals, blood, and thyroid, a steady state was not reached after 14 days daily administration. In the study report a half-life in kidney cortex of 168-840 hours was estimated. The concentrations of radioactivity associated with the kidney and urinary bladder suggested renal excretion as a main route. Radioactivity in the bile ducts, and GI tract suggested some elimination via biliary secretion.

Radioactivity after single dose administration of both catechol-14C- and thiazole-14C cefiderocol were observed in the brain but at very low concentrations and BLQ after 6 and 24 h, respectively. After two weeks administration of thiazole-14C cefiderocol, radioactivity was detected at low levels in the brain. These data indicate low brain penetration in the rat.

Pigmented and albino rats showed similar tissue distributions including similar distribution to melatonin rich tissues and with a similar elimination rate – suggesting that binding to melanin is negligible.

In pregnant rats, a minor placenta crossing of cefiderocol was observed which is accordingly stated in SmPC 4.6. In the foetus's low concentrations were detected in kidneys, blood, brain that was not detected 24 h post dose. It is not known to what extent the foetuses are exposed to the degradation product PCBA and its conjugated metabolites (since only thiazol-14C-cefiderocol was used in the distribution study of pregnant rats). But considering that these are minor metabolites, and the absence of foetal toxicity such study is not warranted.

Metabolism

The in vitro metabolism profiling study was conducted with catechol-14C cefiderocol in liver hepatocytes from human, rats, monkeys, mouse and rabbits. All degradation and metabolic products identified were minor and all metabolites identified in humans were also abundant in any of the other species tested. The in vivo metabolism studies in rats and monkeys unchanged cefiderocol was mainly found (34-39% of the administered radioactivity). Also PCBA was detected in plasma and urine (1.3-2.6% of the administered radioactivity). In both rats and monkeys, around 15-19% of administered radioactivity was detected as unknown metabolites/degradation products (for example ATAA) whereas in humans, the presence of radioactivity from unknown metabolites were negligible. Since all of the metabolites were found at < 10% based on the total radioactivity AUC in plasma in humans (see clinical pharmacokinetic AR) the Applicant judged that no further safety assessment for the metabolites are needed, which was agreed upon by CHMP. It was noted that all the minor metabolites/degradation products formed in rats and monkeys are covered for in the toxicity studies.

Elimination

Urinary excretion appears to be the main elimination pathway in rat and monkeys (as well has humans), i.e. more than 90% of radioactive catechol-14C cefiderocol are detected in urine. Most of the radioactive excreted in urine were unchanged cefiderocol. In addition, metabolites were found in low levels in the urine. In faces, a minor elimination route for cefiderocol, PCBA was the main metabolite detected.

Cefiderocol was excreted in the milk of rats administered with a single dose of [thizole-14C-]-cefiderocol, and the radioactivity in milk decreased slowly post-dose.

2.3.3. Toxicology

A comprehensive set of non-clinical studies to evaluate the toxicity of cefiderocol sodium has been completed in accordance with the ICH M3 (R2) guideline. All pivotal studies have been performed in accordance with the GLP regulations. In these studies, and unless otherwise stated, the dose levels are expressed as cefiderocol.

The substance has been evaluated with the active substance administered by the intravenous route in Sprague-Dawley rats and Cynomolgus monkeys. There is no justification for the use of these species in the studies; the Applicant only states that these species are "standard species for evaluation of toxicity in animals". While this is true, the use of Cynomolgus monkey should be reserved to situations where this species is the only relevant species. Given that this is an antibiotic, it is possible that other species would have been equally useful, despite the fact that intravenously administered antibiotics have traditionally been evaluated in cynomolgus monkey.

New Zealand White rabbit was the species of choice for the EFD study. However, due to excessive toxicity (body weight loss and GI-intolerability) and moribundity/euthanasia in the DRF-study, it was concluded that this species was unsuitable. GI intolerability is considered well-known in rabbits exposed to high doses of antibiotics, as the antibiotic sensitive enterobacterial microflora is critical to rabbit digestion. The Applicant decided to use an additional rodent model (CD-1 mouse) and subcutaneous administration instead of intravenously administered rabbits, because repeated-dosing with intravenous administration in mice is not feasible. Advantages and disadvantages of the selected species were considered in relation to the specific substance with regards to study designs, administration routes, interpretability of the results etc. The Applicant was asked to justify the use of cynomolgus monkey in the general toxicology program and explain the rational for using the CD-1 mouse in the EFD study. In the response, the Applicant explained that in exploratory single-dose studies in dog, vomiting was observed several times from during dosing to 1 hour after the end of dosing at 1000 mg/kg, reason for which the Applicant considered that dogs would not tolerate repeat-dosing at the 1000 mg/kg dose level. While this consideration is supported, it is not clear why cynomolgus monkey was considered as the only alternative. CHMP agreed however that since the studies had already been completed in the monkey, this would not be further pursued.

Regarding the animal model use in the EFD studies it was clear that the rabbit was not suitable and, as pointed out by the Applicant, GI intolerability is considered well-known in rabbits exposed to high doses of antibiotics. The antibiotic sensitive enterobacterial microflora is critical to rabbit digestion why excessive toxicity (including weight-loss and GI intolerability) and moribundity/euthanasia was evident in the DRF-study. The mouse model is well-characterized and a relevant species for EFD-studies, and often serves as a substitute for the rat as a rodent model. In addition, the mouse model could be dosed such that sufficient exposure level was reached. Overall the justifications for the species use in the general toxicology and EFD studies is considered acceptable.

Single dose toxicity

One single-dose study in rats at receiving cefiderocol sodium at doses of 2000 mg/kg q.d or 1000mg/kg b.i.d was performed in mice. 5/8 animals in the q.d. group died from convulsions and abnormal respiration with no acute symptoms noted in the b.i.d.-group. The Cmax in the q.d. group was about twice as high as in the b.i.d. group, why it was suspected that the effect may be Cmax-driven. In any case, 2000mg/kg was clearly above MTD.

Repeat dose toxicity

Repeated-dose toxicity has been evaluated in Sprague-Dawley rat and Cynomolgus monkey in studies of up to three months duration in both species. The study findings were similar across studies from 2-weeks up to three months, with no new adverse toxicity emerging in the longer studies. This was considered reassuring by CHMP. While the toxicity profile of the product is likely manageable for the intended indication, there are toxicity findings in the studies that are of particular focus. Important such findings include convulsions noted in rats for which no likely mechanism has been presented by the Applicant and QTc-prolongation. Additional findings that have been recurring in the studies include injection site toxicity, low RBCs, hyaline droplets in the kidneys and dilatation of the cecum. Further analyses of the findings including a discussion on their potential clinical relevance are included below.

Mortalities

Mortalities were noted in the rat, both in the DRF-studies (2000mg/kg/day) and also in the 3-month study (10 main study animals and 10 TK animals administered doses at and above 1000mg/kg/day). Based on the data presented, it appears that all deaths were related to convulsions and abnormal respiration. The convulsion findings are further discussed below. In the 3-month GLP-study in monkey, one female at 1000mg/kg/day was terminated due to excoriation on one of the tail injections sites which was supported by necropsy findings. The death is considered attributed to the infusion of cefiderocol sodium.

Convulsions

Convulsions related to dosing were noted in the rat at doses from 1000mg/kg/day and above. In the 3-month study, they started during dosing or within 16 minutes of completion of dosing between SD 2-91. The relation to the actual dosing indicates that there may be a relation of the convulsion to the Cmax of cefiderocol. Convulsions were also evident in the single-dose studies at 2000mg/kg and in the in vivo micronucleus test where 3 animals died from convulsions at 2000mg/kg/day. In that study, a decrease in locomotor activity and convulsion were observed in animals early after each administration. However, while similar doses (at or above 1000mg/kg/day) were used in the shorter general toxicology studies, no such findings were reported from the 2-week and 1-month studies. The reason for this variability in results between studies is unclear, and as no TK-data are available from the shorter studies (or the micronucleus study) we cannot find support in plasma concentration data. The Applicant was asked to further discuss these issues. In the response, the applicant suggested that the differences seen are likely due to the systemic exposure achieved at 1000 and 1500 mg/kg being close to the threshold for which convulsions can occur. Due to the variability between animals, some of the animals at the 1000 or 1500 mg/kg may have passed this threshold and experienced convulsions. Furthermore, it is argued that the incidence of convulsions was low in the 3-month study and considering it had greater animals per group, overall there is not significant differences in the proconvulsive liability between the 1- and 3-month repeat-dose toxicity studies. Based on the totality of the data, CHMP agreed that these arguments can be deemed reasonable. It is accepted that the risk of convulsions for patients at the clinical dose is low.

Based on the convulsions noted in at 1000mg/kg/day, the NOAEL for the 3-month rat study was set at 300mg/kg/day. To evaluate more in depth the dose-response relationship of convulsions between 300 and 1000 mg/kg/day, a follow-up study was undertaken by the Applicant where the intermediate dose levels 500 and 750 mg/kg/day were used. In that study, no convulsions were noted up to 750mg/kg/day which was then the NOAEL in the study. According to the Applicants summary-document, the NOAEL was set to 750 "in terms of assessment of electroencephalogram and behaviour". However, the study report does not mention either behaviour (except cage-side observation) or electroencephalograms why the basis for this justification is unclear or even erroneous.

Given the intra-study differences in convulsions, it would have been useful with animals at a pro-convulsive dose-level (as a study positive control and for TK-level reasons) as no convulsions were noted at either dose-level in this study. On the other hand, CHMP agreed that the decision to not include animals in such a dose-group is acceptable from the 3R perspective.

Comparing TK-data from the 3-month study and the supplemental 3-month study show that the serum levels of cefiderocol show a dose-proportional pattern in both studies, and that the 500 and 750mg/kg/day dose groups in the supplemental study were exposed to the expected cefiderocol levels.

The Cmax-levels at the NOAEL (750mg/kg/day corresponding to plasma cefiderocol levels of 1500 or 1610 µg/ml) correspond to an exposure margin of 13 to clinical exposure at the intended dosing regimen. No convulsions were evident in the monkey studies, despite cefiderocol serum concentrations in the 3-month study up to 22-fold the human clinical Cmax-value.

It was noted that, despite the lack of convulsions in the monkey studies at doses up to 22-fold the human clinical concentration, the findings noted in the rat studies were not fully reassuring, as no mechanism for the effect has been suggested, and margin to human exposure for this potentially lethal effect is modest.

Injection-site effects

Injection-site effects were common in the studies as cefiderocol sodium was administered by the intravenous route. In rats, blackening, loss, trauma, crust, and/or scar of injection site supported by histopathologic gross lesion findings up to serious grade was a relatively common finding throughout the repeated-dose studies in rats. In monkey, red foci in the subcutaneous tissue at the injection sites were observed across all groups including controls in studies from 2 weeks duration and longer. In the 3-month study, one 1000mg/kg/day female was terminated early due to excoriation on one of the tail injections sites why dosing could not be continued due to loss of vessel patency at all injection sites. Other HD animals did also display injection site thrombus with thickening vascular intima sometimes accompanied by very slight or slight chronic inflammation. It is thus clear that the substance causes irritation effects during administration, even if the irritation effect at 300 is considered slight with only one affected animal. It should however, be noted that in monkeys, irritation to the vein was observed mainly at 1000 mg/kg/day (the concentration of cefiderocol in dosing formulation: 50 mg/mL), slight irritation was observed at 300 mg/kg/day (15 mg/mL) at a low incidence, and no irritation was detected at 100 mg/kg/day (5 mg/mL) after 3-month dosing. Thus, it seems that the actual concentration of the solution is important and comparing the concentration of dosing formulation planned for clinical use (20 mg/mL or less) and the concentration of 15 mg/mL which caused only slight irritation in monkey, it is not considered likely that this will represent an important clinical toxicity. Also, only mild-moderate injection site effects have been reported from the clinical studies, further supporting this position.

QTc Prolongation

QTc prolongation was observed in all studies in monkey at doses of 600 and/or 1000mg/kg/day. This effect apparently increased in magnitude with dosing time, as the effect was most pronounced (up to 27% on SD 85 compared to pre-dosing values) in the 3-month study, whereas increases of 10-15% were noted in the 1-month and 2-week studies. However, there was no or only marginal increase from SD 49 to SD 85 in the 3-month study, suggesting that the effect would not increase further with even longer dosing. QTc-prolongation was also noted in the safety-pharmacology evaluation of cefiderocol sodium at 1000mg/kg using the same dosing-regime (1h infusion at 20ml/kg). There, the QTc values reached the maximum levels 0.25 hours post dose compared to the mean value in the vehicle control group (19% increase compared to control and 34% increase compared to predosing values). The QTc values returned to control levels up to 2 hours post dose (except for one animal, which recovered by

24 hours post dose). The exposure margin for the NOAEL for QTc-prolongation in the 3-month study (300mg/kg/day) compared to clinical exposure is around 7. It should however be noted that no cardiac arrythmias were observed throughout the study. Further, a clinical thorough QT study (at supra therapeutic dosing) did not find evidence for QTc prolongation.

Hyaline droplets in the kidney

Hyaline droplets were evident in the proximal tubules of the kidney in all the repeat-dose toxicity studies in rats and monkeys at all dose levels between 100 and 1500 mg/kg/day. The Applicant describes that it has been reported that hyaline droplets in the proximal tubules are observed in animals administered cephalosporin antibiotics and the change is associated with absorption and secretion of these compounds in lysosome. Thus, the finding should then reflect reabsorption or excretion of cefiderocol in the proximal tubules. However, no data have been provided to support that the droplets are indicative of cefiderocol absorption/excretion. Further kidney findings in the 1-month study in monkey include increased kidney weights from 600mg/kg/day and increased protein urine concentration at 1000mg/kg/day. In the 3-month study in monkey, the hyaline droplet effect was still graded very slight-slight, but increases were seen in kidney weights and serum creatinine from 300mg/kg/day. Increased urine protein is reported in animals exposed to cefiderocol sodium at 1000mg/kg/day. CHMP agreed that it was evident from the data that cefiderocol sodium exposure at clinically relevant doses have effects on kidney weights, physiological function (evidenced from serum and urine biomarkers) and deposition of hyaline droplets. Because of the minimal grade also at the HD in the longest studies and the lack of degeneration/necrosis and regeneration of tubule epithelial cells this has not been considered an adverse effect in any study.

Dilatation of the cecum

Cecal dilatation was observed in all repeated-dose toxicity studies in the rat and at all dose levels from 300 to 1500 mg/kg/day. The findings were often associated with atrophy of the mucosa or hypertrophy of the mucosal epithelium. The effect was time- and dose-related but was not graded as more than slight and with no evidence of necrosis of the mucosal epithelium in any study. This effect of antibiotics is considered well-known and is related to the antibacterial effect of the antibiotic on the enterobacterial flora. Similar (but dramatically increased) effects were evident in rabbits treated with cefiderocol in the preliminary EFD-study. No cecum dilatation effects were noted in the studies in monkey, and in the clinical studies performed with cefiderocol to date there have been no clear reports on abdominal/intestinal adversities. Thus, there is no data to support that this effect is relevant for humans exposed to clinical doses of cefiderocol.

Effects on blood parameters

Effects on erythrocytes, haematocrit, and haemoglobin were evident in the cynomolgus studies from 300mg/kg/day in the 3-month study and 1000mg/kg/day in the 1-month study. Increases in reticulocyte count and/or hyperplasia in the femoral or sternal bone marrow were also observed. The Latter changes were considered to be a hematopoietic response to the decreased erythrocyte parameters. Similar effects on red blood cell parameters, but to a lesser extent was found in rats. No haemorrhagic lesions (except for the injured injection site due to local irritation in rats) have been identified in the studies and no evidence of haemolysis either. In a separate haemolysis assay, there were no data supporting haemolytic effects of cefiderocol sodium presented. Thus, the mechanism(s) underlying the decrease in red blood-cell parameters is (are) not clear.

Interestingly, throughout the study program, abnormal urine colour was observed in both sexes in all test article groups throughout the dosing period. The coloured urine showed positive occult blood reaction by urinary test paper and the frequency of the positive occult blood reaction was mostly dose related. However, erythrocytes were not observed in coloured urine and no haemorrhage was observed

in the urinary tract in histopathology. In addition, no data suggestive of severe haemolysis leading to such urine colour was observed, or no corresponding changes related to myolysis were observed in blood chemistry or histopathology.

To further evaluate the coloured urine, two separate studies were performed where effects of inorganic ions (Fe, Mg, Ca, Zn) on the coloration of cefiderocol sodium solutions were analysed, and also to test different cefiderocol solutions in an assay with urinary test paper. The conclusions of these analyses were that cefiderocol solutions form a complex with ferric ions which under basic conditions which results in a reddish solution colour. In addition, cefiderocol sodium affected the urinary test paper analysis and therefore urine which contains cefiderocol might cause false positive results depending on its concentration or urinary ph. Thus, while coloured urine and erythrocyte loss seems possible correlated, it seems that the coloured urine is artefactual and not related.

It should however be noted that the margins to clinical exposure from NOAEL (100mg/kg/day in the 3-month monkey study) is only 3-fold and 0.3-fold of the Cmax and AUC-values in humans respectively. Given no clear mechanism or reasonable explanation to the findings and that we have no reason to believe that this effect would not be present in human, anaemia is a potential adversity that may be become present in humans. However, so far no clinical study data have identified this effect in humans.

Genotoxicity

Based on a bacterial reverse mutation test (Ames test) using five tester strains (Salmonella typhimurium TA98, TA100, TA1535 and TA1537, and Escherichia coli WP2uvrA) it was concluded that cefiderocol has no potential to induce gene mutations.

However, in a chromosomal aberration test that was performed in a human lymphoblast cell line (TK6), significant increases in the incidence of cells with structural chromosomal aberrations were found in the 24-hour assay, suggesting that cefiderocol has the potential to induce structural chromosomal aberrations.

In addition, a positive response was noted In the Mouse lymphoma assay (MLA). The MLA can be used to evaluate potential of the cefiderocol sodium drug product to induce both gene mutation and chromosomal aberration as a wide variety of mutagenic events can lead to TFT resistance, including small mutations within the tk1 gene (genetic mutations), larger clastogenic chromosomal events within and beyond the tk1 gene. Mutant clones can have slow or more wild-type growth rates. The difference in mutant clone growth has been attributed to different mechanisms of DNA damage where chromosomal mutations extending beyond the TK gene produce small slow-growing mutant clones, and intragenic mutations produce large wild-type growing clones. The increase in MF at 400 µg/mL in the 24-hour continuous treatment was considered by the Applicant to be chromosomal aberration-related under highly cytotoxic condition rather than due to point mutations since the percentage of small colonies, at 400 µg/mL (55.3%) was higher than that of the concurrent negative control values (38.8%), and the relative total growth rate at this dose level (22.0%) was close to the limit of evaluation due to cytotoxicity (20% of growth rate).

However, because it has also been shown that small mutants can result from other mechanisms, mutant colony size should be used only as an indicator and not as a definitive measure of a chemical's mode of mutagenic action. Given the negative (bacterial) Ames and a negative HPRT Gene Mutation Test in Chinese hamster lung cells, CHMP agreed that it was reasonable to assume no mutagenic potential of cefiderocol and that the modest positive response in the MLA assay was a false positive. Further follow-up studies included a negative in vivo micronucleus test and a negative comet assay. In

the studies, the cefiderocol sodium drug product showed negative results at the highest dose level of 2000 which was estimated to provide a 31-fold margin to clinical exposure.

Collectively, positive results in the MLA and the chromosomal aberration test that was performed in a human lymphoblast cell line (TK6) are suggestive of possible chromosomal-aberration effects of cefiderocol sodium. However, given that other approved cephalosporins have shown a similar genotoxicity profile (i.e. non-mutagenic in Ames test, increased chromosomal aberrations in vitro but not considered clastogenic in the in vivo rat micronucleus assay and did not induce DNA damage in the Comet assay in rat hepatocytes) is it concluded by CHMP that the administration of cefiderocol for up to 14 days is unlikely to pose a genotoxic risk in humans.

Carcinogenicity

Carcinogenicity studies were not conducted. CHMP agreed that carcinogenicity studies were not needed as the SmPC states that the duration of dosing will be generally 14 days or less (not exceeding 21 days). In addition, intermittent dosing is not considered likely.

Reproduction and developmental toxicity

A full program of reproductive and developmental studies has been performed, which also included a 3-week juvenile toxicity study in rats. Pale urine, infusion-site findings and dilatation of cecum were present throughout the studies in rats and mice with similar incidence and severity as in the repeated-dose toxicity studies in rat.

In the fertility and early embryonic development study in rats, no effects were noted on the reproductive or developmental parameters evaluated up to 1000mg/kg/day which was the highest dose tested.

In the rat EFD-study, low food consumption and suppression of body weight gain (up to 40% suppression) was evident in dams exposed to 1000mg/kg/day on days 7-10 day 11-20 of gestation respectively. These are considered adverse. In addition, food-consumption was lower also in the 100 and 300mg/kg/day dose-group on GD 7-8. However, these effects were of lower magnitude and without effects on bodyweight (or weight gain) and were not considered adverse.

No malformations and few and scattered foetal variation findings were noted. Substantial reductions in maternal weight gain (or absolute weight loss) are frequently linked with other manifestations of developmental toxicity, such as decreased foetal weight, and skeletal anomalies (e.g., wavy ribs). In this study, the pup-weights were significantly reduced at the highest dose in females and a weight reduction trend was evident in male pups. Although statistically significant the weights measured are less than 5% different from the controls. When examined in the context of the historical control data, the mean of the 1000 mg/kg (3.63g) is actually higher than the historical control data mean (3.53 g). Thus, this effect is not considered biologically meaningful and the foetal NOAEL is 1000 mg/kg. Because of the effects on maternal bodyweight and weight-gain at 1000mg/kg, the maternal NOAEL is set to 300mg/kg/day.

In the mouse EFD-study, suppression of body weight gain and low body weight were noted in all treated groups during the latter half of the gestation period, but this did apparently not translate into foetal toxicity. Low numbers of corpora lutea, implantations and live foetuses were observed in all test substance groups. However, according to the Applicant, these changes are unrelated to treatment, as the numbers of corpora lutea and implantations were determined before initiation of dosing of the test substance. This reduction in implantations and corpora lutea is also claimed by the Applicant to explain the reduced body-weight increase seen in the dams during the latter half of gestation. Considering the

body-weight effects noted in the rat EFD dams during gestation, this explanation is not fully agreed upon by CHMP. However, it was noted that in mouse, no effects were noted on foetal weights.

While it is unfortunate that the control animals (prior to treatment) had more implantations and corpora lutea than all the other groups prior to treatment just by chance, no malformations were noted and overall the findings noted are similar to the EFD study in rats. Considering the infusion-related findings at 2000 and 1000 mg/kg/day and the lack of embryo-foetal effects, the maternal and developmental NOAELs are 500mg/kg/day and 2000 mg/kg/day respectively.

No toxicokinetic data were collected in the pre- and postnatal development study, which is surprising. While no adversities have been identified, there are no data to support appropriate exposure of the dams or to make an evaluation of the concentration levels of the substance transferred to the embryos/foetuses and pups.

Maternal toxicities were noted which included injection site findings, effects on food consumption and bodyweight during the gestation period and dilatation of the cecum. All these effects have been noted previously in the toxicology program, including the findings of pale urine in all treated animals. The effects on food consumption in the 1000mg/kg/day group also translated to reductions in body weight and suppression of body-weight gain and is considered adverse. While significant effects on food-consumption was noted also in the 100- and 300 mg/kg/day groups, no effects were noted on body weights, why these findings were not considered adverse. No F1-generation effects were identified neither prior to weaning nor after weaning, why the reproductive NOAEL is set to the highest dose.

Juvenile toxicity

Juvenile toxicity studies (DRF and pivotal) were performed in the rat using to cohorts (PND 7-13 and PND 28-34 for cohorts 1 and 2 respectively). The kidney is a target organ for toxicity (as is the case in adult rats), and the effects were more pronounced in cohort 1, where organ-weight increases (in both sexes with dose-relation from the lowest dose of 100mg/kg/day) correlated with microscopic findings in males and females of dose-relatedly altered proximal tubules consisting of small, cortical segments lined by tubular cells with expanded, pale, foamy to vacuolated cytoplasm. In addition, hyperplastic tubules were observed in 0, 1, 1, and 2 males administered 0, 100, 300, and 1000 mg/kg/day of the test article. These tubules exhibited a minimal to marked proliferation of tubular epithelial cells, often in association with tubular cysts. While these findings mostly recovered (kidney- weight changes remained), and the Applicant argues that the findings are of spontaneous nature, they are considered adverse at the highest dose. In cohort 2 (with older animals), the kidney effects were overall milder (but the HD was limited to 600mg/kg/day) and histopathologically only correlated with increased hyaline droplets without any evidence of cell damage.

FOB-assessments revealed some effects on behaviour in cohort 1 including significantly shorter mean time to the first step in the open-field analysis. In cohort 2, the Biel maze showed longer overall mean escape time for females in the 600 mg/kg/day group. However, CHMP agreed that the absence of a corresponding increase in the overall mean number of errors during this evaluation makes the finding of unclear significance and since all behavioural findings recovered, it was decided that these findings should not be further pursued.

The mean age of attainment of vaginal patency was increased in the 1000 mg/kg/day group in cohort 1 with 33.8 days compared to 32.0 days in controls. Mean body weight at the age of attainment was 128.2 g in the same group compared to 120.8 g in the control group. According to the Applicant, the delay was slight, and the value was within the range of values (31.3 to 37.0 days). It is agreed that all data were within historical control data, suggesting that the control group was not markedly below historical controls. Thus, the effect is considered treatment-related why the NOAEL in cohort 1 is set to 300mg/kg/day.

Toxicokinetic data

The toxicokinetics of cefiderocol was almost linear in rats from 100 to 1500 mg/kg and in monkeys from 100 to 1000mg/kg after repeated intravenous cefiderocol sodium administration. In mice, the AUC of cefiderocol was almost linear from 500 to 2000 mg/kg/day (250 to 1000 mg/kg bid) after repeated subcutaneous administration in pregnant mice. Across all repeat-dose toxicology studies, cefiderocol sodium exposure was similar in male and female animals and no clear accumulation of cefiderocol sodium was observed with repeated administration. Since no human metabolites at or above 10% were identified, no specific safety assessment for metabolites has been performed.

Other toxicity studies

Phototoxicity

A phototoxicity study was performed and submitted with this Application. However, there is no background to the decision to perform the study, neither in the non-clinical overview, nor in the toxicology summaries. The initial consideration for assessment of photoreactive potential is whether a compound absorbs light at a wavelength between 290 and 700nm. A compound with a MEC not greater than 1000 L mol-1 cm-1 is not considered photoreactive enough to result in phototoxicity. It is currently unclear if such an evaluation has been performed. Further, the 3T3 Neutral red Uptake phototoxicity test in vitro is considered the most appropriate assay to screen for phototoxicity, because it is animal sparing, it is a sensitive assay and a negative 3T3-assay would obviate the need for further phototoxicity studies. Performing an in vivo phototoxicity study in rats without prior absorption evaluation is considered a violation of the 3Rs principle.

CHMP agreed that the in vivo study as such was appropriately conducted and the negative result indicates no phototoxicity potential of cefiderocol sodium.

Antigenicity

In an antigenicity study in Guinea pigs, anaphylactic reactions including the production of specific antibodies against cefiderocol were noted when adjuvated cefiderocol was used for immunization, but no such reactions were noted when immunization had been performed with cefiderocol sodium alone. Thus, while weak, antigenicity was noted for cefiderocol sodium under the conditions of this study. The relevance of this finding for clinical use of the product is unclear. No anaphylactic reactions have been reported in the clinical studies. Given the and a positive result only after adjuvant-stimulated immunization and the lack of clinical findings to date, the clinical relevance of this finding is considered low.

Metabolites and Impurities

No specific studies on metabolites were warranted, and none have been performed. However, several actual and potential impurities have been tested for mutagenic potential (Ames test). No comments have been provided in the non-clinical overview or toxicology summaries regarding how the MAH will handle the positive results for a number of impurities in table 21. It is anticipated that the levels of the impurities are limited in accordance with ICH M7 and that a full disposition is available in the quality section of the dossier.

2.3.4. Ecotoxicity/environmental risk assessment

An ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, 01 December 2006) was submitted. Overall the submitted

studies were appropriate. However, a few questions emerged during the assessment, which received further attention. Regarding the Water/sediment study (OECD 308), the Applicant was asked to normalise the reported DT50 values for parent compound and transformation products to 12°C. In accordance with ECHA, R 7b (2017) p.220: Simulation testing on soil, sediment and water: If information on degradation half-life is already available from existing simulation degradation tests performed at a higher temperature, they should be normalised to a half-life corresponding to 12°C by using the Arrhenius equation. In the response, the Applicant provided with DT50 values for unchanged cefiderocol and Met A and Met B which had been extrapolated to 12°C using the Arrhenius equation. However, the provided normalization to 12°C had been done using an outdated conversion factor (Q10 = 2.2) which was considered not acceptable. For the normalization to 12°C, the Arrhenius equation with a specific activation energy Ea of 65.4 kJ/mol (current Q10 factor of 2.58) has to be used (see REACH R.7b, p. 222). The applicant was asked to provide the normalization of all DT50 values to 12 °C for Cefiderocol sulfate tosilate and the transformation product "Met A" according to the ECHA REACH guidance R.11 [version 3.0, June 2017], using the Arrhenius equation and the current conversion factor. The applicant updated the normalization values accordingly. The Transformation product "Met A" is mainly found in water and exceeds the persistence criterion > 40 d for water. Therefore, cefiderocol sulfate tosilate is persistent in water.

The Applicant was asked to submit an updated ERA report which included the data provided in the answers to the final questions and any conclusions drawn. Further, regarding the Sediment-Water Chironomid Toxicity Test (OECD 218), taking into account that the substance concentrations are below 80% of the nominal concentrations on day 0 and degradation of the test item occurs during the test period, mean measured concentrations should be used for the derivation of NOEC/LOEC. The Applicant was thus asked to derive LOEC/NOEC derivations based on mean concentrations. In the response, the geometric mean of the measured concentrations on days 0, 7 and 28 were used to update the RQ of sediment toxicity. The calculated RQ was 0.022 why it is agreed that cefiderocol is unlikely to represent a risk to sediment dwelling organisms. Further, all remaining data and conclusions were included in the revised ERA report.

Summary of main study results

Substance (INN/Invented Name): Cefiderocol			
CAS-number (if available): 1225208-94-5(Free form)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log K_{ow}	OECD107	pH 5:-3.5 pH7: <-3.5 pH 9: <-3.5	Potential PBT: No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH 5:-3.5 pH7: <-3.5 pH 9: <-3.5	B (No)
	BCF	-	N/A
Persistence	DT_{50} or ready biodegradability	Met A: 54.8 The degradation half-life in fresh or estuarine water is higher than 40 days	P (Yes)
Toxicity	NOEC	7.5mg/l	T (No)
PBT-statement:	Cefiderocol sulfate tosilate is persistent in water		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{SW}, default or refined	Default Fpen:	2.3 µg/L µg/L	> 0.01 µg/L (N)
Other concerns (e.g. chemical class)			
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*Kd in sludge was < 3700 L/kg and the Koc in sludge was < 10000 L/kg*	

Ready Biodegradability Test	OECD 301B	32% biodegradation after 28 days			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50total system = 0.346 / 0.894 d 47.8% / 59.8% shifting to sediment (99 d, total radioactivity); CO2 (99 d): 28.3% / 22.2%			DT50 at 12ºC. No decline rate in the sediment is available.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC10	0.043	mg/l	*Yield*
Daphnia sp. Reproduction Test	OECD 211	NOEC	88	mg/l	*Reproduction*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	7.5	mg/l	Hatching Survival Growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/l	DRF study, no statistically significant effects
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF/BMF	-	-	log Pow below 3 in the environmental pH range, why no study was performed
Aerobic and anaerobic transformation in soil	OECD 307	DT_{50}	-	-	-
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	NOEC	-	-	-
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	-	-	-
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	-	-	-
Collembola, Reproduction Test	OECD 232/ISO 11267	NOEC	-	-	-
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	415.68	mg/kg dw	-

2.3.5. Discussion and conclusion on non-clinical aspects

The PK of cefiderocol showed dose-linearity in rats, monkeys and humans. Cefiderocol is widely distributed in the body and is mainly excreted unchanged in urine in rats, monkeys and humans. Moreover, all the cefiderocol metabolites/degradation products identified are found below 10 % in serum in rats, monkeys and humans. Conclusively, in regards of PK, rats and monkeys are relevant species for toxicity studies. Safety concerns include convulsions (observed in rodents) and QT-prolongation (observed in monkeys).

The toxicity profile of cefiderocol has been characterized in a program appropriate for the intended patient population and proposed use of the product. Toxicities have been identified in the general toxicology program that may be of clinical relevance and which may require dose-adjustments for certain patient populations.

Convulsions (at a margin of exposure to clinical exposure around 13x) were noted in rats, but not in monkeys. No mechanisms have been identified for this effect. While no findings were evident in monkey (up to 22x clinical exposure) and no clinical findings of convulsions have been identified to date, this is a serious toxicity. Interestingly, the timing of the convulsions in the 13-week rat study occurred at a time period covered in the previous 1-month study in which no similar notable effects were seen and at similar exposure levels. Thus, these intra-study inconsistencies do not support a clear relation to exposure (Cmax) or timing in the study. Therefore, during the assessment the

Applicant was asked by CHMP to further elaborate on these issues. In the response, the applicant suggested that the differences seen are likely due to the systemic exposure achieved at 1000 and 1500 mg/kg being close to the threshold for which convulsions can occur. Due to the variability between animals, some of the animals at the 1000 or 1500 mg/kg may have passed this threshold and experienced convulsions. Furthermore, it was argued that the incidence of convulsions was low in the 3-month study and considering it had greater animals per group, overall there is not significant differences in the proconvulsive liability between the 1- and 3-month repeat-dose toxicity studies. Based on the totality of the data, CHMP considered these arguments to be reasonable and accepted that the risk of convulsions for patients at the clinical dose is low.

QTc-prolongations was observed in all studies in monkey and in the cardiac safety-pharmacology study. The exposure margin for the NOAEL for QTc-prolongation in the 3-month study (300mg/kg/day) compared to clinical exposure is around 7x. No cardiac arrythmias were observed throughout the study. Further, a clinical thorough QT study (at supra therapeutic dosing) did not find evidence for QTc prolongation.

Effects on erythrocytes, haematocrit, and haemoglobin were evident in the cynomolgus studies from 300mg/kg/day in the 3-month study and 1000mg/kg/day in the 1-month study. Increases in reticulocyte count and/or hyperplasia in the femoral or sternal bone marrow were also observed suggestive of a compensatory response. The margins to clinical exposure from NOAEL (100mg/kg/day in the 3-month monkey study) is only 3-fold and 0.3-fold of the Cmax and AUC-values in humans respectively No evidence for haemorrhagic lesions or haemolysis have been found, and no likely mechanism for the effect has been identified. Given no clear mechanism or reasonable explanation to the findings and that we have no reason to believe that this effect would not be present in human, anaemia is a potential adversity that may become present in humans.

A complete package of genotoxicity studies was completed by the Applicant, including follow-up studies to further evaluate positive in-vitro clastogenicity findings. Collectively, positive results in the MLA and the chromosomal aberration test was performed in a human lymphoblast cell line (TK6) are suggestive of possible chromosomal-aberration effects of cefiderocol sodium. But given that other approved cephalosporins have shown a similar genotoxicity profile (i.e. non-mutagenic in Ames test, increased chromosomal aberrations in vitro but not considered clastogenic in the in vivo rat micronucleus assay and did not induce DNA damage in the Comet assay in rat hepatocytes) is it concluded that administration of cefiderocol for up to 14 days is unlikely to pose a genotoxic risk in humans.

In conclusion, CHMP considered the nonclinical program provided for cefiderocol as adequate for this marketing authorisation application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study	Study Design	Number of Subjects (exposed to cefiderocol) and Population	Treatment Dose and Duration
Clinical Pharmacology Studies			
R2111	Phase 1 randomised, double-blind, placebo-controlled, single and multiple ascending dose study conducted at 1 site in Japan	Part 1:40 (30) Part 2: 30 (24) Healthy adult subjects	Part 1: Single cefiderocol 100-mg, 250-mg, 500-mg, 1-g, 2-g IV doses or matching placebo infused over 1 hour Part 2: Multiple cefiderocol 1-g (iodide contaminated or iodide-free) or 2-g IV doses or matching placebo, infused over 1-hour q8h x 10 days (single doses on Days 1 and 10, and doses q8h on Days 2 through 9)
R2112	Phase 1 open-label intrapulmonary PK (BAL ELF) study conducted at 1 site in Japan	20 (20) Healthy adult subjects	Single cefiderocol 2-g IV dose infused over 1 hour
R2113	Phase 1 open-label renal impairment study conducted at 2 sites in the US	38 (38) 8 subjects each with normal renal function, mild renal impairment, and moderate renal impairment; 6 subjects with severe renal impairment; 8 subjects with ESRD requiring HD (Cohorts 1, 2 and 3, 4 and 5, respectively)	Cohorts 1, 2, 3 and 4: single cefiderocol 1-g IV dose infused over 1 hour; Cohort 5: single dose on 2 separate occasions, 1 hour after completion of HD and 2 hours prior to the subsequent HD session with minimum of a 72-hour washout interval between doses
R2114	Phase 1 open-label, nonrandomised, single-dose mass balance study conducted at 1 site in the US	6 (6) Healthy adult male subjects	Single 1-g IV dose of [^{14}C]-cefiderocol (~ 100 µCi) infused over 1 hour
R2115	Phase 1 open-label, randomised, 2-sequence, 2-period crossover study (3 parts) DDI study conducted at 1 site in the US	38 (37) Part 1: 12 (12) Part 2: 13 (12) Part 3: 13 (13) Healthy adult subjects	Part 1: furosemide (20 mg oral) with and without cefiderocol (2 g IV over 3 hours) Part 2: metformin (1 g oral) with and without cefiderocol (2 g IV over 3 hours) Part 3: rosuvastatin (10 mg oral) with and without cefiderocol (2 g IV over 3 hours)

Study	Study Design	Number of Subjects (exposed to cefiderocol) and Population	Treatment Dose and Duration
R2116	Phase 1 study Part 1: randomised, double-blind, placebo-controlled, single ascending dose Part 2: randomised, single dose, double-blind (with respect to cefiderocol only), placebo- and active-controlled, 4-period, crossover thorough QT/QTc study conducted at 1 site in the US	64 (57) Part 1: 16 (12) Part 2: 48 (45) Healthy adult subjects	Part 1: single-dose of cefiderocol IV 3 g/ 4 g or matching placebo infused over 3 hours Part 2: single-dose of cefiderocol IV 2 g, 4 g or matching placebo infused over 3 hours Moxifloxacin 400 mg single oral dose
Efficacy and Safety Studies			
CREDIBLE-CR R2131	Phase 3 multicentre, multinational, open-label, parallel-group, randomised (2:1), active-controlled study conducted at 45 sites in 10 countries Interim report on first 70 subjects	70 (47) Adult subjects with HAP/VAP/ HCAP, cUTI, or BSI/sepsis caused by a carbapenem-resistant Gram-negative pathogen	Cefiderocol: 2-g IV doses q8h[a] (3-hour infusion) with or without another single adjunctive Gram-negative antibiotic (eg, avibactam, tazobactam) BAT: locally sourced by study sites, within the local standard of care determined by the investigator Study treatment for 7 to 14 days (may be extended up to 21 days)
cUTI R2121	Phase 2 multicentre, multinational, double-blind, randomised (2:1), active-controlled, noninferiority study conducted at 67 sites in 14 countries	452 (300) Adult subjects with cUTI with or without pyelonephritis or with acute uncomplicated pyelonephritis, who had a Gram-negative pathogen likely to be susceptible to IPM	Cefiderocol: 2-g IV dose q8h[b] (1-hour infusion) Imipenem/cilastatin: 1-g IV dose q8h (1-hour infusion) Study treatment for 7 to 14 days (5 days permitted in certain circumstances)
Ongoing Study			
APEKS-NP R2132	Phase 3 multicentre, double-blind, randomised (1:1), active-controlled study conducted at 145 sites in 19 countries	Planned 300 (150) Adult subjects with nosocomial pneumonia caused by a suspected Gram-negative pathogen	Cefiderocol 2-g IV dose q8h (3-hour infusion) Meropenem 2-g IV dose q8h (3-hour infusion) Study treatment for 7 to 14 days (may be extended up to 21 days) To provide MRSA coverage, linezolid 600-mg IV dose q12h administered to all subjects

Study	Study Design	Number of Subjects (exposed to cefiderocol) and Population	Treatment Dose and Duration
Initiated Study			
ELF Study R2117	Phase 1b multicentre, single-arm, open-label study in 1 country (USA) First subject visit not achieved at the time of writing this document	Planned minimum of 3 to approximately 18 subjects Hospitalised adult subjects with bacterial pneumonia on treatment with SOC antibiotics and requiring mechanical ventilation	Cefiderocol 2-g IV dose q8h (3-hour infusion) Study treatment is expected to be for minimum of 3 doses and up to a total of 6 doses in subjects with normal renal function and subjects with mild or moderate renal impairment, and for an expected minimum of 6 doses and up to a total of 9 doses in subjects with severe renal impairment

BAL = bronchoalveolar lavage; BAT = best available therapy; BSI = bloodstream infection; cUTI = complicated urinary tract infection; DDI = drug-drug interaction; ELF = epithelial lining fluid; ESRD = end-stage renal disease; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; HD = haemodialysis; IPM = imipenem; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; No. = number; PK = pharmacokinetics; q8h = every 8 hours; q12h = every 12 hours; QTc = QT interval corrected for heart rate; SOC = standard of care; VAP = ventilator-associated pneumonia

a Dose (0.75 to 2 g) or interval (6 to 12 hours) based on renal function.

b Six to 8 hours based on renal function and/or body weight.

2.4.2. Pharmacokinetics

The PK of cefiderocol was evaluated in 6 clinical pharmacology studies and 8 in vitro studies. A population PK analysis using data from two Clinical Pharmacology studies (Studies R2111 and R2113), the Phase 2 study in subjects with cUTIs (cUTI Study), and the phase III CREDIBLE-CR and APEKS-NP studies was performed.

Methods

Bioanalysis

An LC-MS/MS method for the quantification of cefiderocol upon treatment with ammonium acetate pH 5 buffer was validated for human plasma, urine, ultrafiltrate, haemodialysis dialysate, epithelial lining fluid (ELF) and alveolar macrophages. Of note, the method is validated for 1% but not 2% haemolytic plasma. Where available, ISR criteria were met.

Evaluation and qualification of models

The initial models were based on two Phase 1 studies (2111 and 2113) and the data obtained from APEKS-UTI (2121). A subsequent model (CPK-002-B) incorporated data from CREDIBLE-CR. The final pop PK model (CPK-004-B) incorporated data of all studies (including APEKS-NP) with a total of 3427 valid observations from 516 subjects. 9.6% of data were BQL and were previously excluded.

Non-linear mixed effects modelling was used to build a population PK model using NONMEM. The data was best described with a 3-compartment model with CrCL (Cockcroft-Gault) as renal function marker. An exponential error model was used for interindividual variability, and proportional error model was used for intraindividual variability. During model development, renal function, body weight, age, sex, ALB, AST, ALT, BIL, race, infection, and ventilation were tested as a covariate on CL, and body weight, age, sex, ALB, race, infection, and ventilation were tested as a covariate on V1. Body weight data were tested as a covariate on other PK parameters (Q2 and V2). The parameter estimates for the base and final model are shown in the table below:

Table 1: Population PK parameter estimates for the final model

		Final model [a]			
				Bootstrap estimates	
Pharmacokinetic parameters	Units	Estimates	%RSE	Median	95% CI (lower - upper)
CL	(L/hr)	4.04	1.8	4.04	3.89 - 4.20
V1	(L)	7.78	5.2	7.93	7.07 - 8.85
Q2	(L/hr)	6.19	5.7	5.97	4.57 - 7.24
V2	(L)	5.77	3.2	5.68	5.02 - 6.15
Q3	(L/hr)	0.127	14.1	0.119	0.0792 - 0.228
V3	(L)	0.798	6.4	0.772	0.621 - 1.09
Effect of CrCL on CL (CrCL cut-off value of 150 mL/min)		0.682	4.0	0.681	0.626 - 0.735
Effect of body weight on V1 and V2		0.580	12.2	0.571	0.433 - 0.725
Effect of infection with cUTI/AUP in phase 2 cUTI study on CL		1.27	3.1	1.27	1.20 - 1.35
Effect of infection with cUTI in phase 3 CREDIBLE-CR study on CL		0.872	6.4	0.869	0.769 - 1.01
Effect of infection with BSI/sepsis on CL		1.08	10.4	1.07	0.894 - 1.37
Effect of infection with HAP/VAP/HCAP on CL		0.981	4.1	0.978	0.893 - 1.07
Effect of albumin on V1		-0.617	10.9	-0.624	-0.985 - -0.244
Effect of infection on V1		1.39	6.7	1.36	1.22 - 1.54
Inter-individual variability (CV%) [sh_ηp]					
CL	%	37.5 [3.6]	10.4	37.0	32.9 - 40.7
V1	%	56.9 [13.6]	19.8	57.9	45.3 - 71.0
V2	%	33.6 [18.2]	35.0	35.5	19.7 - 50.2
Covariance between CL and V1		0.0886 (R = 0.415)	29.1	0.0807	0.0338 - 0.146
Covariance between CL and V2		0.0792 (R = 0.629)	33.2	0.0767	0.0187 - 0.140
Covariance between V1 and V2		0.150 (R = 0.784)	27.3	0.115	-0.0930 - 0.218
Intra-individual variability (CV%) [sh_ε]					
Proportional residual error	%	20.5 [13.2]	5.1	20.3	18.5 - 22.5

CI = confidence interval; CrCL = creatinine clearance calculated by Cockcroft-Gault equation; CV = coefficient of variation; sh_ηp = shrinkage in the standard deviation of inter-individual variability parameters η; sh_ε = shrinkage in the standard deviation of intra-individual variability parameters ε; %RSE = relative standard error in percent, R = coefficient of correlation.

[a] CrCL < 150 mL/min; CL = 4.04 * (CrCL/83.0)$^{0.682}$ * (1.27 for patients with cUTI/AUP in phase 2 cUTI study) * (0.872 for patients with cUTI in phase 3 CREDIBLE-CR study) * (1.08 for patients with BSI/sepsis) * (0.981 for patients with HAP/VAP/HCAP)

CrCL ≥ 150mL/min; CL = 4.04 * (150/83.0)$^{0.682}$ * (1.27 for patients with cUTI/AUP in phase 2 cUTI study) * (0.872 for patients with cUTI in phase 3 CREDIBLE-CR study) * (1.08 for patients with BSI/sepsis) * (0.981 for patients with HAP/VAP/HCAP)

V1 = 7.78 * (body weight/72.6)$^{0.580}$ * (albumin/3.9)$^{-0.617}$ * (1.39 for patients with infection)

V2 = 5.77 * (body weight/72.6)$^{0.580}$

As depicted in **Figure 1**, CrCL was the most significant covariate on CL, and time-varying CrCL was a better predictor than baseline CrCL. The other significant covariates were: body weight on V1 and V2, and infection on CL and V1, and albumin on V1.

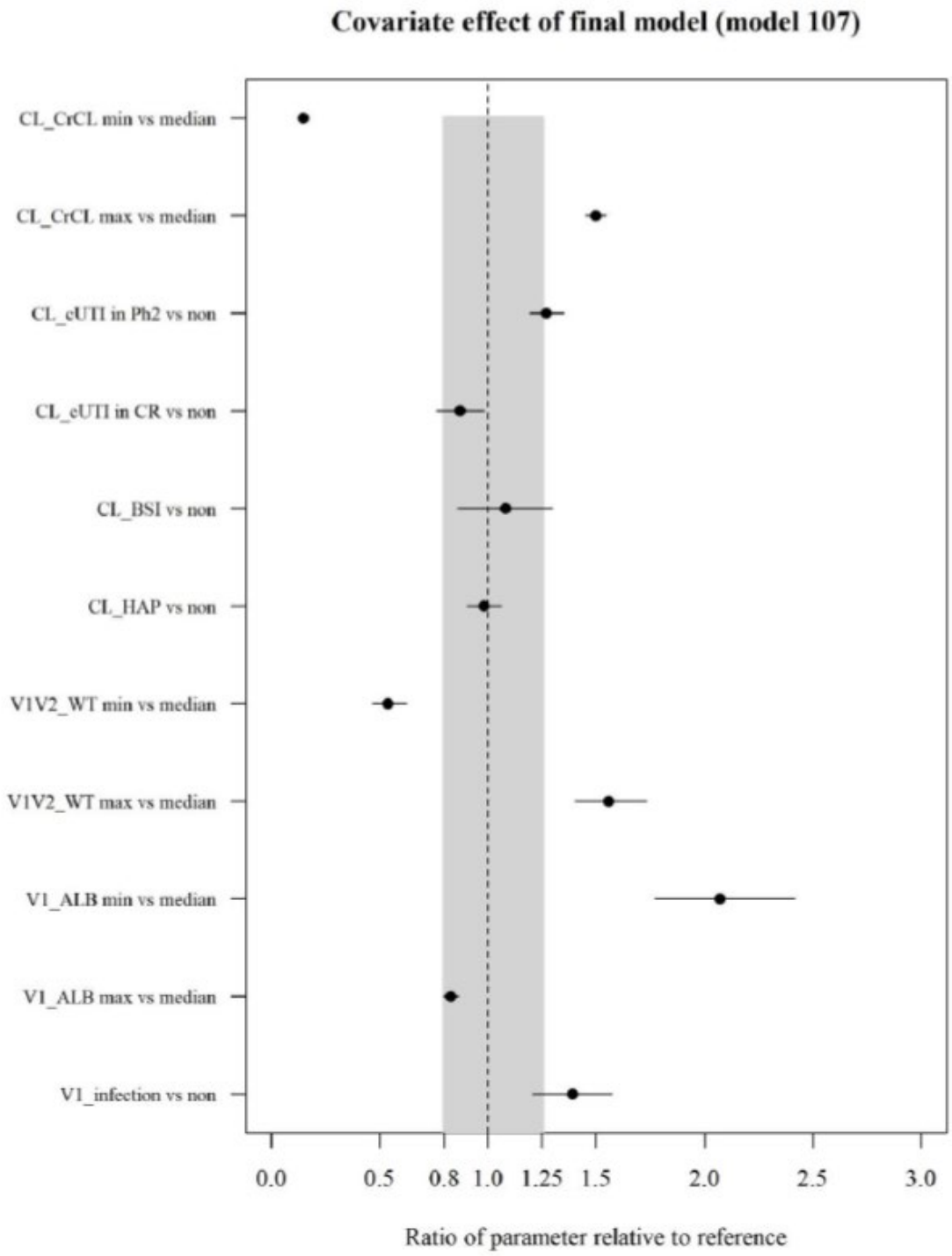


Figure 2: Plots for the Covariate Effect of the Final Model

The results of the prediction-corrected visual predictive check (pcVPC) for the final model are presented by renal function group for each study in the figure below.

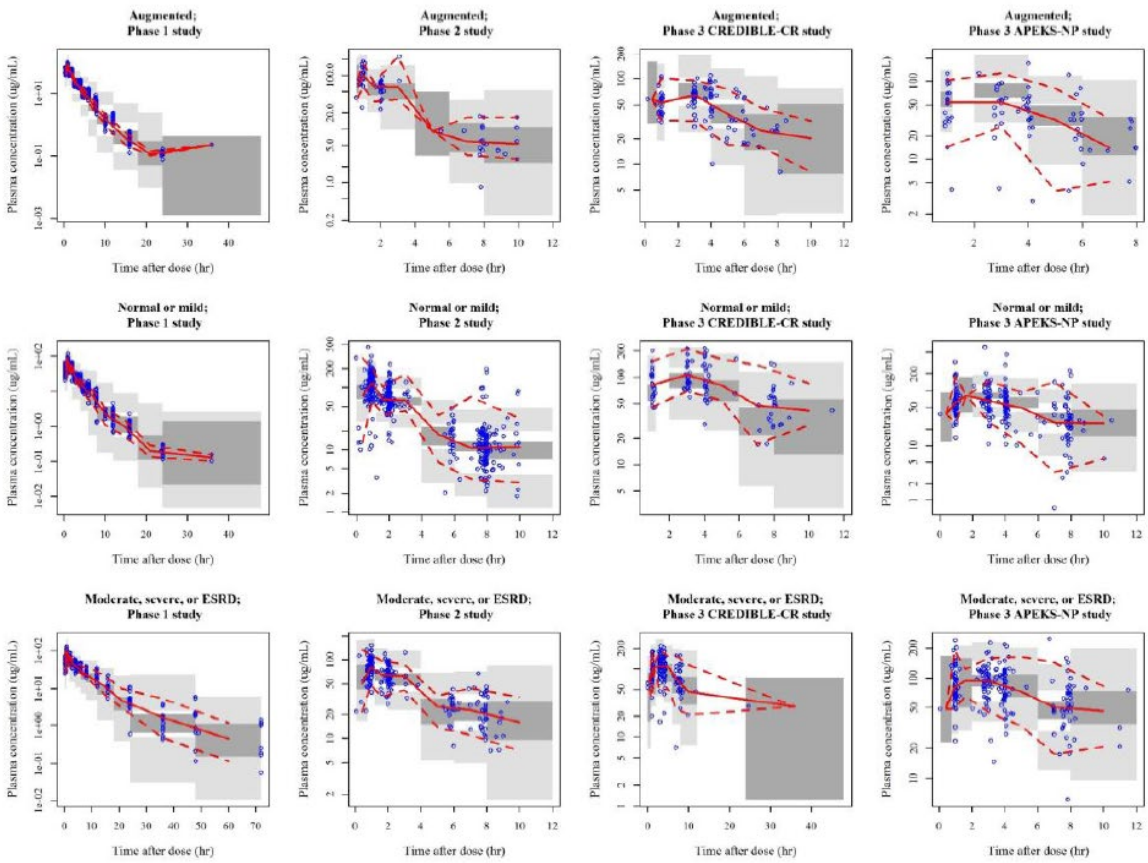


Figure 3: Prediction-corrected Visual Predictive Check for the final model stratified by renal function group.

(Solid line: observed median. Dashed line: observed 2.5th and 97.5th percentiles. Dark grey shaded area: model predicted 95% CI of median. Grey shaded area: model predicted 95% CIs of 2.5th and 97.5th percentiles. 500 simulations.)

Monte-Carlo simulations with 1000 virtual patients per subgroup were performed for PTA analyses. 75% fT>MIC was identified as the PD driver for efficacy (1 log kill) in preclinical studies and 90% PTA at MIC is the selected cut-off. Regarding the relevant MIC, please refer to the pending EUCAST decision.

Absorption

Not applicable as cefiderocol is administered by i.v. infusion.

Distribution

After administration of a single 2-g dose of cefiderocol infused over 3 hours, the geometric mean volume of distribution during the terminal elimination phase (Vz) (CV%) was 18.0 L (18.1%) (Study R2116).

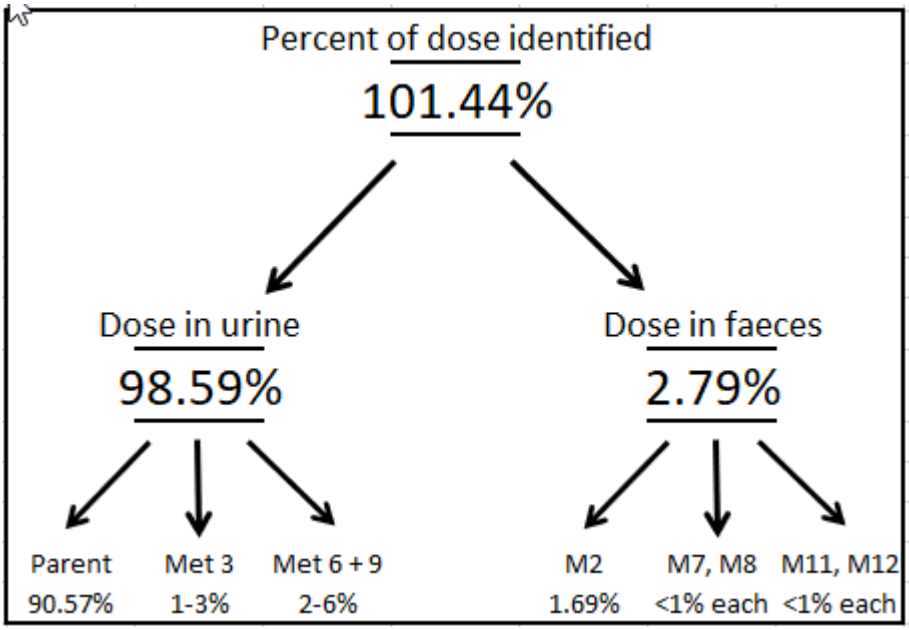
The plasma protein binding ratios for cefiderocol over concentrations of 1 to 1000 µg/mL ranged from 40.8% to 60.4% (study R-649266-PF-037-L).

In the mass balance study (R2114), the total radioactivity concentration in whole blood was half of that in plasma (approximating the physiologic ratio of plasma to whole blood), indicating that total radioactivity was predominantly associated with plasma, with little partitioning into red blood cells. The whole blood/plasma partitioning ratio was approximately 0.54.

Study 1214R2112 evaluated the concentrations of cefiderocol in the epithelial lining fluid (ELF) and alveolar macrophages (AM) using bronchoscopy with bronchoalveolar lavage following a single 2g intravenous administration (1h) of cefiderocol in 20 healthy Japanese adult male subjects. The geometric mean concentration ratios of ELF to plasma over 6 hours ranged from 0.0927 to 0.116 indicating a low distribution (ca 10 %) to ELF relative to plasma concentrations.

Elimination

Figure 4: Percent of dose identified in urine and faeces following administration of 14C-cefiderocol (Study R2114)



The terminal half-life of cefiderocol is approximately 2 to 3 hours in healthy volunteers (study R2111 and R2116).

Based on data from the mass balance study, the main route of elimination for cefiderocol is renal excretion of unchanged drug. Following a single infusion of [^{14}C]-cefiderocol over 1 hour, the majority of total radioactivity was excreted unchanged in urine (98.6% as total radioactivity; 90.6% as unchanged) with a negligible amount excreted in faeces (2.8% as total radioactivity). Urine data from study R2111 and R2113 also support renal excretion of unchanged drug as main elimination pathway for cefiderocol. In faeces, the M2 component (PCBA, a degradation product) was the predominant radioactive component and accounted for 1.69% of the administered dose. (Study R2114).

The renal clearance was 3.24 L/h in healthy volunteers in study R2113. In study R2111 the renal clearance was reported to be 3.03-4.06 L/h in the single dose part and 3.73-4.36 L/h in the multiple dose part. Filtration (fu*GFR) is expected to be around 3-4 L/h. Thus, there is no indication of active renal secretion of cefiderocol.

No major metabolites were detected in plasma. Unchanged drug was the main compound found in plasma and accounted for 92% of the total radioactivity (0-16 hours). The M2 component (PCBA, a degradation product) accounted for 4.70%, and other minor metabolites each accounted for < 2% of

the plasma AUC0-16 for total radioactivity. Similar metabolite profiles were detected in the in vitro studies (albeit with an inconsistent designation) and there were no human specific metabolites.

Cefiderocol has two chiral centres at its β lactam moiety. Interconversion in vivo to the possible S-649266-7-epi and S-649266-anti structures has been demonstrated to be negligible.

Dose proportionality and time dependencies

The results of study R2111 and study R2116 indicate dose-proportionality of cefiderocol in the dose range of 100 mg to 4000 mg.

In the single dose part of study R2111, single doses in the dose range of 100 mg to 2000 mg given via 60 minutes infusion were studied and the slope estimates of AUC and C_{max} were close to 1 and there was no indication of dose-dependent changes in $t_{1/2}$, CL or CL_r. In the multiple dose part of study R2111, doses of 1000 and 2000 mg were studied. Ratios of C_{max} and $AUC_{0-\tau}$ between dose groups on Day 10 were close to the ratio of dose (ie, 2), suggesting dose-proportional increase in Cmax and $AUC_{0-\tau}$ following multiple dose. Dose-proportionality was also investigated in study R2116, where cefiderocol was given as 3-hour infusions, which is the recommended dosage time. The C_{max} and AUC of cefiderocol increased in a dose-proportional manner after administration of single 3- and 4-g doses (Part 1) and 2- and 4-g doses (Part 2) of cefiderocol, infused over 3 hours. Half-life and clearance estimates remained fairly consistent across the doses. The results are summarised in **Table 2**.

Table 2: Summary of Cefiderocol PK Parameters in study R2116

Part	Dose (g)	N	C_{max} (µg/mL)	T_{max}[a] (hr)	AUC_{0-last} (µg·hr/mL)	AUC_{0-inf} (µg·hr/mL)	$t_{½,z}$ (hr)	CL (L/hr)	V_z (L)
1	3	6	132 (25.5)	2.86 (2.00, 2.90)	524.9 (28.5)	525.9 (28.4)	2.29 (19.3)	5.70 (28.3)	18.9 (21.7)
	4	6	186 (28.4)	2.90 (2.90, 2.93)	722.2 (13.3)	723.3 (13.2)	2.71 (9.8)	5.53 (13.2)	21.6 (20.6)
2	2	43	89.7 (20.5)	2.90 (2.08, 4.58)	384.8 (17.3)	386.1 (17.2)	2.41 (14.0)	5.18 (17.2)	18.0 (18.1)
	4	44	183 (17.3)	2.90 (2.08, 2.97)	790.5 (17.1)	791.6 (17.1)	2.57 (7.5)	5.05 (17.1)	18.8 (18.5)

AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-last} = area under the plasma concentration-time curve from time 0 to the time point of the last measurable plasma concentration; CL = total clearance; C_{max} = maximum plasma concentration; $t_{½,z}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration; V_z = volume of distribution during the terminal phase
Geometric Mean (CV% Geometric Mean).

a Median (Minimum, Maximum).

There was no significant accumulation of cefiderocol at steady state, since the geometric mean accumulation ratio for C_{max} and AUC in the multiple-dose part of study R2111 were from 1.069 to 1.084 and 1.053 to 1.164, respectively. There are no indications of time-dependent pharmacokinetics since CL did not change between day 1 and day 10 and since AUC_{inf} following first dose was similar to AUC0-τ at steady state.

Interindividual variability on Cmax and AUC ranged from 13-21 %CV and 14-17% in healthy individuals, and 41-53% and 45-60% in patients, respectively. Interindividual variability on CL, V1 and V2 is presented in Table 1. Intra-individual variability estimated were not provided, because estimation of multiple Cmax or AUC values per subject were not performed for each subject population and each dose regimen.

Pharmacokinetics in the target population

Infections are significant covariates on cefiderocol PK, but the PK in patients is described with the same model as healthy volunteers PK.

The final model suggested CL in patients with cUTI/AUP in the phase 2 study was 27% higher than that in subjects without infection. The CL in patients with cUTI (CREDIBLE-CR study), BSI/sepsis, or HAP/VAP/HCAP were suggested to be comparable to that in subjects without infection.

The final model also suggested V1 in patients with infection was 39% higher than that in subjects without infection. Although the effect of infection site was a covariate on CL and V1, individual Cmax and daily AUC overlapped among infection sites (see **Figure 1**).

The effect of ventilation was not a covariate on cefiderocol PK and the post-hoc estimates of Cmax and daily AUC were similar between HAP/VAP/HCAP patients with and without ventilation.

The geometric mean values of estimates of Cmax and daily AUC in all patients with infection are presented in Table 3. The Cmax values in patients were similar to those in healthy subjects, but the daily AUC in patients was higher than in healthy subjects (Cmax of 89.7 μg/mL and daily AUC of 1158 [= AUC0-inf 386.1 × 3] μg·hr/mL, Study R2116). The Cmax and daily AUC values overlapped among survival cases and death cases in the phase 3 studies, and survival cases in the phase 2 study. The daily AUC value in one death case in the CREDIBLE-CR study (patient with cUTI and moderate renal impairment) was higher than the maximum AUC in survival cases.

Table 3: Summary of Post-hoc Estimates of Cmax and Daily AUC for Patients with Infection

Subject Population	Background Data	Sub-population		N	C_{max} (μg/mL)[a]	AUC (μg·hr/mL)[a]
Patients in phase 2 study	---	All (cUTI/AUP)		238	114 (41.5)	1062 (40.3)
Patients in phase 3 CREDIBLE-CR and APEKS-NP studies	Infection	cUTI		21	106 (37.8)	1768 (42.5)
		BSI/sepsis		20	85.4 (48.6)	1402 (55.9)
		HAP/VAP/HCAP		146	99.7 (46.9)	1560 (53.0)
	Age	< 65 years old		76	86.7 (47.2)	1314 (51.6)
		65 to < 75 years old		61	101 (36.2)	1629 (40.2)
		75 to < 85 years old		40	111 (50.8)	1793 (56.5)
		≥ 85 years old		10	147 (37.3)	2656 (42.7)
	Body weight	< 55 kg		31	115 (37.2)	1826 (43.9)
		55 to < 70 kg		49	106 (48.3)	1695 (52.5)
		70 to < 90 kg		70	93.9 (45.4)	1467 (53.3)
		≥ 90 kg		37	86.8 (48.0)	1395 (52.9)
	Sex	Male		126	95.3 (48.3)	1493 (53.7)
		Female		61	106 (41.2)	1722 (47.9)
	Dose group	2g q6hr		34	81.8 (38.7)	1365 (47.3)
		2g q8hr		96	101 (51.6)	1494 (58.4)
		1.5g q8hr		37	115 (40.2)	1930 (41.9)
		1g q8hr		15	95.2 (30.1)	1778 (35.0)
		0.75g q12hr		5	79.3 (16.1)	1377 (17.7)
	Ventilation in patients with HAP/VAP/HCAP	With		73	98.7 (48.9)	1591 (55.6)
		Without		73	101 (45.3)	1530 (50.6)
	Albumin	< 2.8 g/dL		81	97.0 (48.5)	1635 (55.2)
		≥ 2.8 g/dL		106	100 (44.7)	1512 (49.9)
	Race	Phase 3 studies	White	120	94.6 (45.5)	1475 (51.5)
			Asian	58	112 (47.0)	1830 (51.8)
			Others	9	79.3 (31.7)	1244 (36.8)
		CREDIBLE-CR study	White	42	92.9 (46.9)	1560 (52.6)
			Asian	22	124 (34.4)	1972 (44.0)
			Others	8	79.4 (34.0)	1239 (39.5)
		APEKS-NP study	White	78	95.6 (45.1)	1431 (51.1)
			Asian	36	105 (53.0)	1748 (56.4)
			Others	1	79.0	1284
	Vital status	Phase 3 studies	Survival	143	96.7 (44.8)	1514 (49.4)
			Death	44	106 (50.9)	1739 (60.2)
		CREDIBLE-CR study	Survival	54	92.5 (39.4)	1495 (42.5)
			Death	18	125 (52.2)	2130 (63.3)
		APEKS-NP study	Survival	89	99.3 (47.8)	1526 (53.6)
			Death	26	94.4 (46.9)	1511 (53.6)

[a] Geometric mean (CV%)

Special populations

Impaired renal function

The effect of impaired renal function was studied in a dedicated phase I study in subjects with varying degree of renal impairment (study R2113) who received a fixed dose of 1 g of cefiderocol infused over 1 hour. A summary of the pharmacokinetic parameters of cefiderocol in the different groups is given in **Table 4** with statistical analysis in **Table 5**.

Not reflected in **Table 4** and **Table 5** is that HD removed 62.3% of cefiderocol.

Table 4: Summary of Pharmacokinetic Parameters of Cefiderocol Following Single IV Infusion of 1 g of Cefiderocol Over a 1-hour Infusion by Renal Function Group

PK Parameter	Renal Function Group					
	Normal (N = 8)	Mild (N = 8)	Moderate (N = 7)	Severe (N = 6)	ESRD (w/o HD) (N = 8)	ESRD (with HD) (N = 8)
C_{max} (µg/mL)	81.0 (27.4)	73.4 (21.3)	78.0 (31.1)	80.1 (19.8)	93.0 (27.8)	75.4 (31.1)
T_{max} (hr)	1.00 (1.00, 1.03)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.07)	1.00 (1.00, 1.02)	1.00 (1.00, 1.53)
$AUC_{0\text{-last}}$ (µg·hr/mL)	212.0 (26.7)	217.8 (22.2)	311.0 (38.6)	540.3 (23.6)	872.5 (23.9)	314.9 (20.3)
$AUC_{0\text{-inf}}$ (µg·hr/mL)	213.4 (26.5)	218.7 (22.2)	312.3 (38.4)	543.2 (23.6)	880.7 (24.2)	318.1 (20.3)
$t_{½,z}$ (hr)	2.82 (16.5)	2.98 (8.4)	4.13 (12.6)	6.91 (30.6)	9.60 (33.4)	9.45 (32.8)
CL (L/hr)	4.69 (26.5)	4.57 (22.2)	3.20 (38.4)	1.84 (23.6)	1.14 (24.2)	3.14 (20.3)
V_{ss} (L)	13.5 (30.2)	14.8 (17.7)	15.4 (28.7)	16.4 (23.4)	14.2 (22.5)	26.6 (33.5)
$Feu_{0\text{-}72}$ (%)	68.6 (17.3)	68.3 (14.0)	55.5 (19.6)	26.0 (43.6)	0.988 (143534.8)	0.513 (2245033.7)
CL_R (L/hr)	3.24 (28.0)	3.14 (30.3)	1.78 (41.9)	0.409 (76.5)	0.0122 (175476.0)	0.0125 (24562503.9)
CL_{HD} (L/hr)	–	–	–	–	–	7.47 (9.8)
f_u (1 hr)	0.420 (12.7)	0.372 (43.5)	0.353 (38.9)	0.360 (31.4)	0.424 (26.6)	0.466 (19.8)
f_u (8 hr)	0.437 (9.8)	0.419 (19.1)	0.448 (18.5)	0.436 (10.1)	0.367 (27.0)	0.422 (21.5)

$AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the time point of the last measurable plasma concentration; CL = total clearance; CL_{HD} = clearance with haemodialysis; CL_R = renal clearance; C_{max} = maximum plasma concentration; ESRD = end-stage renal disease; ESRD (w/o HD) = ESRD (dosing post haemodialysis); ESRD (with HD) = ESRD (dosing prior to haemodialysis); $feu_{0\text{-}72}$ = fraction of dose excreted in urine over 72 hours; f_u = unbound fraction; IV = intravenous; $t_{½,z}$ = terminal elimination half-life;

T_{max} = time to maximum plasma; V_{ss} = apparent volume of distribution at steady state

Geometric mean (CV% Geometric Mean) is shown except for T_{max} where median and range (minimum, maximum) are shown.

Table 5: Statistical Analysis of the Effect of Renal Impairment on Cefiderocol PK

PK Parameter	Geometric Least Squares Mean Ratio (90% confidence interval)			
	Mild vs Normal	Moderate vs Normal	Severe vs Normal	ESRD (w/o HD) vs normal
C_{max}	0.905 (0.729 - 1.124)	0.962 (0.769 - 1.204)	0.989 (0.783 - 1.249)	1.148 (0.925 - 1.425)
$AUC_{0\text{-last}}$	1.027 (0.818 - 1.290)	1.467 (1.159 - 1.857)	2.549 (1.993 - 3.260)	4.116 (3.278 - 5.169)
$AUC_{0\text{-inf}}$	1.025 (0.817 - 1.287)	1.464 (1.157 - 1.852)	2.546 (1.992 - 3.254)	4.128 (3.289 - 5.181)
λ_z	0.945 (0.786 - 1.137)	0.683 (0.564 - 0.827)	0.407 (0.334 - 0.497)	0.293 (0.244 - 0.353)
$t_{½,z}$	1.058 (0.879 - 1.272)	1.465 (1.210 - 1.773)	2.454 (2.010 - 2.996)	3.409 (2.834 - 4.100)
CL	0.975 (0.777 - 1.224)	0.683 (0.540 - 0.864)	0.393 (0.307 - 0.502)	0.242 (0.193 - 0.304)
V_{ss}	1.096 (0.891 - 1.348)	1.138 (0.918 - 1.410)	1.211 (0.968 - 1.514)	1.048 (0.852 - 1.289)
CL_R	0.970 (0.323 - 2.912)	0.552 (0.177 - 1.722)	0.149 (0.045 - 0.488)	0.004 (0.001 - 0.015)

$AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the time point of the last measurable plasma concentration; CL = total clearance; CL_R = renal clearance; C_{max} = maximum plasma concentration;

ESRD = end-stage renal disease; ESRD (w/o HD) = ESRD (dosing post haemodialysis); λ_z = elimination rate constant; $t_{½,z}$ = terminal elimination half-life;

V_{ss} = apparent volume of distribution at steady state

Renal function was also investigated as a covariate in the population PK analyses and dose recommendations for different renal functions (including augmented clearance) have been proposed based on 90% PTA analysis for 75% fT>MIC.

Impaired hepatic function

Because results of the Mass Balance Study (Study R2114) showed that cefiderocol is primarily (more than 90%) excreted unchanged in the urine, a study to assess the potential effect of hepatic impairment on the PK of cefiderocol was not considered to be necessary and was therefore not conducted.

Albumin was a significant covariate on V1 of cefiderocol but estimated steady-state Cmax and daily AUC were similar between patients with and without hypoalbuminaemia (albumin concentration < 2.8 or ⩾ 2.8 g/dL) suggesting the effect of albumin was not clinically significant.

Weight

No dedicated study to assess the effect of body weight on cefiderocol PK was performed. The population PK analyses of cefiderocol showed that body weight was a significant covariate on V1 and V2. The geometric mean CL values for the categorised body weight range (< 55, 55 to < 70, 70 to < 90, and ≥ 90 kg) in patients were 3.20, 3.75, 4.54, and 4.61 L/hr, respectively. The geometric mean values of Bayesian estimated V1 for categorised body weight range (< 55, 55 to < 70, 70 to < 90, and ≥ 90 kg) in patients were 10.0, 9.94, 11.6, and 13.6 L, respectively. The V1 was higher in patients with a body weight ≥ 90 kg than in patients with a body weight < 90 kg. However, the Monte-Carlo simulations demonstrated a high PTA was also achieved in patients with a body weight ≥ 90 kg of body weight and therefore no cefiderocol dose adjustment based on body weight is required.

Gender, race and age

No dedicated study to assess the effect of gender, race or age on cefiderocol PK was performed. The population PK analyses showed that they were not significant covariates on cefiderocol PK. Differences in CL among age groups was attributed to the difference in renal function for the different age groups, as age negatively correlates with renal function.

No studies were performed in paediatric patients.

Pharmacokinetic interaction studies

Effect of other medicines on cefiderocol

Due to very low metabolic turnover, cefiderocol has a low potential for victim drug drug interactions.

In the in vitro studies using human transporter expressing cells, cefiderocol is not a substrate for OAT1, OAT3, OCT2, MATE1, MATE2-K, P-gp, or BCRP. Therefore, coadministration of inhibitors or inducers of these transporters is expected to have no impact on the PK of cefiderocol.

Iron does not influence the cefiderocol PK.

Effect of cefiderocol on other medicines

Cefiderocol does not show concentration- or time-dependent inhibition to CYP1A2, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4 by cefiderocol at concentrations 1330 µmol/L (1000 µg/mL as cefiderocol) and up to 5320 µmol/L (4000 µg/mL as cefiderocol) for CYP2C8.

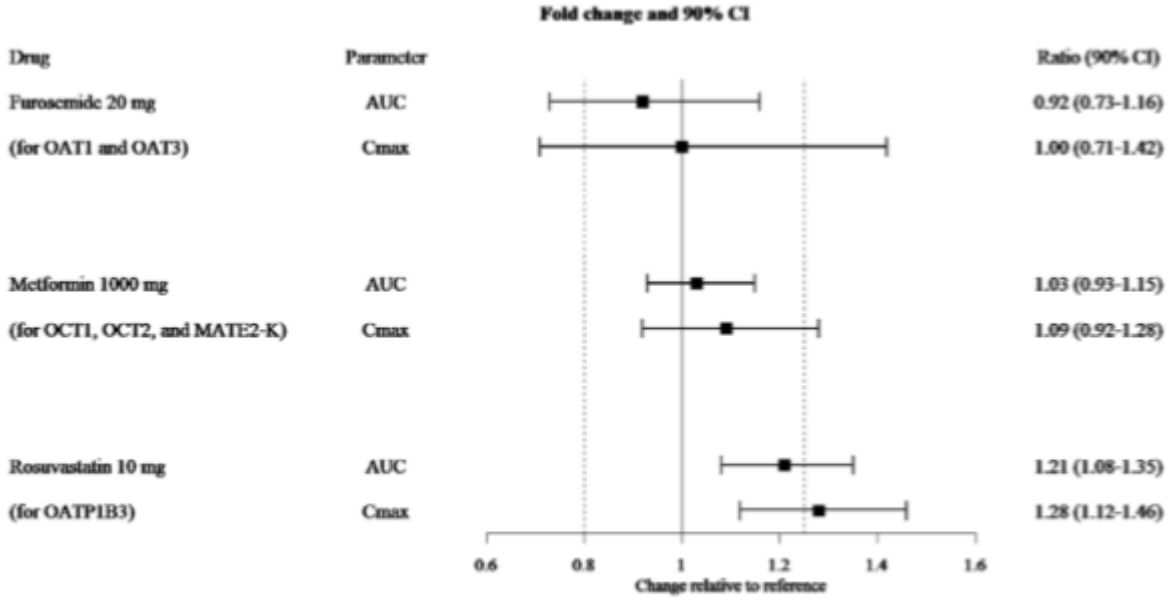
No significant induction of CYP1A2, and 2B6 by cefiderocol was shown in human hepatocytes. Induction of CYP 3A4 was however observed in vitro.

Cefiderocol was not an inhibitor of PgP, OATP1B1, MATE1, P-gp, BCRP, and BSEP at clinically relevant concentrations (50x $C_{max,u}$ 2500 µM). Cefiderocol is thus not expected to affect the PK of coadministered drugs that are substrates of these transporters.

Transporters	IC50 (μM)
P-gp	> 10000
BCRP	4700
OATP1B1	4850
OATP1B3	2570
OAT1	141
OAT3	292
OCT2	2170
OCT1	1550
MATE1	4730
MATE2-K	1230
BSEP	> 10000

As cefiderocol showed the potential for a DDI with substrates of the OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K transporters, a clinical DDI study was conducted to investigate the potential inhibitory effects of cefiderocol on the PK of substrates for these various transporters.

The in vivo studies with furosemide (substrate of OAT1 and OAT3) and metformin (substrate of OCT1, OCT2, and MATE2K) showed no increase in AUC upon coadministration with cefiderocol. In the study with rosuvastatin (substrate of OATP1B3), AUCR was slightly elevated (Figure 4), which was not clinically significant.



AUC = area under the plasma concentration-time curve; CI = confidence interval; C_{max} = maximum plasma concentation; MATE = multidrug and toxin extrusion; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter

Source: Figure derived from Study R2115 data.

Figure 5: Summary of the perpetrator interactions of cefiderocol as studies in in vivo drug drug interaction studies.

Cefiderocol did not significantly affect iron homeostasis.

Exposure relevant for safety evaluation

After administration of a single 2-g dose of cefiderocol infused over 3 hours, the geometric mean (percent coefficient of variation [CV%] Geometric Mean) C_{max} and $AUC_{0\text{-}inf}$ values were 89.7 µg/mL (20.5%) and 386.1 µg·hr/mL (17.2%), respectively (Study R2116).

2.4.3. Pharmacodynamics

Introduction

This section highlights the studies that describe the in vitro activity of cefiderocol and the most important studies and analyses for dose selection. It should be noted that because of the limited clinical development programme performed for this product in keeping with what is described in the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (EMA/CHMP/351889/2013) for products that are candidates to address an unmet medical need, the PK/PD analyses incorporating non-clinical PK/PD data and patient PK data are considered pivotal for dose justification for the proposed indication.

Mechanism of action

Cefiderocol is a catechol substituted siderophore cephalosporin β-lactam antibacterial agent that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (mainly PBP3). The bacterial entry of cefiderocol differs from authorised β-lactams. Cefiderocol binds to ferric iron via its catechol moiety forming a chelating complex. This allows cefiderocol to be actively transported into the periplasmic space through siderophore uptake systems in addition to passive diffusion through outer membrane porin channels. The catechol group is also assumed to be the cause of enhanced stability of cefiderocol to both serine- and metallo-type β-lactamases.

The stability of cefiderocol against class A to D β-lactamases including carbapenemases seems to be a result of relatively high K_m and/or lower k_{cat}. In addition, cefiderocol had low ability of chromosomal AmpC induction. Moreover, cefiderocol has been found to be able to circumvent innate bacterial permeability barriers such as the overproduction of multidrug efflux pumps and the loss of outer membrane porins which are known methods for antibacterial penetration, according to studies using genetically modified *P. aeruginosa* strains.

Primary and Secondary pharmacology

In vitro

In vitro activity studies

Antimicrobial susceptibility testing

Methodology for antimicrobial susceptibility testing of cefiderocol in iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB) approved by the Clinical and Laboratory Standards Institute (CLSI) was used to determine the minimum inhibitory concentration (MIC) of cefiderocol. Iron concentration in excess of 0.03 mg/L resulted in an upward shift of the MIC of cefiderocol. The sensitivity of the cefiderocol MIC methodology to changes in the iron concentration of growth medium is considered to be due to differences in the level of induction of iron transporters in the outer membrane of bacteria under iron-depleted conditions compared to iron-replete conditions. According to the Applicant the low concentration of free iron available for bacterial growth in ID-CAMHB, better reflects the physiological environment found at the site of bacterial infections. PK/PD analysis of the in vivo efficacy of

cefiderocol in neutropenic murine thigh/lung infection models caused by strains which have different MICs between CAMHB and ID-CAMHB indicated that the MIC determined in ID-CAMHB had a better correlation with in vivo efficacy than the MIC determined in CAMHB.

Antibacterial spectrum

The antibacterial spectrum of cefiderocol includes mainly Enterobacteriaceae and non-fermenting bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Burkholderia cepacia* and *Stenotrophomonas maltophilia*. Cefiderocol lacks clinically relevant activity against Gram-positive bacteria and anaerobic bacteria.

The table below summarises susceptibility data for key pathogens from randomly collected clinical isolates from three multi-national surveillance studies and one multi-national surveillance study including Proteeae isolates only. Cefiderocol had MIC_{90} values up to 2 mg/L against various Gram-negative bacteria other than *B. multivorans* (belonging to *B. cepacia* complex with an MIC_{90} of 32 mg/L).

Table PD1. Susceptibility data of cefiderocol against clinical isolates collected in year 1, year 2, year 3, and Proteeae from multi-national surveillance studies (Pooled data from SIDERO-WT-2014/2015/2016)

Species	Number of Strains	MIC (mg/L)			S [b]
		Range	MIC_{50}	MIC_{90}	(%)
E. coli	5139	≤ 0.002 - 8	0.12	0.5	99.96
K. pneumoniae	4627	≤ 0.002 - 8	0.12	1	99.78
K. oxytoca	1434	≤ 0.002 - 4	0.06	0.25	100
E. aerogenes	1017	≤ 0.002 - 8	0.12	0.5	99.90
C. freundii	828	≤ 0.002 - 8	0.06	0.5	99.88
C. koseri	517	0.008 - 8	0.25	0.5	99.81
E. cloacae	1800	≤ 0.002 - 128	0.25	1	99.89
M. morganii	697	≤ 0.002 - > 256	0.12	0.25	99.86
P. vulgaris	537	≤ 0.002 - 0.5	0.015	0.12	100
P. mirabilis	819	≤ 0.002 - > 256	0.015	0.12	99.51
P. rettgeri	341	≤ 0.002 - > 256	0.015	0.12	99.41
S. marcescens	2382	≤ 0.002 - 32	0.12	0.5	99.83
P. aeruginosa	4942	≤ 0.002 - 8	0.12	0.5	99.96
A. baumannii	2896	≤ 0.002 - > 256	0.12	2	95.61
S. maltophilia	1173	≤ 0.002 - 64	0.06	0.25	99.83
B. cepacia complex [a]	164	≤ 0.002 - 64	0.015	0.25	95.73

MIC = minimum inhibitory concentration; $MIC_{50\ (90)}$ = MIC at which 50% (90%) of tested strains are inhibited

a *B. cepacia* complex include *B. cepacia*, *B. cenocepacia*, *B. dolosa*, *B. multivorans*, and *B. vietnamensis*

b Percentage (%) of susceptible strains were calculated by using the following criteria: S: ≤ 4 mg/L

A. baumannii = Acinetobacter baumannii, B. cepacia = Burkholderia cepacia, C. freundii = Citrobacter freundii, C. koseri = Citrobacter koseri, E. cloacae = Enterobacter cloacae, E. coli = Escherichia coli, K. aerogenes = Klebsiella aerogenes, K. oxytoca = Klebsiella oxytoca, K. pneumoniae = Klebsiella pneumoniae, M. morganii = Morganella morganii, P. aeruginosa = Pseudomonas aeruginosa, P. mirabilis = Proteus mirabilis, P. rettgeri = Providencia rettgeri, P. vulgaris = Proteus vulgaris, S. maltophilia = Stenotrophomonas maltophilia, S. marcescens = Serratia marcescens.

The percentages of strains with cefiderocol and comparative agent MICs below the cut-offs shown are displayed in the table below.

Table PD2. Summary of percentage of susceptible strains to cefiderocol and comparators in multi-national surveillance studies

Species (Number of Strains)	Percentage (%) of susceptible strains[a]						
	Cefiderocol			CAZ/ AVI	CEF/ TAZ	CPFX	CST
	MIC ≤ 2 mg/L	MIC ≤ 4 mg/L	MIC ≤ 8 mg/L				
All Gram-negative (30459)	98.27	99.45	99.68	90.20	82.75	66.21	95.49 (n = 25372)[e]
Enterobacteriaceae (20949)	98.61	99.86	99.95	99.23	89.21	74.47	96.54 (n = 16026)[f]
Non-fermenters (9510)[b]	97.53	98.53	99.08	70.33	68.52	48.01	93.67 (n = 9346)[g]
CarbNS Enterobacteriaceae (578)[c]	81.14	97.92	99.48	75.95	4.67	6.92	74.27 (n = 517)[f]
ESCR Enterobacteriaceae (2547)[d]	91.32	99.13	99.72	93.95	53.23	11.42	92.34 (n = 2379)[f]
CarbNS non-fermenters (4331)[b,c]	95.82	97.57	98.63	40.96	34.61	9.60	86.65 (n = 4208)[g]
CarbNS *P. aeruginosa* (1154)[c]	98.52	99.91	100	75.38	76.08	27.90	98.35
CarbNS *A. baumannii* (1891)[c]	91.80	94.87	97.19	16.23	7.77	0.47	85.14
S. maltophilia (1173)	99.65	99.82	99.82	42.88	34.27	5.20	78.17

AVI = avibactam; CarbNS = carbapenem nonsusceptible; CAZ = ceftazidime; CEF = ceftolozane; CPFX = ciprofloxacin; CST = colistin; ESCR = extended-spectrum cephalosporin-resistant; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration; TAZ = tazobactam

a Percentage (%) of susceptible strains was calculated according to the EUCAST interpretative clinical breakpoint criteria as follows: CAZ/AVI: ≤ 8 mg/L, CEF/TAZ: ≤ 1 mg/L for Enterobacteriaceae, ≤ 4 mg/L for non-fermenters CPFX: ≤ 0.25 mg/L for Enterobacteriaceae, ≤ 0.5 mg/L for *P. aeruginosa*, *Burkholderia* spp., and *S. maltophilia*, and ≤ 1 mg/L for *Acinetobacter* spp., CST: ≤ 2 mg/L.

b Non-fermenters include *P. aeruginosa*, *Burkholderia* spp., *S. maltophilia*, and *Acinetobacter* spp.

c CarbNS strain was defined as meropenem MIC ≥ 4 mg/L.

d ESCR Enterobacteriaceae strain was defined as cefepime MIC ≥ 8 mg/L for Enterobacteriaceae.

e *Serratia* spp., Proteeae, and *Burkholderia* spp. were excluded because they are intrinsically resistant to CST.

f *Serratia* spp. and Proteeae were excluded.

g *Burkholderia* spp. was excluded.

The activity of cefiderocol against various carbapenemase-producers collected in the SIDERO-CR-2014/2016 study was evaluated using molecularly characterised meropenem-resistant Enterobacteriaceae (n=1021) and meropenem non-susceptible *P. aeruginosa* (n=262) and *A. baumannii* (n=368). In summary, cefiderocol had a MIC_{90} of ≤ 4 mg/L against Enterobacteriaceae producing KPC, VIM and OXA-48-like carbapenemase, *P. aeruginosa* producing VIM and *A. baumannii* producing OXA-23 type carbapenemase. The cefiderocol MIC_{90} was 8 mg/L for NDM-producing Enterobacteriaceae and OXA-24/40-like carbapenemase-producing *A. baumannii*. In addition, cefiderocol MICs were ≤ 4 mg/L against *P. aeruginosa* producing IMP, GES, and NDM and *A. baumannii* producing OXA-58.

Resistance to cefiderocol

Resistance in surveillance studies

From the 9205 isolates tested in the SIDERO-WT 2014 study, 38 isolates with elevated MIC values for cefiderocol (≥ 8 mg/L) were further characterised. The activity of cefiderocol against 33/38 isolates was significantly enhanced by the addition of avibactam (AVI), a serine-type β-lactamase inhibitor which suggests that elevated MICs were in part due to the presence of an unknown β-lactamase enzyme. The remaining 5 isolates contained NDM-1, a metallo-β-lactamase that is not inhibited by avibactam. Among these 33 isolates, 24 were *A. baumannii* isolates from Russia or Turkey and contained the PER-1 β-lactamase. However, cefiderocol demonstrated good activity against other PER-1 producing isolates with a MIC_{90} of 4 mg/L. Against the remaining 5 NDM-producers (also from Turkey), addition of both AVI and the metallo-type β-lactamase inhibitor, dipicolinic acid (DPA), enhanced the activity of cefiderocol. These results further suggest that presence of NDM-1 and some serine-type β-lactamases such as PER-1 may contribute to elevated cefiderocol MICs in clinical isolates.

Similar characteristics were also observed when assessing 26 isolates with cefiderocol MIC ≥ 8 mg/L from the multi-national surveillance study SIDERO-CR-2014/2016.

Frequency of spontaneous resistance

The frequency of spontaneous resistance of *E. coli*, *E. cloacae*, *K. pneumoniae*, and *P. aeruginosa* (8 strains in total) in the presence of 10 × MIC of cefiderocol was determined. If resistant mutants were isolated, the in vitro activity of cefiderocol against the mutant strains was determined and compared to the susceptibility of the parent strains. The magnitude of the order of frequency of the resistance for cefiderocol was 10^{-7} to 10^{-8} except for *P. aeruginosa* for which the frequency ranged from 10^{-6} to 10^{-8}. Cefiderocol MIC increase was shown to be associated with the mutation in the upstream region of *pvdS* (pyoverdine synthesis gene) and *fadD3* (fatty acyl-CoA synthetase) in *P. aeruginosa*, and *baeS*, *envZ*, *ompR* (all are 2-component signal transduction gene), and *exbD* (biopolymer transport gene) in *K. pneumoniae*.

Resistance acquisition assay by serial passage

Resistance acquisition was evaluated for *K. pneumoniae*, and *P. aeruginosa* (5 strains in total) by a 10 times serial passage in two different media. The MIC of cefiderocol increased in general 1 to 4-fold but for one strain up to 8-fold.

Resistant acquisition by using an in vitro pharmacodynamic model

To estimate the risk of emergence of cefiderocol-resistant mutants during the treatment of patients, in vitro PD models simulating the free concentration-time curves in human plasma was used. The simulated concentration-time curves were determined for a 2-g cefiderocol q8h administration with 3-hour infusion, 2-g/0.5 g CAZ/AVI q8h administration with 2-hour infusion, and 1-g MEPM q8h administration with 1-hour infusion. Against all 3 strains, cefiderocol showed rapid bacterial reduction within 4 hours. Regrowth was observed for one strain, but no growth was observed with a MIC of ≥ 10 mg/L and no resistant colonies to cefiderocol were detected at the 24- and 72-hour time points.

Emergence of resistance in the clinical studies

In the cUTI study there were 7 subjects in the Micro-ITT population with an increase in cefiderocol MIC of at least 4-fold from baseline in the cefiderocol group. For all but one subject infected with *P. aeruginosa* that had a MIC of 8 mg/L at follow-up all isolates´ post-baseline MICs were at least two dilutions below the proposed susceptibility breakpoint of 4 mg/L (*E. coli* in 3 subjects and *E. cloacae*, *E. aerogenes* and *P. mirabilis* in one subject each).

In the CREDIBLE-CR study there were also seven subjects in the Micro-ITT population with an increase in MIC to cefiderocol of at least 4-fold from baseline in the cefiderocol group. The pathogens that showed the increases in MIC from baseline values at either EOT or TOC were: *A. baumannii* in 2 subjects, *K. pneumoniae* in 1 subject, *P. aeruginosa* in 2 subjects, and *S. maltophilia* in 2 subjects. All except 1 had an MIC value of ≤ 2 mg/L at EOT or TOC. One subject with an isolate of *A. baumannii* had an MIC of >64 mg/L at TOC.

Effects of human body fluids and other factors on in vitro activity of cefiderocol

The effect of various factors on the in vitro activity of cefiderocol was examined against 4 Gram-negative bacteria. The MIC of cefiderocol was increased by high inoculum size for all four strains tested and by acidic pH and high iron content for three out of four strains. For one strain of *P. aeruginosa* MIC testing in 10% pulmonary surfactant and in 50% human serum resulted in a 4-fold and 10-fold increase in MIC, respectively, whereas minimal effects were seen for the other strains tested. For one strain of *A. baumannii* MIC testing in 80% urine resulted in a nearly 10-fold increase in MIC.

In vivo

Cefiderocol evaluated in animal models of infection

The therapeutic efficacy of cefiderocol has been assessed using various animal infection models. Type of infection model, test organisms, dosages and cefiderocol MICs.

Throughout these animal studies, cefiderocol showed dose-dependent bacterial reductions in each infection site. In the murine thigh model simulated human PK resulted in >2 $\log_{10}$ kill for all but one strain for which the colony count however was reduced by >1 $\log_{10}$.

In in vivo efficacy studies conducted with other siderophore β-lactams such as MB-1 and SMC-3176 adaptive resistance phenotypes have been observed. No adaptive resistance phenotypes were observed with cefiderocol in similar studies.

In the rat model of pneumonia, an enhanced efficacy of cefiderocol was observed with a prolonged infusion (from 1-hour to 3-hour infusion) at the same dosage of 2 g, human dose regimen suggesting that cefiderocol efficacy could be correlated with the %*f*T>MIC values.

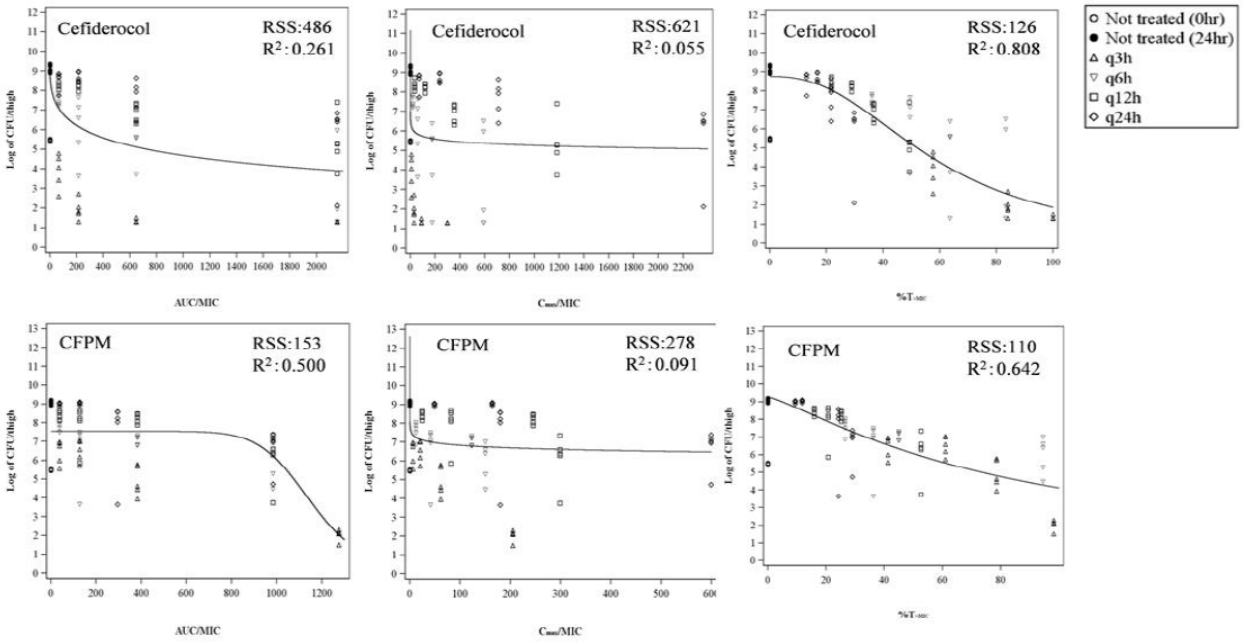
Control antibacterial agents were included in all the in vivo studies. A disparity was noted in the lung infection model between the in vitro and in vivo activities of meropenem and CAZ/AVI against metallo-type β-lactamase producing strains with significant CFU reductions despite high MICs. It has previously been hypothesised that the in vivo expression of MBLs may not be enough in murine lung infection models (Zmartlicka et al, 2015).

Support for dose selection

The principal support for dose selection was based on nonclinical PK/PD studies to determine the PK/PD index best correlated with cefiderocol efficacy, the magnitude of that PK/PD index (or PK/PD target) required for 1-$\log_{10}$ CFU reductions in murine thigh or lung infections, and Monte-Carlo simulations using human population PK model to determine the probability of target attainment in plasma and epithelial lining fluid (ELF) at different MICs for subjects with various degree of renal function.

Dose fractionation studies for cefiderocol in a neutropenic murine thigh infection model confirmed that consistent with other β-lactam antibacterials T>MIC was the PK/PD index best correlated with in vivo efficacy with the highest coefficient of determination (R^2) and lowest value of residual sum of squares (RSS).

Figure PD1. Determination of PK/PD index best correlated with in vivo efficacy from a dose fractionation study using neutropenic murine thigh infection caused by *P. aeruginosa*



AUC = area under the plasma concentration-time curve; CFPM = cefepime; CFU = colony forming unit; C_{max} = maximum plasma concentration; MIC = minimum inhibitory concentration; q3h = every 3 hours; q6h = every 6 hours; q12h = every 12 hours; q24h = every 24 hours; R2 = coefficient of determination; RSS = residual sum of squares; $\%T_{<MIC}$ = percentage of the time above the MIC of free cefiderocol concentrations

The magnitude of the %*f*T>MIC required for bacteriostatic and bactericidal effects was determined in murine thigh or lung infection models caused by a total of 23 strains of Gram-negative bacilli with divergent MICs including 18 carbapenem-resistant strains.

The %*f*T>MIC values required for efficacy in the lung infection model was slightly smaller than that of the neutropenic murine thigh infection model. There was a fairly wide range of both static and cidal values within and between bacterial species.

Table PD3. Magnitude of %*f*T>MIC required for efficacy of cefiderocol in the murine thigh and lung infection models caused by multiple bacterial species

Test Organisms (Number of Strains Used for Each Infection Models)	$\%fT_{>MIC}$ (mean ± SD)			
	Thigh Infection		Lung Infection	
	Static	1-$\log_{10}$ Reduction	Static	1-$\log_{10}$ Reduction
E. coli, K. pneumoniae **(10 thigh, 9 lung)**	62.5 ± 27.4	73.3 ± 23.3	54.7 ± 24.1	64.4 ± 22.5
P. aeruginosa **(2 thigh, 3 lung)**	70.8	87.1	57.4 ± 10.2	70.3 ± 9.0
A. baumannii **(0 thigh, 3 lung)**	Not done	Not done	82.0 ± 4.6	88.1 ± 3.4
S. maltophilia **(0 thigh, 4 lung)**	Not done	Not done	45.6 ± 18.9	53.9 ± 18.1
Total (12 thigh, 19 lung)	63.9 ± 25.2	75.6 ± 22.5	57.5 ± 21.6	66.9 ± 20.2

SD = standard deviation; $\%fT_{>MIC}$ = percentage of the time above the MIC of free cefiderocol concentrations

Abbreviated species name: *A. baumannii* = *Acinetobacter baumannii*, *E. coli* = *Escherichia coli*, *K. pneumoniae* = *Klebsiella pneumoniae*, *P. aeruginosa* = *Pseudomonas aeruginosa*, *S. maltophilia* = *Stenotrophomonas maltophilia*.

The %*f*T>MIC value of 75% which was the mean PK/PD target required to achieve 1-$\log_{10}$ reduction determined in the neutropenic thigh model was initially used in the PTA estimations (table below). Cefiderocol concentrations in ELF were estimated based on the ELF:plasma (free) ratio of 0.239 derived from the intrapulmonary PK study conducted in healthy subjects who received a 2-g dose with 1-hour infusion. In the PTA estimations depicted below all available PK data was used.

Table PD4. PTA for 75% *f*T>MIC in simulated patients with HAP/VAP/HCAP, BSI/Sepsis, or cUTI/AUP by renal function at the selected dosage regimen

Probability of target attainment for 75% $fT_{>MIC}$ or 75% $fT_{>MIC,ELF}$										
Infection		Renal function group	Dose regimens with 3-hr infusion	MIC (μg/mL)						
				0.25	0.5	1	2	4	8	16
cUTI/AUP (APEKS-cUTI study)[a]	Plasma	Augmented renal function	2 g q6h	100	100	100	99.6	95.6	74.7	27.6
		Normal renal function	2 g q8h	100	100	99.9	98.1	89.0	56.5	13.8
		Mild renal impairment	2 g q8h	100	100	100	99.8	97.7	80.8	35.1
		Moderate renal impairment	1.5 g q8h	100	100	100	99.9	99.2	93.0	52.6
		Severe renal impairment	1 g q8h	100	100	100	100	100	98.4	70.0
		ESRD	0.75 g q12h	100	100	100	100	100	95.8	61.3
cUTI (CREDIBLE-CR study)[b]	Plasma	Augmented renal function	2 g q6h	100	100	100	100	99.9	96.9	73.3
		Normal renal function	2 g q8h	100	100	100	100	99.6	93.6	56.3
		Mild renal impairment	2 g q8h	100	100	100	100	99.8	98.4	81.2
		Moderate renal impairment	1.5 g q8h	100	100	100	100	100	99.6	90.4
		Severe renal impairment	1 g q8h	100	100	100	100	100	100	95.9
		ESRD	0.75 g q12h	100	100	100	100	100	100	91.6
BSI/sepsis	Plasma	Augmented renal function	2 g q6h	100	100	100	100	99.4	91.3	49.6
		Normal renal function	2 g q8h	100	100	100	99.9	97.3	80.6	32.6
		Mild renal impairment	2 g q8h	100	100	100	99.9	99.6	94.4	57.7
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.9	98.0	74.8
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.8	84.8
		ESRD	0.75 g q12h	100	100	100	100	100	99.2	79.2
HAP/VAP/HCAP	Plasma	Augmented renal function	2 g q6h	100	100	100	100	99.7	94.5	60.4
		Normal renal function	2 g q8h	100	100	100	99.9	98.9	87.1	43.4
		Mild renal impairment	2 g q8h	100	100	100	100	99.8	97.0	69.7
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.9	98.7	83.3
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.9	90.7
		ESRD	0.75 g q12h	100	100	100	100	100	99.6	86.3
	ELF	Augmented renal function	2 g q6h	100	100	99.6	93.6	57.4	9.0	0.1
		Normal renal function	2 g q8h	100	99.9	98.4	85.4	40.3	3.7	0.0
		Mild renal impairment	2 g q8h	100	100	99.8	96.7	66.1	14.9	0.4
		Moderate renal impairment	1.5 g q8h	100	100	99.9	98.6	80.9	24.9	1.1
		Severe renal impairment	1 g q8h	100	100	100	99.9	88.7	37.1	3.1
		ESRD	0.75 g q12h	100	100	100	99.4	84.6	28.5	1.5

[a] Simulated using the parameters for cUTI/AUP patients in the phase 2 APEKS-cUTI study.

[b] Simulated using the parameters for cUTI patients in the phase3 CREDIBLE-CR study.

PK steady state was assumed. PTA is shown in percent (%).
Augmented: CrCL ≥ 120 mL/min (120 to < 150 = 50%; ≥ 150 = 50%). Normal: CrCL 90 to < 120 mL/min.
Mild: CrCL 60 to < 90 mL/min. Moderate: CrCL 30 to < 60 mL/min. Severe: CrCL 15 to < 30 mL/min. ESRD: CrCL 5 to < 15 mL/min.
1000 simulated patients in each simulation scenario.
Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%.
Albumin was assumed to be log-normal distributed with mean of 4.2 g/dL (cUTI/AUP in phase 2 APEKS-cUTI study) or 2.8 g/dL (cUTI in CREDIBLE-CR study, BSI/sepsis, and HAP/VAP/HCAP) and CV of 30%.

The following tables shows PTA simulations using more conservative PDTs (up to 100% *f*T>MIC):

Table PD5. PTA for 90% *f*T>MIC in simulated patients with HAP/VAP/HCAP, BSI/Sepsis, or cUTI/AUP by renal function at the selected dosage regimen

Probability of target attainment for 90% $fT_{>MIC}$ or 90% $fT_{>MIC,ELF}$										
Infection		Renal function group	Dose regimens with 3-hr infusion	MIC (µg/mL)						
				0.25	0.5	1	2	4	8	16
cUTI/AUP (APEKS-cUTI study)[a]	Plasma	Augmented renal function	2 g q6h	100	100	99.7	96.2	83.5	50.4	14.3
		Normal renal function	2 g q8h	99.9	99.8	97.9	91.6	70.4	34.1	5.8
		Mild renal impairment	2 g q8h	100	100	99.8	98.3	89.2	60.6	20.0
		Moderate renal impairment	1.5 g q8h	100	100	100	99.5	96.8	81.2	38.8
		Severe renal impairment	1 g q8h	100	100	100	100	99.6	93.6	59.7
		ESRD	0.75 g q12h	100	100	100	100	99.4	91.0	52.4
cUTI (CREDIBLE-CR study)[b]	Plasma	Augmented renal function	2 g q6h	100	100	100	100	99.0	91.1	55.3
		Normal renal function	2 g q8h	100	100	100	99.8	96.9	82.5	40.5
		Mild renal impairment	2 g q8h	100	100	100	99.8	99.6	95.2	66.0
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.9	98.3	83.1
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.9	91.8
		ESRD	0.75 g q12h	100	100	100	100	100	99.5	87.8
BSI/sepsis	Plasma	Augmented renal function	2 g q6h	100	100	100	99.6	95.1	75.6	31.6
		Normal renal function	2 g q8h	100	99.9	99.9	98.0	90.2	61.9	18.8
		Mild renal impairment	2 g q8h	100	100	99.9	99.7	97.9	84.3	41.8
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.4	94.2	61.6
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.0	78.1
		ESRD	0.75 g q12h	100	100	100	100	100	97.7	70.8
HAP/VAP/HCAP	Plasma	Augmented renal function	2 g q6h	100	100	100	99.8	97.1	83.2	40.8
		Normal renal function	2 g q8h	100	100	99.9	99.4	94.1	72.8	28.4
		Mild renal impairment	2 g q8h	100	100	100	99.8	98.8	90.1	51.9
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.8	96.6	71.9
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.6	84.6
		ESRD	0.75 g q12h	100	100	100	100	100	98.9	79.8
	ELF	Augmented renal function	2 g q6h	100	99.7	96.7	82.0	38.4	5.4	0.1
		Normal renal function	2 g q8h	99.9	99.3	93.0	69.8	26.1	2.1	0.0
		Mild renal impairment	2 g q8h	100	99.8	98.6	88.3	48.2	9.4	0.2
		Moderate renal impairment	1.5 g q8h	100	100	99.6	96.2	68.2	18.4	0.8
		Severe renal impairment	1 g q8h	100	100	100	99.6	82.6	31.2	2.5
		ESRD	0.75 g q12h	100	100	100	98.4	76.8	24.2	1.3

[a] Simulated using the parameters for cUTI/AUP patients in the phase 2 APEKS-cUTI study.

[b] Simulated using the parameters for cUTI patients in the phase3 CREDIBLE-CR study.

PK steady state was assumed. PTA is shown in percent (%).

Augmented: CrCL ≥ 120 mL/min (120 to < 150 = 50%; ≥ 150 = 50%). Normal: CrCL 90 to < 120 mL/min.

Mild: CrCL 60 to < 90 mL/min. Moderate: CrCL 30 to < 60 mL/min. Severe: CrCL 15 to < 30 mL/min. ESRD: CrCL 5 to < 15 mL/min.

1000 simulated patients in each simulation scenario.

Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%.

Albumin was assumed to be log-normal distributed with mean of 4.2 g/dL (cUTI/AUP in phase 2 APEKS-cUTI study) or 2.8 g/dL (cUTI in CREDIBLE-CR study, BSI/sepsis, and HAP/VAP/HCAP) and CV of 30% .

Table PD6. PTA for 100% *f*T>MIC in simulated patients with HAP/VAP/HCAP, BSI/Sepsis, or cUTI/AUP by renal function at the selected dosage regimen

Probability of target attainment for 100%$fT_{>MIC}$ or 100%$fT_{>MIC,ELF}$										
Infection		Renal function group	Dose regimens with 3-hr infusion	MIC (μg/mL)						
				0.25	0.5	1	2	4	8	16
cUTI/AUP (APEKS-cUTI study)[a]	Plasma	Augmented renal function	2 g q6h	100	100	99.3	94.5	79.4	44.5	11.1
		Normal renal function	2 g q8h	99.9	99.6	96.1	88.0	63.4	27.5	4.2
		Mild renal impairment	2 g q8h	100	99.8	99.3	96.6	84.4	52.9	15.0
		Moderate renal impairment	1.5 g q8h	100	100	99.9	99.2	95.4	76.1	33.8
		Severe renal impairment	1 g q8h	100	100	100	100	99.5	91.1	55.5
		ESRD	0.75 g q12h	100	100	100	100	99.2	88.2	47.9
cUTI (CREDIBLE-CR study)[b]	Plasma	Augmented renal function	2 g q6h	100	100	100	100	98.0	88.3	51.1
		Normal renal function	2 g q8h	100	100	99.9	99.4	95.1	77.6	34.3
		Mild renal impairment	2 g q8h	100	100	100	99.8	98.9	93.2	59.4
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.8	97.7	79.1
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.7	90.1
		ESRD	0.75 g q12h	100	100	100	100	100	99.4	85.7
BSI/sepsis	Plasma	Augmented renal function	2 g q6h	100	100	100	99.4	93.6	71.6	28.5
		Normal renal function	2 g q8h	100	99.9	99.5	96.2	85.8	54.0	14.1
		Mild renal impairment	2 g q8h	100	100	99.8	99.4	96.0	78.0	36.1
		Moderate renal impairment	1.5 g q8h	100	100	100	99.9	98.7	91.2	55.8
		Severe renal impairment	1 g q8h	100	100	100	100	100	98.3	74.7
		ESRD	0.75 g q12h	100	100	100	100	100	96.8	68.0
HAP/VAP/HCAP	Plasma	Augmented renal function	2 g q6h	100	100	100	99.7	95.9	79.8	37.0
		Normal renal function	2 g q8h	100	100	99.9	98.3	91.2	64.6	23.2
		Mild renal impairment	2 g q8h	100	100	99.9	99.7	98.2	85.9	46.4
		Moderate renal impairment	1.5 g q8h	100	100	100	100	99.5	94.8	66.7
		Severe renal impairment	1 g q8h	100	100	100	100	100	99.5	81.8
		ESRD	0.75 g q12h	100	100	100	100	100	98.3	77.1
	ELF	Augmented renal function	2 g q6h	100	99.7	95.7	78.3	34.8	4.7	0.1
		Normal renal function	2 g q8h	99.9	98.1	90.5	62.8	19.8	1.4	0.0
		Mild renal impairment	2 g q8h	99.9	99.7	98.1	84.9	44.0	7.5	0.1
		Moderate renal impairment	1.5 g q8h	100	100	99.4	94.6	63.5	15.2	0.6
		Severe renal impairment	1 g q8h	100	100	100	99.2	80.0	28.6	2.1
		ESRD	0.75 g q12h	100	100	100	98.2	74.6	21.7	1.3

[a] Simulated using the parameters for cUTI/AUP patients in the phase 2 APEKS-cUTI study.

[b] Simulated using the parameters for cUTI patients in the phase3 CREDIBLE-CR study.

PK steady state was assumed. PTA is shown in percent (%).

Augmented: CrCL ≥ 120 mL/min (120 to < 150 = 50%; ≥ 150 = 50%). Normal: CrCL 90 to < 120 mL/min.

Mild: CrCL 60 to < 90 mL/min. Moderate: CrCL 30 to < 60 mL/min. Severe: CrCL 15 to < 30 mL/min. ESRD: CrCL 5 to < 15 mL/min.

1000 simulated patients in each simulation scenario.

Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%.

Albumin was assumed to be log-normal distributed with mean of 4.2 g/dL (cUTI/AUP in phase 2 APEKS-cUTI study) or 2.8 g/dL (cUTI in CREDIBLE-CR study, BSI/sepsis, and HAP/VAP/HCAP) and CV of 30% .

Other issues

Susceptibility testing breakpoints

Susceptibility interpretive criteria were set for Enterobacterales and *P. aeruginosa* (2/2 mg/L, respectively). The EUCAST believed there was insufficient evidence to set breakpoints for *A. baumannii* and *S. maltophilia* due to the low number of clinical cases and the low response rate despite the high degree of in vitro activity against these species.

Pharmacodynamic interactions

The in vitro combination activities of cefiderocol with other commercially available antibacterial agents have been evaluated. No antagonism was observed in the checkerboard or fixed concentration studies between cefiderocol and other antibiotics such as vancomycin, daptomycin, linezolid, clindamycin, metronidazole, tigecycline, CAZ/AVI, CEF/TAZ, and colistin, or in the time-kill studies using a combination of cefiderocol with meropenem, amikacin, or ciprofloxacin against KPC-producing *K. pneumoniae*, MDR *P. aeruginosa*, and MDR *A. baumannii*.

Relationship between plasma concentration and effect in the clinical studies

The relationship between the %*f*T>MIC and efficacy was evaluated for patients in the APEKS-cUTI, the CREDIBLE-CR and the APEKS-NP studies. No PK/PD relationships were identified for any of efficacy responses (composite, clinical or microbiological response).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The applicant has performed a clinical pharmacology program to describe the pharmacokinetics and elimination of cefiderocol, and to identify special populations and drug interactions with risks for altered drug exposure.

Methods

Iron chelation is prevented by acid treatment during sample preparation, which gives access to robust bioanalytics in all tested matrices except 2% haemolytic plasma. All provided bioanalysis methods were adequately validated for the intended purpose.

Given the small number of patients in the phase III CREDIBLE study, pop PK based probability of target attainment (PTA) analyses and simulations are pivotal. The first pop PK model is also the base for all dose recommendations for RI and different dialysis types. The models were considered adequate for PTA simulations.

The final POPPK model was a 3-compartment linear model with the effects of CrCL and infection on CL; the effects of body weight, albumin and infection on V1; and the effect of body weight on V2. PK parameters were estimated with good precision (%RSE<20%). The inter-individual variability for parameters reduced from the base model to the final model and there was an improvement in the diagnostic plots for the final model compared to the base model, with no major trends. By inspection of the pcVPCs, the predictive performance of the model appears reasonable.

The estimated exponents on BW are acceptable for an adult population. For future paediatric application, it should be considered to use theoretical allometric scaling.

Overall, the updated popPK model is considered adequate to use for PTA simulations. The parameter estimates and PTA simulations were generally consistent with earlier models. The previous conclusions regarding the posology based on renal function are valid.

Distribution

Regarding distribution to lungs, the ELF study seems adequately performed. Single dose data is considered acceptable as no accumulation is seen following repeated dosing and the ELF concentration profile appeared to be parallel to the plasma concentration. The geometric mean concentration ratios of ELF to plasma over 6 hours ranged from 0.0927 to 0.116 indicating a low distribution to ELF relative to plasma concentrations. An additional Phase 1b study, (ELF study, Study 1713R2117) in hospitalised subjects with bacterial pneumonia on treatment with standard of care antibiotics and requiring mechanical ventilation has been initiated and may further elucidate lung penetration.

The applicant has re-estimated the ELF to plasma ratio to be 24% based on free drug in plasma. The applicant reports that this adjusted penetration ratio of cefiderocol into ELF is comparable to that of ceftazidime (0.229 based on free drug in plasma using protein unbound fraction of 0.9), which is approved for treatment of nosocomial pneumonia. This estimate is based on data reported in the literature dating back >15 years. Furthermore, it is not just the ELF to plasma ratio that determines efficacy but the PDT in ELF (which is unknown for either drug) and any effects there may be of ambient conditions, such as pH. Therefore, just because the derived ratios are comparable does not necessarily mean that these agents will be similarly efficacious. Thus, even if the applicant's derived ratio of 24% is taken at face value, it raises some concern for use of cefiderocol to treat infections in the lungs when

there are no clinical data available to support this. During the assessment, the applicant provided data from the APEKS-NP study, see clinical efficacy assessment.

Regarding the protein binding in ELF: based on literature, the applicant considers the protein binding in ELF to be low. This may be true, but no consideration is taken for the iron chelating properties of cefiderocol and their possible impact on protein binding in patients ELF. No new data could be provided, therefore the use of total concentration is still to be viewed as the best case scenario in the PTA analyses.

Elimination

The main elimination pathway of cefiderocol is renal excretion of unchanged drug. No major metabolites were detected in plasma, and there are no metabolites that need to be screened for enzyme inhibitory potential.

Based on the low concentrations/amounts of metabolites in plasma, there is no need for a detailed presentation of metabolite PK.

Dose-proportionality, time dependence & inter-individual variability

The results of study R2111 and study R2116 indicate dose-proportionality of cefiderocol in the dose range of 100 mg to 4000 mg.

There was no significant accumulation of cefiderocol at steady state. There are no indications of time-dependent pharmacokinetics.

Inter individual variability on Cmax and AUC was < 30% in healthy volunteers and 41-60% in patients. The lack of intra-individual variability data is acceptable.

Target population

The PK in the target population could be described using the same population PK model as for the healthy individuals, using renal function as a covariate. The infection status was however significant covariates as well.

Special populations

Renal impairment and augmented renal clearance

The results of the dedicated renal impairment study showed a significant effect of renal function on the pharmacokinetics of cefiderocol, which is expected for a substance that is predominantly renally excreted.

The proposed dosage adjustment for renally impaired patients is not based directly on the results of the RI study but on population-PK models and Monte Carlo simulations of PTA. During model development, different renal function markers were tested (CrCL, adjusted eGFR and absolute eGFR) and were found to simulate similar PTA. The proposed posology in section 4.2. of the SPC is based on Cockcroft-Gault CrCL which is supported.

Regarding safety in renally impaired patients, the prosed doses lead to similar AUC across the different renal impairment groups which is adequate from a PK perspective. Regarding efficacy in renally impaired patients, the reader is referred to the PD section where the PTA analyses are presented and assessed.

A dosage adjustment in patients with augmented renal clearance is also suggested from 120 ml/min. The upper limit of 200 ml/min used for PTA simulations reflects the target patient population. Only 8 patients had CrCL > 200 ml/min in CREDIBLE-CR, and their cefiderocol clearance did not necessarily

correlate with their renal function. Therefore, the unique dosing regimen for augmented clearance without upper cut-off is acceptable.

Hepatic impairment, gender, race & age

No hepatic impairment study is necessary, since hepatic impairment is not considered likely to significantly affect the pharmacokinetics of cefiderocol based on the results from the mass balance study. No cefiderocol dose adjustment is necessary for subjects with hepatic impairment.

No dedicated study to assess the effect of gender, race or age on cefiderocol PK was performed. It is agreed that no dose adjustment other than based on the renal function is required in these populations, as shown by the population PK models.

The POPPK model evaluated effects on cefiderocol CL and V1 by age. The CL was lower in older subjects with infection (≥ 85 years) and the V1 was similar in all age groups. The applicant concluded that the difference in CL reflected age-related change in CrCL. Hence it was considered to adjust dose by CrCL and not by age *per se*, which is further supported by safety data.

Body weight

It is agreed that despite of BW being a significant covariate, PTA is similar in patients ≥ 90kg to normal weight patients. Thus, no dose adjustment based on body weight is required, provided a cut-off of 4 µg/mL MIC.

Interactions

Effect of other medicines on cefiderocol

In the in vitro studies using human transporter expressing cells, cefiderocol is not a substrate for OAT1, OAT3, OCT2, MATE1, MATE2-K, P-gp, or BCRP. Therefore, coadministration of inhibitors of these transporters is expected to have no impact on the PK of cefiderocol, in particular since it is eliminated by renal filtration.

Effect of cefiderocol on other medicines

CYP inhibition experiments were performed with cefiderocol concentrations up to 1330 µM, except for CYP2C8 (5320 µM). 1330 µM is lower than 50 times Cmax,u (2500 µM) and the study is thus formally not compliant with the guideline. AUCR calculations using the mechanistic static model however suggest that no in vivo studies are required, which is acceptable.

The CYP induction study design was appropriate with adequate model substrates and inducers. The applicant did not investigate protein binding in the induction experiment, which is acceptable since it was run under serum-free conditions.

The applicant´s conclusion that no significant induction of CYP1A2, 2B6, and 3A4 by cefiderocol was shown are agreed to for CYP 1A2 and 2B6. For CYP 3A4 however, it is considered that cefiderocol shows an induction potential in vitro that requires an in vivo study with a sensitive CYP 3A4 substrate unless justified using the in vitro RIS correlation approach (GL on the investigation of drug interactions section 5.3.3.2, A2). These data will be provided post approval (recommendation).

Furthermore, since a signal for PXR mediated induction of CYP3A4 has been seen, the caution wording in section 4.5 was expanded to substrates of other relevant PXR inducible proteins, for example the CYP2C family and PgP. The applicant will be able to remove this wording if the PXR mediated induction of CYP3A4 is deemed nonsignificant in vivo.

The choice of substrates and inhibitors and their concentrations in the transporters studies is considered adequate. The concentration of cefiderocol in the transport inhibition studies was adequate for each type of transporter.

In the in vitro studies using human transporter expressing cells, Caco-2 cells, or BSEP expressing vesicle, the IC50 values of cefiderocol for OATP1B1, MATE1, P-gp, BCRP, and BSEP transporters were all 4700 µmol/L (3540 µg/mL as cefiderocol) or more. These findings demonstrate that cefiderocol is not expected to affect the PK of coadministered drugs that are substrates of these transporters.

As cefiderocol showed the potential for a drug-drug interaction (DDI) with substrates of the OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K transporters, a clinical DDI study was conducted to investigate the potential inhibitory effects of cefiderocol on the PK of substrates for these various transporters.

All 3 in vivo DDI studies were performed in accordance with the guideline regarding perpetrator and victim doses, including coverage of 90% of the c/t of the victim.

The studies with furosemide (substrate of OAT1 and OAT3) and metformin (substrate of OCT1, OCT2, and MATE2K) showed no increase in AUC upon coadministration with cefiderocol and it is agreed that no interaction with substrates of OAT1, OAT3, OCT1, COT2, and MATE2K is expected in vivo.

For the study with rosuvastatin, AUCR was slightly elevated (1.24, 1.1 to 1.4 for 90% CI). Concerns were raised regarding the timing of the administration (not reaching tmax simultaneously). No increased AUCR was observed in the two subject that had a rosuvastatin tmax close to the tmax of cefiderocol (ie end of infusion, 3h), suggesting that the worst case scenario of concomitant tmax did not lead to a clinically relevant drug drug interaction between cefiderocol and rosuvastatin, as a probe substrate for OATP1B3. While the number of patients this conclusion is based on is very small, this is considered sufficient for an assessment of the worst-case interaction in this case. The SmPC section 5.2 mentions this interaction as a 21% increase in AUCR, and not clinically relevant; which is appropriate.

Cefiderocol contains an iron chelating moiety, and limited data was provided on interactions with iron containing products. An interaction with cefiderocol as the victim has been excluded, and iron homeostasis was shown not to be significantly affected by cefiderocol. Ionophore toxicosis was also addressed and is considered unlikely.

Cefiderocol contains a catechol moiety and is metabolized by COMT (catechol o-methyl transferase), as detected in M9 and further downstream metabolites. The risk of interaction with substrates of COMT is considered low.

Based on the current data, the risk for clinically relevant PK interactions for cefiderocol as a victim is low. The risk for interactions as a perpetrator is low, though there remain uncertainties regarding CYP 3A4 and PXR mediated induction, and further post-approval action is required (REC1).

PK/PD

The analyses are adequately performed. Regarding assessment of PTA data, please see "pharmacodynamics" below.

Pharmacodynamics

Mechanism of action

Cefiderocol is a novel cephalosporin that like other β-lactam antibacterial agents inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins. Cefiderocol uptake differs from other β-lactams in that cefiderocol binds to ferric iron via its catechol moiety forming a chelating complex which allows

cefiderocol to be actively transported into the periplasmic space through siderophore uptake systems. The catechol group is also assumed to be the cause of enhanced stability of cefiderocol to both serine- and metallo-type β-lactamases. Likely because of its ability to utilise active transportation through the outer membrane of Gram-negative bacteria cefiderocol seems less adversely affected by efflux pumps and loss of outer membrane porins.

Susceptibility testing

The methodology for antimicrobial susceptibility testing has been agreed between the Applicant and the EUCAST.

In vitro activity

The antibacterial spectrum of cefiderocol includes mainly Enterobacteriaceae and non-fermenting bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Burkholderia cepacia* and *Stenotrophomonas maltophilia*.

In multi-national surveillance studies cefiderocol had MIC_{90} values up to 2 mg/L against various Gram-negative bacteria other than *B. multivorans* (belonging to *B. cepacia* complex with an MIC_{90} of 32 mg/L).

For carbapenem nonsusceptible Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* the MIC_{90s} were ≤4 mg/L in the surveillance studies. In a study where carbapenemase-producers were investigated somewhat higher MIC_{90s} (8 mg/L) were noted against NDM-producing Enterobacteriaceae and OXA-24/40-like carbapenemase-producing *A. baumannii*.

The MBC/MIC ratios of cefiderocol ranged from 1 to 2 against Enterobacteriaceae except for *S. marcescens* for which the MBC/MIC ratio were higher which was also the case for the majority of non-fermenters isolates tested. This indicates that a true bactericidal activity ($>1\times10^3$ $\log_{10}$ colony count reduction) may be more difficult to achieve in patients against non-fermenters than against Enterobacteriaceae.

As described above, cefiderocol resistant strains (defined as a MIC ≥ 8 mg/L) appeared at low frequencies in multi-national surveillance studies. However, despite the relative stability of cefiderocol to both serine- and metallo-type β-lactamases results from surveillance studies indicate that presence of NDM-1 and some serine-type β-lactamases such as PER-1 may contribute to elevated cefiderocol MICs (≥ 8 mg/L).

The frequency of spontaneous resistance was similar to, or lower than that of ceftazidime used for comparison. Cefiderocol resistance was shown to be associated with mutations of various genes. Considering the mode of action of cefiderocol, the mutation on the iron uptake systems could be a risk factor for causing resistance to cefiderocol. In the frequency of resistance studies, the mutation of the upstream region of *pvdS* resulting in the overproduction of pyoverdine increased the cefiderocol MIC. Although the iron transporter mutants did not appear in the resistance acquisition studies a mutation in 1 or 2 iron transporters has been shown in other experiments to increase the cefiderocol MIC.

No resistant mutants were detected when human PK profiles of cefiderocol were simulated against two strains of *K. pneumoniae* and one strain of *P. aeruginosa* in an in vitro infection model. However, the reason for the regrowth noted in the model for one of the *K. pneumoniae* isolates with a MIC of 4 mg/L was not further investigated. This finding may indicate that the clinical dose of cefiderocol is not sufficient to suppress regrowth (which may be a result of resistance development) for strains with borderline MICs. The Applicant has explained that the strains tested in the in vitro experiments were selected based on the perceived high risk to acquire resistance based on high cefiderocol MICs or based on the worst-case results in frequency of resistance (FoR) assays. The incubation time were longer in these experiments compared with the incubation time in the FoR studies. Because no

resistant colonies appeared during the 72-hour incubation against these high-risk strains in the in vitro pharmacodynamic studies, the risks for the appearance of the resistant colonies were considered by the Applicant to be low. In the clinical studies there were a few subjects treated with cefiderocol that had post-baseline isolates with at least a 4-fold increase in cefiderocol MIC. The Applicant has clarified that for the isolates which showed an increase in MIC during the treatment periods of clinical studies, an additional analysis was conducted for isolates which had a MIC of ≥ 8 µg/mL. For the cUTI study, no isolates with a MIC of ≥ 8 µg/mL were observed. Whole genome sequencing analysis for the isolates which showed a MIC increase in the CREDIBLE-CR study is ongoing. This analysis should be provided as a post-authorisation measure once available.

Although the overall results of the effects of in vitro activity in human body fluids indicates that the in vitro activity of cefiderocol is unaffected by the presence of pulmonary surfactant, serum and urine it should be noted that only four strains were tested and there were significant increases in MICs for single strains tested in these media compared with in standard media. The Applicant suggests that the up to 8-fold increase in cefiderocol MIC in the presence of relevant biological fluids may be attributable to iron content in the respective media. This explanation is reasonable. Moreover, the increase in cefiderocol MIC in the presence of biological fluids is several folds lower than the increase in daptomycin MIC noted in the presence of pulmonary surfactant, an increase that is clinically significant and likely the cause of clinical failure of daptomycin in the treatment of pulmonary infections. The in vitro increase in cefiderocol MICs in different media is likely non-significant taking also the clinical efficacy results from the APEKS-cUTI, the CREDIBLE-CR and APEKS-NP studies into account.

In vivo activity

The therapeutic efficacy of cefiderocol has been assessed using various animal infection models including systemic infection model in neutropenic or immunocompetent mice, lung infection model in neutropenic mice, urinary tract infection model in immunocompetent mice, thigh infection model in neutropenic mice and lung infection model in immunocompetent rat. Different doses of cefiderocol including dose regimens equivalent to human dosing have been investigated against a number of relevant bacterial test organisms with varying MICs. Relevant comparators were included although it is unclear whether the effect of the same amount of cefiderocol and comparator drugs in mg/kg is an adequate comparison. Nevertheless, cefiderocol overall showed dose-dependent bacterial reductions in each infection site. Moreover, prolonged infusion (from 1-hour to 3-hour infusion) which can be expected to increase the %fT>MIC improved the bacterial killing in the rat model of pneumonia.

A disparity was noted in the lung infection model between the in vitro and in vivo activities of meropenem and CAZ/AVI against metallo-type β-lactamase producing strains with significant CFU reductions despite high MICs. It has previously been hypothesised that the in vivo expression of MBLs may not be enough in murine lung infection models (Zmartlicka et al, 2015). The Applicant has however provided support that cefiderocol at the clinical dose regimen caused significant reductions in bacterial counts against two MBL-producers also in an in vitro model of infection.

Support for dose selection

Because of the limited clinical development programme performed for cefiderocol, in keeping with what is described in the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (EMA/CHMP/351889/2013) for products that are candidates to address an unmet medical need, the PK/PD analyses incorporating non-clinical PK/PD data and patient PK data is considered pivotal for dose selection for the proposed indication.

The principal support for dose selection was based on nonclinical PK/PD studies to determine the PK/PD index best correlated with cefiderocol efficacy, the magnitude of that PK/PD index (or PK/PD target) required for 1-$\log_{10}$ CFU reductions in murine thigh or lung infections, and Monte-Carlo simulations

using human population PK model to determine the probability of target attainment in plasma and epithelial lining fluid (ELF) at different MICs for subjects with various degree of renal function.

In the dose fractionation study to determine the PK/PD index best correlated with in vivo efficacy the total drug concentration has been used. Although the fraction unbound to plasma proteins normally is applied in these determinations for drugs for which the protein binding not is negligible, it is unlikely that considering the free fraction would change which index is best correlated with efficacy.

The Applicant has chosen to focus their PK/PD target studies on animal models. Because of the in vitro/in vivo activity discordance noted against MBL-producing strains for the comparator agents used in other animal model studies the activity of cefiderocol could possibly be overestimated also in the determination of PK/PD targets when MBL-producing strains were tested. Although PDTs were not calculated based on in vitro model data, the Applicant has provided support that cefiderocol at the clinical dose regimen caused significant reductions in bacterial counts against two MBL-producers also in an in vitro model of infection.

The %*f*T>MIC value of 75% which was the mean PK/PD target required to achieve 1-$\log_{10}$ reduction determined in the neutropenic thigh model was initially chosen for the PTA estimations. Due to the wide range of values noted for non-fermenters in thigh and lung models, there is concern that estimating PTA against this mean value PDT may over-estimate the anticipated efficacy of cefiderocol. There is additional concern that, with low ELF penetration, inadequate PTA may be achieved in this compartment to cover the MIC_{90} values for certain Gram-negative pathogens. Therefore, the Applicant was requested to use all available PK data to re-estimate the PTA in plasma and ELF by renal function category using the fT>MIC 75% PDT and also using alternative PDTs of 80%, 90% and 100%.

The PTA values in plasma are satisfactory (>90%) up to an MIC of 2 mg/L even at the highest PDT simulated (>100% fT>MIC) for all infection types and all renal function categories except for those with normal renal function and cUTI/pyelonephritis for which the PTA value was slightly below 90% (88.0). This supports the adequacy of the dose up to an MIC of 2 mg/L.

At the PDT of 75%, the PTA values in ELF are >90% at MIC 2 mg/L except for those with normal renal function and cUTI/pyelonephritis for which the PTA value was 85.4%. At the highest PDT simulated, the PTA values in ELF are >90% at MIC 1 mg/L and range from 62.8 to 99.2% for different renal function categories at MIC 2 mg/L.

The majority of species within the spectrum of cefiderocol have MIC_{90} values up to 2 mg/L. As noted above, in the pooled dataset from multi-national surveillance studies, the cefiderocol MIC_{90} values for Enterobacteriaceae and non-fermenters varied between strains and were highest (2 mg/L) for *A. baumannii*. However, when only carbapenemase-producing pathogens are taken into account, which are the main targets for cefiderocol, the MIC_{90} values are in general 4 mg/L and are highest (8 mg/L) for the subsets of NDM-producing Enterobacteriaceae and OXA-24/40-like carbapenemase-producing *A. baumannii*. Overall, based on PTA simulations in plasma, and even with a PDT of 75% *f*T>MIC, the dose of cefiderocol may not be sufficient for the treatment of infections caused by a minority of pathogens for which there at present is an unmet need.

Susceptibility testing breakpoints

Susceptibility breakpoints are established by the EUCAST.

Relationship between plasma concentration and effect in the clinical studies

No clear relationship between cefiderocol %*f*T>MIC and efficacy was noted for patients enrolled in the Phase 2 study in the APEKS-cUTI, the CREDIBLE-CR and the APEKS-NP studies.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

All issues are resolved, provided the proposed SmPC text and REC1 on CYP3A4 induction are agreed to.

Pharmacodynamics

It should be noted that because of the limited clinical development programme performed for this product the PK/PD analyses incorporating non-clinical PK/PD data and patient PK data are considered pivotal for dose justification for the proposed indication.

Based on plasma PTA simulations using relevant PDTs, the doses of cefiderocol in different renal function categories are predicted to be sufficient for the treatment of infections caused by pathogens having MICs up to 2 mg/L.

2.5. Clinical efficacy

In line with CHMP guidance for agents that are expected to address an unmet medical need the Applicant has conducted an abbreviated clinical programme to support the proposed indication *treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options*. The programme includes a phase 2 study in cUTI/pyelonephritis (APEKS-cUTI) and a small descriptive phase 3 study in infections caused by carbapenem-resistant Gram-negative pathogens (CREDIBLE-CR). Additionally, data from a phase 3 study in HAP/VAP (APEKS-NP) was provided in the responses to the Day 90 LoQ. This study is presented below in the section for supportive studies.

Table E1. Summary of designs for phase 2 and phase 3 clinical studies

Study Identifier	Number of Study Centers Location(s)	Start date Study status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study Objective	Study & Ctrl Drugs Dose, Route & Regimen	No. Subjs by Arm Entered/ Compl.	Duration	Gender M/F Median Age, (Range) years	Diagnosis Inclusion Criteria	Primary Endpoint (s)
CREDIBLE -CR Study (R2131)	45 sites Countries with subjects enrolled at the time of datacut: Brazil, France Greece, Israel, Japan, South Korea, Spain, Taiwan, Thailand, US	07 Sep 2016 Ongoing Completed enrolment of first 70 subjects 03 May 2018 Data cut for interim CSR on first 70 subjects 15 Aug 2018 150 subjects planned	Phase 3 Multicentre, open-label, parallel-group, randomised (2:1), active-controlled	Efficacy and safety	Cefiderocol 2 g infused IV over 3 hours q8h[a]	47/32	Planned: 7 to 14 days (up to 21 days) For subjects with cUTI, treatment could be stopped after a minimum of 5 days if the subject's infection had been cured and it was in the best interests of the subject per investigator opinion	31/16 70 (28-91)	Hospitalised adults with clinically documented infection (HAP/VAP/ HCAP, cUTI, or BSI/sepsis) caused by a carbapenem-resistant Gram-negative pathogen	Per subject at TOC: clinical outcome in subjects with HAP/ VAP/ HCAP or BSI/ sepsis Microbiological outcome (for Gram-negative pathogen) in subjects with cUTI
					BAT: locally sourced by study sites, within the local standard of care determined by the investigator for each infection diagnosis	23/18		18/5 62 (36-83)		

Study Identifier	Number of Study Centers Location(s)	Start date Study status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study Objective	Study & Ctrl Drugs Dose, Route & Regimen	No. Subjs by Arm Entered/ Compl.	Duration	Gender M/F Median Age, (Range) years	Diagnosis Inclusion Criteria	Primary Endpoint (s)
cUTI Study (R2121)	67 sites 14 countries Bulgaria, Croatia, Czech Republic, Georgia, Germany, Hungary, Italy, Japan, Latvia, Poland, Romania, Russia, Spain, US	05 Feb 2015 Completed 16 Aug 2016 452 subjects randomised/ 450 subjects planned	Phase 2 Multicenter, double-blind, randomised (2:1), active-controlled, noninferiority	Efficacy and safety	Cefiderocol 2 g infused IV over 1 hour q8h[b]	300/283	7 to 14 days (5 days permitted if it was in the best interests of the subject per investigator opinion)	137/163 65 (18-93)	Hospitalised adults with cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis	Composite of clinical cure rate and micro-biologic eradication at TOC
					Imipenem 1g and cilastatin 1 g infused IV over 1 hour q8h[b]	148/138		66/82 65 (18-89)		

BAT = best available therapy; BSI = bloodstream infection; cUTI = complicated urinary tract infection; F = female; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; IV = intravenous; M = male; q8h = every 8 hours; TOC = Test of Cure (visit); US = United States; VAP = ventilator-associated pneumonia

a Dose (0.75 to 2 g) or interval (6 to 12 hours) based on renal function.

b Dose ranges for cefiderocol and imipenem/cilastatin were 0.75 g to 2 g and 0.25 g to 1 g, respectively, every 6 to 8 hours based on renal function and/or body weight.

2.5.1. Dose response studies

No clinical dose response studies have been conducted.

2.5.2. Main studies

Title of study: APEKS-cUTI

This was a phase 2, randomised, double-blind, multicentre study of cefiderocol compared with imipenem/cilastatin (IMP/CS) in hospitalised adult subjects with cUTI/acute pyelonephritis caused by Gram-negative pathogens.

Methods

Study Participants

Key inclusion criteria included the following:

1. Hospitalised adults (18 years and older).
2. Clinical diagnosis of cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis.

The specific clinical diagnosis included cUTI with at least one of the following:

- Indwelling urinary catheter or recent instrumentation of the urinary tract
- Urinary retention caused by benign prostate hypertrophy.
- Urinary retention of at least 100 mL of residual urine after voiding (neurogenic bladder).
- Obstructive uropathy
- Azotaemia caused by intrinsic renal disease

OR

- Acute uncomplicated pyelonephritis (no more than 30% of subject enrolment)

3. At least two of the following signs or symptoms:
    - Chills or rigors or warmth associated with fever (≥38°C)
    - Flank pain (pyelonephritis) or suprapubic/pelvic pain (cUTI)
    - Nausea or vomiting
    - Dysuria, urinary frequency or urinary urgency
    - Costovertebral tenderness on physical examination
4. Evidence of pyuria
5. Positive urine culture within 48 hours prior to randomisation that contained ≥10^5 CFU/mL of a Gram-negative uropathogen likely susceptible to IMP.

Key exclusion criteria included the following:

1. Subject´s urine culture identified only a Gram-positive pathogen and/or identified a Gram-negative uropathogen resistant to IMP
2. Subject´s urine culture isolated more than 2 uropathogens or subject had a confirmed fungal UTI
3. Asymptomatic bacteriuria
4. Subjects receiving dialysis
5. Subject had a concomitant infection at the time of randomisation which required nonstudy systemic Gram-negative antibacterial therapy in addition to study therapy
6. Subject concurrently used systemic nonstudy antibacterial therapy that would have a potential effect in outcome evaluations in subjects with cUTIs
7. A documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam
8. AST, ALT, ALP or total bilirubin level >3 × the upper limit of normal, absolute neutrophil count <100/µL, platelet count <40,000/ µL
9. Bacterial prostatitis
10. Ileal loop for urine outflow
11. Subject was considered unlikely to survive the study period or an illness associated with a high risk of mortality
12. Subject received any amount of potentially therapeutic antibacterial(s) treatment of the current UTI within 96 h prior to obtaining the study qualifying pre-treatment baseline urine.

The study was conducted at 67 sites in 14 countries.

Treatments

Subjects were randomised to cefiderocol 2 g q8h administered over 1 h or IMP/CS 1 g q8h administered over 1 h.

The dose of cefiderocol and IMP/CS had to be reduced in subjects with renal impairment and in the case of IMP/CS also in subjects weighing <70 kg. The recommended duration of treatment (IV only) was 7 to 14 days but could be shortened to 5 days at the discretion of the investigator.

Objectives

The primary objective was to compare the composite outcome (microbiological and clinical response) of cefiderocol with that of IMP/CS in a subject population at risk for MDR Gram-negative pathogens originating from cUTIs with or without pyelonephritis or acute uncomplicated pyelonephritis at test of cure (TOC) approximately 7 days after end of treatment (EOT), defined as the last day of study treatment.

Outcomes/endpoints

The primary efficacy endpoint was the composite of microbiological eradication and clinical response outcomes at the TOC in the Micro-ITT population.

Clinical cure at TOC was defined as resolution or improvement of the symptoms of cUTI that were present at study entry and no new symptoms; microbiological eradication was defined as the demonstration that the bacterial pathogen found at study entry was reduced to fewer than 10^4 CFU/mL on urine culture at TOC. In addition, a post hoc analysis was performed using the more stringent CHMP criterion for microbial eradication of demonstration that the bacterial pathogen found at study entry was reduced to fewer than 10^3 CFU/mL on urine culture at the TOC (EMA/CHMP/351889/2013).

Secondary efficacy endpoints included the composite of microbiological eradication and clinical response at early assessment (EA), EOT, and follow-up (FU); and microbiological and clinical outcome per pathogen and per subject at EA, EOT, TOC, and FU.

Sample size

The study was planned to randomise 450 subjects in a 2:1 ratio to cefiderocol and IMP/CS. The sample size planned for the study were driven by statistical considerations (see below) but were eventually increased to meet FDA requirements (i.e. at least 300 subjects exposed to cefiderocol) for a safety database large enough for registration in the US.

NI margins of 20% and 15% (the latter was the FDA requirement) were prespecified. Based on the 15% non-inferiority margin, 330 evaluable subjects for Micro-ITT population were required to provide 80% power with a one-sided significance level of 2.5% assuming a 70% composite response rate for both the cefiderocol arm and the IPM/CS arm. If 80% of randomised subjects were evaluable a sample size of 413 would be enough.

The justification of the non-inferiority margin 20% was based on analyses of treatment benefit of antimicrobial therapy in this patient population. Recent reviews indicate that the treatment benefit is large, 30-40%. Preserving nearly half the treatment benefit provides ample evidence of treatment effect of the investigational compound.

The proportion of the Micro-ITT Population was monitored in a blinded fashion during the conduct of the study to ensure the adequacy of the design assumptions.

Randomisation

Interactive response technology was used for randomisation. Each subject was randomised to either the cefiderocol group or the IPM/CS group in a 2:1 ratio. The randomisation was stratified according to the subject´s clinical diagnosis (cUTI with or without pyelonephritis and acute uncomplicated pyelonephritis) and region (North America, European Union, Russia and Japan plus rest of world).

The proportion of subjects randomised with acute uncomplicated pyelonephritis was to be limited to approximately 30%.

Blinding (masking)

The investigator, site personnel, the sponsor, and the sponsor's designees involved in blinded monitoring, data management, or other aspects of the study were blinded to treatment assignment. The site pharmacist or qualified designee who prepared the intravenous infusion solution was unblinded

Statistical methods

The study hypothesis was that the composite efficacy response, microbiological eradication and clinical response at the TOC, with cefiderocol would be non-inferior to IPM/CS. The non-inferiority margin was 20% and non-inferiority was to be concluded if the lower bound of a 2-sided 95% CI for the difference in response rates between the 2 treatment groups was greater than -20%.

Detailed statistical analysis methods were specified in the statistical analysis plan (SAP) including a PK analysis plan. The final SAP (Version 3.0) was dated 10 Nov 2016.

Analysis populations

The Micro-ITT Population was the primary population for efficacy analyses. The ME Population and ITT Population were used for sensitivity analyses.

The **Intent-to-Treat (ITT) Population** included all randomised subjects who received at least 1 dose of study drug (S-649266 or IPM/CS).

The **Microbiological Intent-to-Treat (Micro-ITT) Population** included all ITT subjects who had a baseline Gram-negative bacterial uropathogen on culture of urine or blood ($\geq 10^5$ CFU/mL) that causes UTI. This population did not include subjects who had only baseline Gram-positive bacterial pathogens. Subjects were not to be excluded from this population based upon events that occurred post randomisation (e.g., loss to follow-up). Analyses were performed according to randomised treatment.

The **Microbiological Evaluable (ME) Population** Included the Micro-ITT Population who followed important components of the study as specified in the protocol with no major protocol violations. This population was analysed according to the treatment to which the subjects were randomised. All criteria for major protocol violations and subject evaluability were to be established prior to unblinding of the study drug.

Criteria for evaluation were:

- A culture available at both Baseline and TOC

- An EOT assessment after 5 to 14 days of IV study treatment, unless treatment was assessed a failure
- Underwent TOC assessment 7 days (± 2 days) after the end of infusion, unless treatment was assessed a failure
- No major protocol inclusion or exclusion violations
- No violations of restrictions for concomitant therapy, including concomitant antibiotic(s) effective against Gram-negative bacteria
- No violations of coadministration of valproic acid, probenecid, methotrexate, or procainamide before EOT

Safety Population: Included all randomised subjects who received at least 1 dose of the study drug; this population was analysed according to the treatment that the subjects actually received, rather than the treatment to which the subjects were randomized.

The **Pharmacokinetic Concentration Population**: Included all subjects who underwent plasma or urine PK sampling and had at least 1 evaluable PK assay result for cefiderocol; this population was used for the concentration listing, plotting of the concentration-time data, and the concentration summary.

Primary efficacy endpoint analysis

The composite clinical and microbiological response rate at the TOC was calculated as the proportion of subjects with clinical cure and microbiological eradication at the TOC. The number and percentage of subjects achieving clinical and microbiological response at the TOC were presented by treatment group.

Subjects who were lost to follow-up or had missing or indeterminate clinical or microbiological outcome at the TOC were considered as treatment failures and were included in the denominator for analysis in the Micro-ITT Population. If a subject was a treatment failure prior to TOC and the TOC assessment was not completed, treatment failure was be carried forward to the TOC visit.

For the primary efficacy analysis, adjusted estimates of the difference in the rate of responders between the two arms was presented along with CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights in the Micro-ITT population. All CIs were two-sided. CMH weights were performed with the stratification factor, a specific clinical diagnosis (cUTI with or without pyelonephritis vs acute uncomplicated pyelonephritis).

For the primary analysis, a fixed sequential approach was used; if non-inferiority based on the 20% margin could be concluded, non-inferiority inference based on the 15% margin was to be performed.

The following sensitivity analyses were planned:

Using a different population, i.e., the ME Population

Excluding subjects with indeterminate clinical and microbiological outcomes or missing at TOC in the Micro-ITT Population

Multiple Comparisons/Multiplicity

For the primary analysis, a fixed sequential approach was used implying that if non-inferiority based on the 20% margin had been concluded successfully, non-inferiority inference based on the 15% margin was to be performed.

No further multiplicity adjustment was applied.

Missing Microbiological or Clinical Outcome

For clinical and microbiological outcomes, including sensitivity clinical outcome, subjects who were lost to follow-up or had missing or indeterminate clinical outcome or microbiological outcome were to be included in the denominator for response rate calculation and thus, were considered as not responders. If a subject was a treatment failure prior to the TOC visit (or FUP visit) and the TOC assessment (or FUP assessment) was not completed, treatment failure was carried forward to the TOC visit (or FUP visit).

If a TOC assessment was not completed (missing or out of analysis window) and, the subject was a treatment failure on or after EOT assessment, the treatment failure was carried forward to the TOC visit. Also, if a FUP assessment was not completed (missing or out of analysis window) and, the subject was treatment failure on or after EOT assessment, the treatment failure was carried forward to the FUP visit. For the assessment at EA visit and EOT visit, imputation for missing will not be performed.

Missing values for other individual data points were to remain as missing unless otherwise specified. All analyses were to be based on observed cases unless otherwise stated.

Secondary efficacy analyses

Secondary efficacy analyses were conducted based on the Micro-ITT Population. The ME Population was to be used for sensitivity analyses of the secondary efficacy endpoints if applicable. The ITT Population was to be used for analysis of clinical outcome.

The microbiologic outcome per subject at the TOC was analysed in the same manner as the primary analysis. The same analysis method as described for the primary efficacy endpoint was used also for the composite clinical and microbiologic outcome at EA, EOT, and FUP, the microbiologic outcome per subject at EA, EOT, and FUP, and the clinical outcome per subject at EA, EOT, TOC, and FUP. The outcome was tabulated for each treatment group. The adjusted estimate of the difference in the response rate between the two treatment arms along with the adjusted 95% CIs based on the CMH weights were presented.

Results

Participant flow

A total number of 495 subjects were screened of which 42 subjects failed and 1 subject withdrew during the screening process. The tables below describe the subject disposition among randomised subjects and study numbers per analysis populations and the reasons for exclusion from the respective analysis sets:

Table E2. Subject disposition

	Cefiderocol	IPM/CS
Screened	495	
Randomised:	303	149
Not treated	3 (1.0)	1 (0.7)
Treated	300 (99.0)	148 (99.3)
Completed treatment	293 (96.7)	144 (96.6)
Discontinued treatment:	7 (2.3)	4 (2.7)
Withdrawal by subject	2 (0.7)	2 (1.3)
Adverse event	2 (0.7)	1 (0.7)
Other	3 (1.0)	1 (0.7)

	Cefiderocol	IPM/CS
Completed study	283 (93.4)	138 (92.6)
Discontinued study:	20 (6.6)	11 (7.4)
Withdrawal by subject	3 (1.0)	3 (2.0)
Death	1 (0.3)	0
Protocol violation	1 (0.3)	0
Lost to follow-up	10 (3.3)	4 (2.7)
Adverse event	2 (0.7)	3 (2.0)
Other	3 (1.0)	1 (0.7)

Table E3. Study numbers per analysis populations and reasons for exclusions

	Cefiderocol	**IPM/CS**
Randomised	303 (100%)	149 (100%)
ITT	290 (95.7%) [a]	147 (98.7%) [a]
Micro-ITT	252 (83.2%) [b]	119 (79.9%) [b]
ME	228 (75.2%) [c]	106 (71.1%) [c]

[a] Subjects at sites with Good Clinical Practice noncompliance (11 subjects from 2 sites; 10 of the subjects were in the cefiderocol group) were removed from the analysis populations for efficacy (ITT, Micro-ITT, and ME).

[b] Subjects in the ITT population were excluded from the Micro-ITT population if they had no baseline Gram-negative uropathogen with ≥ 10^5 CFU (38/303 of subjects in the cefiderocol group and 28/149 of subjects in the IPM/CS group).

[c] Subjects in the Micro-ITT population were excluded from the ME population if they a) received nonstudy Gram-negative antibacterial drugs before TOC (8/303 of subjects in the cefiderocol group and 5/149 of subjects in the IPM/CS group); b) did not receive 5 to 14 days of infusion unless they were assessed failure 1/303 of subjects in the cefiderocol group and 1/149 of subjects in IPM/CS group; or c) had no TOC assessment within the window of EOT + 7 (± 2) days unless assessed as failure earlier 15/303 of subjects in the cefiderocol group and 8/149 of subjects in the IPM/CS group).

Recruitment

The first subject´s first visit was 5 February 2015 and last subject´s last visit 16 August 2016.

Conduct of the study

Of the major amendments made to the protocol none were made that would be expected to result in favour for any of the treatment groups.

All major protocol deviations were identified before subject unblinding and subjects were excluded from the efficacy analyses (see reasons above).

Baseline data

Table E4. Demographic characteristics (Micro-ITT population)

	Cefiderocol (N = 252)	IPM/CS (N = 119)
Age (years)		
Mean	62.3	61.3
Standard deviation	16.10	18.48
Gender (n, %)		
Male	119 (47.2)	48 (40.3)

	Cefiderocol (N = 252)	IPM/CS (N = 119)
Female	133 (52.8)	71 (59.7)
Race (n, %)		
White	241 (95.6)	115 (96.6)
Asian	9 (3.6)	4 (3.4)
Other	2 (0.8)	0
Region (n, %)		
North America	4 (1.6)	1 (0.8)
Europe	239 (94.8)	114 (95.8)
Asia-Pacific	9 (3.6)	4 (3.4)
Body mass index kg/m^2		
Mean	27.60	26.98
Standard deviation	4.943	6.777
Creatinine clearance renal grading group		
> 80 mL/min	124 (49.2)	51 (42.9)
> 50 to 80 mL/min (mild)	78 (31.0)	41 (34.5)
30 to 50 mL/min (moderate)	41 (16.3)	23 (19.3)
< 30 mL/min (severe)	7 (2.8)	4 (3.4)

Table E5. Disease characteristics (Micro-ITT population)

	Cefiderocol (n = 252)	IPM/CS (n = 119)
Clinical diagnosis at baseline		
cUTI	187 (74.2)	84 (70.6)
with Pyelonephritis	65 (25.8)	29 (24.4)
without Pyelonephritis	122 (48.4)	55 (46.2)
Acute Uncomplicated Pyelonephritis	65 (25.8)	35 (29.4)
Severity of disease (n, %)		
Mild	26 (10.3)	11 (9.2)
Moderate	176 (69.8)	88 (73.9)
Severe	50 (19.8)	20 (16.8)
Baseline fever (n, %)		
≥ 38.0 grade Celsius	88 (34.9)	38 (31.9)
< 38.0 grade Celsius	164 (65.1)	81 (68.1)
Number of Gram-negative pathogens at baseline (n, %)		
1	241 (95.6)	115 (96.6)
2	11 (4.4)	4 (3.4)

Table E6. Gram-negative pathogens isolated at baseline (Micro-ITT population)

Pathogen[a]	Cefiderocol (n = 252)	IPM/CS (n = 119)
Escherichia coli	152 (60.3)	79 (66.4)
Klebsiella pneumoniae	48 (19.0)	25 (21.0)
Pseudomonas aeruginosa	18 (7.1)	5 (4.2)
Proteus mirabilis	17 (6.7)	2 (1.7)

Pathogen[a]	Cefiderocol (n = 252)	IPM/CS (n = 119)
Enterobacter cloacae complex	9 (3.6)	1 (0.8)
Enterobacter cloacae	4 (1.6)	2 (1.7)
Morganella morganii	3 (1.2)	3 (2.5)
Citrobacter freundii	3 (1.2)	1 (0.8)
Serratia marcescens	3 (1.2)	0
Klebsiella	2 (0.8)	0
Klebsiella oxytoca	1 (0.4)	1 (0.8)
Citrobacter freundii complex	1 (0.4)	0
Enterobacter	1 (0.4)	0
Klebsiella aerogenes	1 (0.4)	0
Providencia rettgeri	0	2 (1.7)
Acinetobacter calcoaceticus-baumannii complex	0	1 (0.8)
Raoultella planticola	0	1 (0.8)

A total of 18/252 subjects in the cefiderocol group and 8/119 subjects in the IMP/CS group had positive blood cultures for the baseline uropathogen.

Few baseline uropathogens isolated from subjects in the IMP/CS group were found non-susceptible to IMP/CS (1/23 *K. pneumoniae* = R [MIC=4 mg/L], 2/2 *P. mirabilis* = I [MIC=2 mg/L], 1/4 *P. aeruginosa* = R [MIC = 8 mg/L], 2/3 *M. morganii* = I [MIC= 2 mg/L], 1/1 *A. calcoaceticus* = R [MIC >8 mg/L]).

Compliance and exposure to study drug

Approximately 96% of subjects in each treatment group received 7 to 14 days of treatment. The mean and median duration of exposure in the Micro-ITT population were similar in both treatment groups (9.6 and 9.0 days, respectively).

Prior and concomitant exposure to other antibiotics

A similar number of subjects in the cefiderocol and IMP/CS treatment groups received prior antimicrobial medications (9.1% and 10.1%, respectively) and concomitant antimicrobial medications (17.1% and 21.0%, respectively) although some differences existed between the treatment groups regarding the type of antimicrobial drug.

Numbers analysed

See table (E3) above.

Outcomes and estimation

Primary endpoint

The response rate for the primary endpoint at TOC was 72.6% of subjects in the cefiderocol group and 54.6% of subjects in the IPM/CS group (table below). The adjusted treatment difference (cefiderocol minus IPM/CS) met the criteria for noninferiority at the prespecified -20% and -15% margins. In addition, the lower limit was above zero which is consistent with superiority of cefiderocol compared with IPM/CS. Similar results were achieved when the response rates in the ME population were considered (data not shown).

Table E7. Composite of clinical outcome and microbiological outcome at TOC (Micro-ITT population)

Clinical and microbiological outcome	Cefiderocol (N = 252) n (%)	IPM/CS (N = 119) n (%)	Treatment Difference (%)	Comparison[a] 95% CI	P-value[b]
Response	183 (72.6)	65 (54.6)	18.58	(8.23, 28.92)	p = 0.0004
Failure	54 (21.4)	46 (38.7)			
Indeterminate	15 (6.0)	8 (6.7)			

[a] Treatment difference (cefiderocol minus IPM/CS) is the adjusted estimate of the difference in the responder rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline (cUTI with or without pyelonephritis vs. acute uncomplicated pyelonephritis).

[b] The P-value is 2-sided and the null hypothesis is that the response rate of cefiderocol is equivalent to that of IPM/CS. The P-value is calculated using the adjusted difference and the standard error with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline

Using the EU-recommended primary endpoint for studies in cUTI and more stringent criterion for microbial eradication ($<10^3$ CFU/mL instead of $<10^4$ CFU/mL) essentially similar results as for the primary analysis were obtained (table below).

Table E8. Microbiological outcome at TOC using the CHMP recommended definition of eradication i.e. a reduction to < 10^3 CFU/mL (Micro-ITT population)

Microbiological outcome	Cefiderocol (N = 252) n (%)	IPM/CS (N = 119) n (%)	Treatment Difference (%)	Comparison 95% CI
Eradication	173 (68.7)	64 (53.8)	15.44	(4.94, 25.94)
Failure	57 (22.6)	45 (37.8)		
Indeterminate	22 (8.7)	10 (8.4)		

Due to concerns over the adequacy of the imipenem dose adjustment schema (which followed US recommendations current when the study started but later revised), and the fact that a greater proportion in the imipenem group (60%) had a dose adjustment vs. the cefiderocol group (45%), the applicant provided additional analyses of the primary endpoint according to whether there was dose adjustment by renal function and body weight at baseline. The microbiological responses at TOC are shown for each treatment group by baseline dose adjustment below.

Microbiological Outcome at TOC for Cefiderocol First Dose Regimen in the cUTI Study (Microbiological Intent-to-treat population)

	Cefiderocol, N=252						
	No dose adjustment	Dose adjusted					
	6g TDD	6g TDD	4.5g TDD	4g TDD	3g TDD	3g TDD	Total
	2g Q8H N=138	1.5g Q6H N=8	1.5g Q8H N=32	1g Q6H N=46	1g Q8H N=25	0.75g Q6H N=3	N=114
Eradication	105 (76.1)	5 (62.5)	21 (65.6)	25 (54.3)	16 (64.0)	1 (33.3)	68 (59.6)
Persistence	23 (16.7)	1 (12.5)	8 (25.0)	17 (37.0)	6 (24.0)	2 (66.7)	34 (29.8)
Indeterminate	10 (7.2)	2 (25.0)	3 (9.4)	4 (8.7)	3 (12.0)	0	12 (10.5)

Microbiological Outcome at TOC by IPM/CS First Dose Regimen in the cUTI Study (Microbiological Intent-to-treat population)

	IPM/CS, N=119					
	No dose adjustment	Dose adjusted				
	3 g TDD	2.25g	2g TDD	1.5g TDD	1g TDD	Total
	1g Q8H N=48	0.75g Q8H N=8	0.5g Q6H N=24	0.5g Q8H N=37	0.25g Q6H N=2	N=71
Eradication	26 (54.2)	6 (75.0)	11 (45.8)	19 (51.4)	2 (100.0)	38 (53.5)
Persistence	18 (37.5)	2 (25.0)	9 (37.5)	16 (43.2)	0	27 (38.0)
Indeterminate	4 (8.3)	0	4 (16.7)	2 (5.4)	0	6 (8.5)

The applicant also confirmed that there was post-baseline dose adjustment allowed in each treatment group and that resistance to imipenem at baseline or emerging on treatment did not explain the overall difference between treatments.

Furthermore, an analysis of those who failed in the primary analysis was provided, which showed that most failures reflected lack of reduction in urinary bacterial counts to below the required CFU/mL level.

Incidence of Clinical or Microbiological Failure at EOT and TOC in the cUTI Study

	Clinical failure		Microbiological Persistence	
	Cefiderocol (N=252)	IPM/CS (N=119)	Cefiderocol (N=252)	IPM/CS (N=119)
EOT	4 (1.6)	0	5 (2.0)	3 (2.5)
TOC	14 (5.6)	8 (6.7)	57 (22.6)	45 (37.8)
FUP	19 (7.5)	13 (10.9)	85 (33.7)	43 (36.1)

No pattern of baseline diagnosis, bacterial species or creatinine clearance could be discerned amongst those who did and did not fail.

Ancillary analyses

Secondary endpoints

The composite outcome at early assessment and EOT were essentially similar between the treatment groups. The difference in favourable response rates in favour of the cefiderocol arm noted at TOC remained at follow-up although the favourable response rates were lower for both treatment groups (table below).

Table E9. Composite of clinical outcome and microbiological outcome by time point (Micro-ITT population)

Time Point Clinical and microbiological outcome	Cefiderocol (N = 252) n (%)	IPM/CS (N = 119) n (%)	Treatment Difference (%)	Comparison[a] 95% CI
Early Assessment				
Response	222 (88.1)	104 (87.4)	0.66	(-6.48, 7.79)
End of Treatment				
Response	243 (96.4)	114 (95.8)	0.72	(-3.48, 4.92)
Test of Cure				
Response	183 (72.6)	65 (54.6)	18.58	(8.23, 28.92)
Follow-up				

Time Point Clinical and microbiological outcome	Cefiderocol (N = 252) n (%)	IPM/CS (N = 119) n (%)	Treatment Difference (%)	Comparison[a] 95% CI
Response	137 (54.4)	47 (39.5)	15.31	(4.69, 25.92)

The composite response rates at TOC for the 4 most commonly occurring uropathogens are summarised in the table below. For subjects infected with *E. coli* and *K. pneumoniae,* which were fairly large groups, the results were in line with the overall results.

Table E10. Composite of clinical and microbiological outcome for *Escherichia Coli, Klebsiella Pneumoniae, Pseudomonas Aeruginosa, Proteus Mirabilis* at TOC (Micro-ITT population)

Pathogen Outcome	Cefiderocol (N = 252) n (%)	IPM/CS (N = 119) n (%)
Escherichia coli	N' = 146	N' = 77
Response	108 (74.0)	45 (58.4)
Failure	29 (19.9)	26 (33.8)
Indeterminate	9 (6.2)	6 (7.8)
Klebsiella pneumoniae	N' = 46	N' = 25
Response	34 (73.9)	12 (48.0)
Failure	10 (21.7)	12 (48.0)
Indeterminate	2 (4.3)	1 (4.0)
Pseudomonas aeruginosa	N' = 15	N' = 4
Response	7 (46.7)	2 (50.0)
Failure	7 (46.7)	2 (50.0)
Indeterminate	1 (6.7)	0
Proteus mirabilis	N' = 13	N' = 1
Response	9 (69.2)	0
Failure	3 (23.1)	1 (100.0)
Indeterminate	1 (7.7)	0

When the response rates were separated between clinical outcome and microbiological outcome it was clear that the composite response rates in favour or the cefiderocol arm at TOC and FU was driven by higher microbiological eradication rates. However, a difference in favour of the cefiderocol group in clinical response rates were detected at FU possibly indicating that the better sustained microbiological eradication at FU translates into a measurable clinical benefit (data not shown).

Emergence of resistance

See clinical pharmacodynamics

Subgroup analyses

The treatment differences in the composite response rate at TOC by different subgroups were consistent with the treatment difference in the overall Micro ITT population (table below). Subgroup analysis by race was not meaningful because most subjects were categorised as White.

For subgroups with different baseline renal function status, subjects with and without prior antimicrobials, and subjects with bacteraemia the results were consistent with the overall results (data not shown).

Table E11. Composite outcome at TOC by Subgroup (Micro ITT Population)

Composite Response Rate Subgroup	Cefiderocol (N = 252) n/N' (%)	IPM/CS (N = 119) n/N' (%)	Treatment Difference (%)	95% CI
Overall	183/252 (72.6)	65/119 (54.6)	18.00	(7.49, 28.50)
Clinical Diagnosis				
cUTI with or without PN	129/187 (69.0)	41/ 84 (48.8)	20.17	(7.60, 32.75)
cUTI with PN	44/ 65 (67.7)	13/ 29 (44.8)	22.86	(1.49, 44.24)
cUTI without PN	85/122 (69.7)	28/ 55 (50.9)	18.76	(3.24, 34.29)
Acute Uncomplicated PN	54/ 65 (83.1)	24/ 35 (68.6)	14.51	(-3.37, 32.38)
Age Group				
< 65 years	87/113 (77.0)	32/ 54 (59.3)	17.73	(2.50, 32.96)
≥ 65 years	96/139 (69.1)	33/ 65 (50.8)	18.30	(3.92, 32.67)
Gender				
Male	84/119 (70.6)	25/ 48 (52.1)	18.50	(2.17, 34.84)
Female	99/133 (74.4)	40/ 71 (56.3)	18.10	(4.38, 31.81)
Race				
White	175/241 (72.6)	64/115 (55.7)	16.96	(6.28, 27.65)
Asian	8/ 9 (88.9)	1/ 4 (25.0)	63.89	

Title of study: CREDIBLE-CR

This was a phase 3, randomised, open-label, multicentre study of cefiderocol compared with best available therapy (BAT) in adult subjects for the treatment of severe infections caused by carbapenem-resistant Gram-negative pathogens.

Methods

Study participants

Key inclusion criteria included the following:

1. Hospitalised adults (18 years and older).
2. Clinical diagnosis of HAP/VAP/HCAP, cUTI, or BSI/sepsis caused by a Gram-negative pathogen with evidence of carbapenem resistance

   Hospital-acquired pneumonia was defined as an acute bacterial pneumonia in a subject hospitalized for more than 48 hours or developing within 7 days after discharge from hospital. Subjects may have had acute respiratory failure and required mechanical ventilation for HAP (ventilated-HAP).

   Ventilator-associated pneumonia was defined as an acute bacterial pneumonia in a subject receiving mechanical ventilation via an endotracheal (or nasotracheal) tube for a minimum of 48 hours.

   Healthcare-associated pneumonia was defined as an acute bacterial pneumonia in a subject who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received IV antibiotic therapy,

chemotherapy, or wound care; or attended a haemodialysis clinic within 30 days of the current infection.

Complicated urinary tract infection was defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local and systemic signs and symptoms including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization and who required hospitalization for the parenteral (IV) treatment of cUTI were enrolled in the study.

The BSI/sepsis category included bacteraemia or sepsis caused by infections other than HAP/VAP/HCAP or cUTI. Subjects were enrolled in the BSI/sepsis group with either:

a. Documented BSI caused by a carbapenem-resistant Gram-negative pathogen

OR

b. Systemic response to infection, meeting the clinical criteria of SIRS and an identified infection source (e.g., severe skin infection, intra-abdominal infection) caused by a carbapenem-resistant Gram-negative pathogen

Key exclusion criteria included the following:

1. Subjects who needed more than 3 systemic antibiotics as part of BAT for the treatment of the Gram-negative infection (subjects with mixed Gram-positive or anaerobic infections may have received appropriate concomitant narrow-spectrum antibiotics [e.g., vancomycin, linezolid, metronidazole, clindamycin])
2. Subjects with coinfection caused by invasive aspergillosis, mucormycosis, or other highly lethal mould
3. Subjects who had central nervous system infection (e.g., meningitis, brain abscess, shunt infection)
4. Subjects with infection requiring > 3 weeks of antibiotic treatment (e.g., bone and joint infection, endocarditis)
5. Subjects with cystic fibrosis or moderate to severe bronchiectasis
6. Subjects in refractory septic shock defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at the time of Randomization
7. Subjects with severe neutropenia, i.e., polymorphonuclear neutrophils < 100 cells/μL
8. Subjects with Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 30
9. Subjects who had received a potentially effective antibiotic regimen for the carbapenem-resistant Gram-negative infection for a continuous duration of more than 24 hours in cUTI, or 36 hours in HAP/VAP/HCAP or BSI/sepsis during the 72 hours prior to Randomization
10. Subjects who were receiving peritoneal dialysis.

The study was conducted at 45 sites. At data cut for the interim analysis subjects had been included in 10 countries.

Treatments

Subjects were randomised to receive cefiderocol 2 g q8h administered over 3 h or best available therapy (BAT) determined by the investigator for each infection diagnosis. BAT consisted of 1 to 3 antibiotic agents selected specifically for the carbapenem-resistant Gram-negative pathogen.

The dose of cefiderocol had to be reduced in subjects with renal impairment. The recommended duration of treatment (IV only) was 7 to 14 days but could be shortened to 5 days (cUTI only) at the discretion of the investigator. The maximum treatment duration was 21 days.

A single adjunctive antibacterial agent for HAP/VAP/HCAP or BSI/sepsis subjects could be added. Adjunctive therapy was locally sourced by study sites and included only marketed drug products available through the investigator's site pharmacy. Investigational agents, a polymyxin (colistin or polymyxin B), and a cephalosporin/carbapenem including combination with β-lactamase inhibitor (e.g., ceftazidime/avibactam or ceftolozane/tazobactam) were not permitted as part of adjunctive antibiotic therapy.

Objectives

The primary objectives were:

- To assess, at test of cure (TOC, defined as end of treatment + 7 days [± 2 days]), the clinical outcome of treatment with cefiderocol or BAT in adult subjects with either HAP/VAP/HCAP or BSI/sepsis caused by carbapenem resistant Gram-negative pathogens
- To assess, at TOC, the microbiological outcome of treatment with cefiderocol or BAT in adult subjects with cUTI caused by carbapenem-resistant Gram-negative pathogens

Outcomes/endpoints

The primary efficacy endpoints were the clinical outcome per subject at TOC in subjects with HAP/VAP/HCAP or BSI/sepsis and the microbiological outcome (for Gram-negative pathogen) per subject at TOC in subjects with cUTI.

Clinical cure of HAP/VAP/HCAP and BSI/sepsis was defined as resolution or substantial improvement of baseline signs and symptoms (for pneumonia including a reduction in SOFA score and CPIS, and improvement or lack of progression of chest radiographic abnormalities and for BSI/sepsis including a reduction in SOFA score and eradication of bacteraemia) such that no antibacterial therapy was required for the treatment of the current infection.

For cUTI, microbiological eradication was defined as a urine culture showed the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFU/mL was reduced to $<10^3$ CFU/mL.

Secondary efficacy endpoints included the clinical and/or microbiological outcome per subject or per pathogen at EOT, TOC and FU for the different infections types, all-cause mortality at day 14 and day 28, composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC, survival time, Clinical Pulmonary Infection Score (CPIS) parameters at EOT, TOC, and FU (HAP/VAP/HCAP only) and Sequential Organ Failure Assessment (SOFA) score at EOT, TOC, and FU.

Sample size

Approximately 150 subjects were planned to be enrolled in the full study and randomised 2:1 to cefiderocol and BAT, respectively.

Randomisation

Interactive response technology was used for randomisation. Randomisation was performed by the stochastic minimization method using their infection site (HAP/VAP/HCAP, cUTI, and BSI/sepsis), APACHE II score (≤ 15 and ≥ 16), and region (North America, South America, Europe, and Asia-Pacific) as allocation factors. To avoid deterministic allocation based on the ongoing allocation results, probabilistic allocation was incorporated.

The randomisation was stratified according to the subject´s clinical diagnosis (HAP/VAP/HCAP, cUTI, and BSI/sepsis). The randomisation system was designed such that the population with HAP/VAP/HCAP would have approximately 50% of randomised subjects; cUTI was limited to no more than 30% of randomised subjects, and the remainder of subjects was enrolled under the BSI/sepsis diagnosis.

Blinding (masking)

The study used an open-label design.

Statistical methods

No inferential testing was performed. Only descriptive statistics were provided. i.e. each response rate was provided with the 95% confidence interval (CI) by treatment group.

Analysis populations

Intent-to-treat (ITT) population: all randomised subjects who received at least 1 dose of study treatment

Microbiological Intent-to-treat (Micro-ITT) population: all subjects in the ITT population who had a baseline Gram-negative pathogen from an appropriate clinical specimen

Carbapenem-resistant Microbiological Intent-to-treat (CR Micro-ITT) population: all subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant (primary efficacy population)

Carbapenem-resistant Microbiologically Evaluable (CR-ME) population: includes all subjects in the CR Micro-ITT population who followed important components of the study as specified in the protocol with no major protocol violations

Analysed for safety:

• **Safety population**: all randomized subjects who received at least 1 dose of the study treatment (identical to the ITT population for this interim report)

Analysed for Pharmacokinetics (PK):

• **PK concentration population**: all subjects who had plasma sampling and had at least 1 evaluable PK assay result for cefiderocol

Below are the analyses as described in the CSR that according to the applicant are those described in the SAP for this interim report (*ver 2.2, dated 29 Oct 2018*), prepared by the sponsor. Descriptive statistics are provided.

Primary efficacy analyses

For the CR Micro-ITT population, the clinical outcomes at TOC were summarized and clinical cure rates and the 95% CIs were calculated by treatment group (cefiderocol or BAT) for subjects with HAP/VAP/HCAP or BSI/sepsis, separately. The clinical response rate was calculated as the proportion of subjects whose clinical outcome was clinical cure at TOC.

The microbiological outcomes at TOC were summarized and microbiological eradication rates and the 95% CIs were calculated by treatment group (cefiderocol or BAT) for the subjects with cUTI. The microbiological response rate was calculated as the proportion of subjects whose baseline Gram-negative uropathogen(s) were eradicated at TOC.

The following supplemental analyses were performed for the primary efficacy endpoint:

• the primary analyses were carried out using different subject populations (Micro-ITT and CR-ME populations)

• for subjects with cUTI in the CR Micro-ITT, Micro-ITT, and CR-ME populations, supplemental analyses for the microbiological outcome were carried out changing the eradication criteria for cUTI

Secondary Efficacy Analyses

Descriptive statistics for all efficacy parameters are provided. The secondary endpoints of clinical response rates and microbiological response rates by treatment group and the 95% CIs were calculated.

Supplementary clinical outcomes (to address indeterminate clinical outcomes) per subject and per pathogen were summarized and the cure rate and its 95% CI were calculated.

Supplementary microbiological outcomes (to address indeterminate microbiological outcomes) per subject and per pathogen were summarized and eradication rate and its 95% CI were calculated.

Composite clinical and microbiological response rates by treatment group and the 95% CIs were calculated.

Analyses of all-cause mortality and survival time were performed.

The SOFA and CPIS scores by infection site as relevant were summarized by time point.

The response rate of a composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related was compared between treatment groups by infection site (HAP/VAP/HCAP, cUTI, or BSI/sepsis) at TOC.

Results

Participant flow

A total number of 258 subjects were screened of which 105 subjects failed. The tables below describe the subject disposition among randomised subjects and study numbers per analysis populations and the reasons for exclusion from the respective analysis sets:

Table E12. Subject disposition

	Cefiderocol	BAT
Screened	258	
Randomised:	101	51
Not treated	0	2

	Cefiderocol	BAT
Treated	101 (100.0)	49 (96.1)
Completed treatment	89 (88.1)	46 (90.2)
Discontinued treatment:	12 (11.9)	3 (5.9)
Withdrawal by subject	0	0
Death	7 (6.9)	0
Protocol violation	0	1 (2.0)
Lack of efficacy	2 (2.0)	1 (2.0)
Adverse event	2 (2.0)	1 (2.0)
Other	1 (1.0)	0
Completed study	69 (68.3)	38 (74.5)
Discontinued study:	32 (31.7)	13 (25.5)
Withdrawal by subject	1 (1.0)	2 (3.9)
Death	30 (29.7)	9 (17.6)
Protocol violation	0	0
Lost to follow-up	1 (1.0)	0
Lack of efficacy	0	1 (2.0)
Adverse event	0	0
Other	0	1 (2.0)

Table E13. Study numbers per analysis populations and reasons for exclusions

	Cefiderocol	BAT
Randomised	101 (100%)	51 (100%)
ITT	101 (100%)	49 (96.1%)
Micro-ITT[a]	86 (85.1%)	44 (86.3%)
CR Micro-ITT[b]	80 (79.2%)	38 (74.5%)
CR-ME[c]	57 (56.4%)	23 (45.1%)

a Twenty subjects were excluded from the Micro-ITT population (N = 130), which was used for supplementary analyses, due to no appropriate baseline Gram-negative pathogen.

b Twelve additional subjects were excluded from the CR Micro-ITT population (N = 118), which was the primary efficacy analysis population, due to no confirmation of carbapenem resistance by central laboratory.

c Thirtyeight additional subjects were excluded from the CR-ME population (N = 80), which was used for supplementary analyses, due to violations of restrictions for concomitant therapy, major protocol inclusion or exclusion violations, treatment uncompliance, and no TOC assessment within EOT + 7 (± 2) days.

Recruitment

The first subject was enrolled 7 September 2016.

Conduct of the study

The protocol was amended 3 times. Of the major amendments made to the protocol none were made that would be expected to result in favour for any of the treatment groups.

Baseline data

Table E14. Demographic characteristics (CR Micro-ITT population)

	Cefiderocol (N = 80)	BAT (N = 38)
Age (years)		
Mean	63.1	62.1
Standard deviation	18.7	17.3
Gender (n, %)		
Male	55 (68.8)	29 (76.3)
Race (n, %)		
White	48 (60.0)	27 (71.1)
Asian	24 (30.0)	9 (23.7)
Other	8 (10.0)	2 (5.3)
Region (n, %)		
North America	4 (5.0)	3 (7.9)
South America	7 (8.8)	3 (7.9)
Europe	45 (56.3)	23 (60.5)
Asia-Pacific	24 (30.0)	9 (23.7)
Body mass index kg/m^2		
Mean	25.39	25.10
Standard deviation	7.14	7.54
Creatinine clearance renal grading group		
80 to <120 (normal)	15 (18.8)	9 (23.7)
≥ 120 (ARC)	17 (21.3)	11 (28.9)
> 50 to 80 mL/min (mild)	15 (18.8)	9 (23.7)
30 to 50 mL/min (moderate)	18 (22.5)	6 (15.8)
< 30 mL/min (severe)	15 (18.8)	3 (7.9)

Table E15. Disease characteristics (CR Micro-ITT population)

	Cefiderocol (n = 80)	BAT (n = 38)
Clinical diagnosis at baseline		
HAP	16 (20.0)	5 (13.2)
VAP	23 (28.8)	12 (31.6)
HCAP	1 (1.3)	2 (5.3)
BSI	16 (20.0)	8 (21.1)
Sepsis	7 (8.8)	6 (15.8)
cUTI	17 (21.3)	5 (13.2)
Severity of disease (n, %)		
Mild	4 (5.0)	3 (7.9)
Moderate	26 (32.5)	15 (39.5)
Severe	50 (62.5)	20 (52.6)
Baseline fever (n, %)		
≥ 38.0 grade Celsius	14 (17.5)	5 (13.2)
< 38.0 grade Celsius	66 (82.5)	31 (81.6)

	Cefiderocol (n = 80)	BAT (n = 38)
Prior antimicrobial therapy within 2 weeks prior to randomisation (n, %)		
Yes	73 (91.3)	38 (100.0)
No	7 (8.8)	0
Number of Gram-negative pathogens at baseline (n, %)		
1	62 (77.5)	30 (78.9)
2	13 (16.3)	8 (21.1)
3	4 (5.0)	0
4	1 (1.3)	0

Table E16. Carbapenem-resistant Gram-negative pathogens isolated at baseline (CR Micro-ITT population)

Diagnosis Pathogen[a]	Cefiderocol (n = 80)	BAT (n = 38)
HAP/VAP/HCAP	N' = 40	N' = 19
Acinetobacter baumannii	26 (65.0)	10 (52.6)
Pseudomonas aeruginosa	11 (27.5)	6 (31.6)
Stenotrophomonas maltophilia	5 (12.5)	0
Klebsiella pneumoniae	10 (25.0)	5 (26.3)
Acinetobacter nosocomialis	2 (5.0)	0
Enterobacter cloacae	2 (5.0)	0
Chryseobacterium indologenes	1 (2.5)	0
Klebsiella oxytoca	1 (2.5)	0
Serratia marcescens	1 (2.5)	0
Enterobacter asburiae	0	1 (5.3)
Escherichia coli	2 (5.0)	2 (10.5)
Klebsiella variicola	0	1 (5.3)
BSI/Sepsis	N' = 23	N' = 14
Klebsiella pneumoniae	11 (47.8)	4 (28.6)
Acinetobacter baumannii	10 (43.5)	7 (50.0)
Escherichia coli	2 (8.7)	0
Pseudomonas aeruginosa	2 (8.7)	3 (21.4)
Klebsiella variicola	1 (4.3)	0
Morganella morganii	0	1 (7.1)
Providencia stuartii	0	1 (7.1)
cUTI	N' = 17	N' = 5
Klebsiella pneumoniae	11 (64.7)	3 (60.0)
Escherichia coli	1 (5.9)	0
Pseudomonas aeruginosa	4 (23.5)	2 (40.0)
Acinetobacter baumannii	1 (5.9)	0

a Gram-negative pathogens are based on data from the central microbiology laboratory (if available).

Blood cultures positive for Carbapenem-resistant Gram-negative pathogens (regardless of diagnosis) were identified in 22/80 of the subjects in the cefiderocol group and 13/38 in the BAT group in the CR Micro-ITT population. Among them, *A. baumannii* and *K. pneumoniae* were each observed in 10/22 of subjects in the cefiderocol group and 6/13 and 5/13, respectively in the BAT group.

Baseline study drug regimen

In the cefiderocol group, 66/80 of subjects received cefiderocol monotherapy and 14/80 received adjunctive therapy, whereas in the BAT group, 10/38 of subjects received monotherapy. In the BAT group, 25/38 of subjects received a colistin-based regimen, of which 6 received colistin only. The remaining 13/38 of subjects in the BAT group received a noncolistin-based regimen, of which 4 received noncolistin-based monotherapy.

Exposure to study drug

The mean duration of exposure in the CR Micro-ITT population for subjects with pneumonia or BSI/sepsis was one day shorter in the cefiderocol treatment group (11.4 days [range 2 to 22 days]) compared to for subjects in the BAT group (12.6 days [range 2 to 22 days]). The mean duration of exposure to cefiderocol for subjects with cUTI were 11.9 days (range 2 to 29 days) and fot BAT 7.4 days (range 6 to 11 days).

Prior and concomitant exposure to other antibiotics

As noted in the table above nearly all subjects had received prior antimicrobial therapy within 2 weeks prior to randomisation. Prior antibacterial agents included agents with activity against aerobic Gram-negative pathogens e.g. carbapenems, cephalosporins, ceftolozane-tazobactam, ceftazidime-avibactam, colistin, fosfomycin, piperacillin-tazobactam, quinolones, aminoglycosides and tigecycline.

Excluding BAT/adjunctive antibiotics, the majority of subjects received "other antibacterials" as concomitant medications. The concomitant medications were reported to be used for other infections such as meningitis after brain surgery, or surgical procedures.

The concomitant antibacterial agents used included agents with activity against Gram-negative pathogens e.g. colistin, polymyxin, fosfomycin, carbapenems, cephalosporins, ceftazidime-avibactam, piperacillin-tazobactam, tigecycline, quinolones, aminoglycosides and trimethoprim-sulfamethoxazole.

Numbers analysed

See table above.

Outcomes and estimation

Primary endpoint

The clinical outcome for HAP/VAP/HCAP and BSI/sepsis and microbiological outcome for cUTI at TOC were the primary endpoints. About half of the subjects with HAP/VAP/HCAP and somewhat lower of subjects with BSI/sepsis in both treatment groups achieved clinical cure. Half of the subjects with cUTI in the cefiderocol group and 20% in the BAT group achieved microbiological eradication (table below).

Table E17. Clinical outcome for HAP/VAP/HCAP and BSI/sepsis and microbiological outcome for cUTI at TOC (CR Micro-ITT population)

Subject Group Clinical/microbiological outcome	Cefiderocol (N = 80) n (%)	95% CI	BAT (N = 38) n (%)	95% CI
HAP/VAP/HCAP	N' = 40		N' = 19	
Clinical cure	20 (50.0)	(33.8, 66.2)	10 (52.6)	(28.9, 75.6)
Clinical failure	16 (40.0)		6 (31.6)	
Indeterminate	4 (10.0)		3 (15.8)	
BSI/Sepsis	N' = 23		N' = 14	
Clinical cure	10 (43.5)	(23.2, 65.5)	6 (42.9)	(17.7, 71.1)
Clinical failure	9 (39.1)		7 (50.0)	
Indeterminate	4 (17.4)		1 (7.1)	
cUTI[a]	N' = 17		N' = 5	
Eradication	9 (52.9)	(27.8, 77.0)	1 (20.0)	(0.5, 71.6)
Persistence	5 (29.4)		1 (20.0)	
Indeterminate	3 (17.6)		3 (60.0)	

Roughly similar results were noted in the ME population although it should be noted that the number of subjects in this analysis population was very small.

Ancillary analyses

Secondary endpoints

Clinical outcome for cUTI and microbiological outcome for HAP/VAP/HCAP and BSI/sepsis at TOC

Table E18. Clinical outcome for cUTI and microbiological outcome for HAP/VAP/HCAP and BSI/sepsis at TOC (CR Micro-ITT population)

Subject Group Clinical/microbiological outcome	Cefiderocol (N = 35) n (%)	95% CI	BAT (N = 18) n (%)	95% CI
cUTI	N' = 17		N' = 5	
Clinical cure	12 (70.6)	(44.0, 89.7)	3 (60.0)	(14.7, 94.7)
Clinical failure	2 (11.8)		1 (20.0)	
Indeterminate	3 (17.6)		1 (20.0)	
HAP/VAP/HCAP	N' = 40		N' = 19	
Eradication	9 (22.5)	(10.8, 38.5)	4 (21.1)	(6.1, 45.6)
Persistence	8 (20.0)		7 (36.8)	
Indeterminate	23 (57.5)		8 (42.1)	
BSI/Sepsis	N' = 23		N' = 14	
Eradication	7 (30.4)	(13.2, 52.9)	4 (28.6)	(8.4, 58.1)
Persistence	3 (13.0)		2 (14.3)	
Indeterminate	13 (56.5)		8 (57.1)	

Clinical and microbiological responses at other time-points for evaluation

The clinical and microbiological responses were essentially similar between treatment groups at other time points for evaluation with a few more subjects achieving a favourable response at EOT and a few less subjects achieving a favourable response at FU (data not shown).

Composite outcome

The composite of clinical and microbiological outcome at TOC and FU for subjects with different infection types was similar to and reflected the overall lower microbiological than clinical favourable response rate (data not shown).

Outcome per pathogen

The microbiological outcome per pathogen at TOC are shown in the table below.

Table E19. Microbiological outcome per pathogen[1] at TOC (CR Micro-ITT population)

Pathogen Microbiological Outcome	Cefiderocol (N = 80) n (%)	BAT (N = 38) n (%)
Acinetobacter baumannii	N' = 37	N' = 17
Eradication	10 (27.0)	5 (29.4)
Persistence	5 (13.5)	4 (23.5)
Indeterminate	22 (59.5)	8 (47.1)
Klebsiella pneumoniae	N' = 32	N' = 12
Eradication	16 (50.0)	3 (25.0)
Persistence	5 (15.6)	4 (33.3)
Indeterminate	11 (34.4)	5 (41.7)
Pseudomonas aeruginosa	N' = 17	N' = 11
Eradication	2 (11.8)	2 (18.2)
Persistence	5 (29.4)	2 (18.2)
Indeterminate	10 (58.8)	7 (63.6)
Escherichia coli	N' = 5	N' = 2
Eradication	2 (40.0)	0
Persistence	2 (40.0)	0
Indeterminate	1 (20.0)	2 (100.0)
Stenotrophomonas maltophilia	N' = 5	N' = 0
Eradication	0	0
Persistence	0	0
Indeterminate	5 (100.0)	0

[1]Only the pathogens that were at least five in total are shown in the table

In line with the higher favourable clinical response rate compared to the microbiological response the clinical outcome per pathogen at TOC were higher in the respective treatment groups for some of the pathogens (data not shown).

Taking the MIC into account it can be noted that for subjects with *A. baumannii* microbiological eradication at TOC occurred only in 9 subjects with whose *A. baumannii* isolates had MIC values for cefiderocol of 0.06 to 1 mg/L. Subjects with failure to achieve eradication had isolates with MIC values evenly spread over the range of MIC values detected (0.06 to 16 mg/L). For *P. aeruginosa* the isolates of the 2 subjects who had microbiological eradication had cefiderocol MIC value of 0.06 and 4 mg/L whereas the 15 subjects that did not achieve eradication had MIC values ranging from 0.06 to 2 mg/L. The 16 subjects in the cefiderocol group with microbiological eradication of *K. pneumoniae* had MIC values ranging from ≤ 0.03 to 4 mg/L whereas the subjects that did not achieve eradication had MIC values ranging from 0.06 to 4 mg/L.

Emergence of resistance

Se clinical pharmacodynamics.

Bacteraemia

For subjects with bacteraemia 7/22 and 4/13 subjects in the cefiderocol and BAT treatment groups, respectively achieved microbiological eradication at TOC.

All-cause mortality

All-cause mortality is shown in the table below,

Table E20. All-cause mortality (CR Micro-ITT population)

Subject Group All-cause Mortality	Cefiderocol (N = 80) n (%)	95% CI	BAT (N = 38) n (%)	95% CI
HAP/VAP/HCAP	N' = 40		N' = 19	
Day 14	10/40 (25.0)	(12.7, 41.2)	2/19 (10.5)	(1.3, 33.1)
Day 28	13/40 (32.5)	(18.6, 49.1)	3/19 (15.8)	(3.4, 39.6)
BSI/Sepsis	N' = 23		N' = 14	
Day 14	5/23 (21.7)	(7.5, 43.7)	1/14 (7.1)	(0.2, 33.9)
Day 28	7/23 (30.4)	(13.2, 52.9)	3/14 (21.4)	(4.7, 50.8)
cUTI	N' =17		N' = 5	
Day 14	2/17 (11.8)	(1.5, 36.4)	2/5 (40.0)	(5.3, 85.3)
Day 28	2/17 (11.8)	(1.5, 36.4)	2/5 (40.0)	(5.3, 85.3)
Overall	N' = 80		N' = 38	
Day 14	17/80 (21.3)	(12.9, 31.8)	5/38 (13.2)	(4.4, 28.1)
Day 28	22/80 (27.5)	(18.1, 38.6)	8/38 (21.1)	(9.6, 37.3)

Similar mortality rates were noted in the ITT population with one additional death recorded at day 14 (and subsequently at day 28) in both treatment groups in the HAP/VAP/HCAP stratum and one additional death at day 28 in the cefiderocol group in the cUTI stratum.

Overall there were 39 deaths recorded until end of study, 30 deaths in the cefiderocol group and 9 deaths in the BAT group. Eighteen of the deaths in the cefiderocol group were among subjects with pneumonia, 9 subjects had BSI/sepsis and 3 subjects were treated for cUTI. In the BAT group four, three and two subjects each were treated for pneumonia, BSI/sepsis and cUTI, respectively.

Subgroup analyses

Although the study size was small which makes subgroup analyses less valuable some of the analyses are noted (CR micro-ITT population):

Clinical cure rates and microbiological eradication rates were essentially similar across treatment groups in the subgroups examined.

All-cause mortality at day 28 were higher in the cefiderocol group for patients treated for HAP/VAP/HCAP (32.5% vs. 15.8%) and BSI/sepsis (30.4% vs. 21.4%) for subjects infected with non-fermenters (36.7% vs. 20.0%).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table E21. Summary of efficacy for trial APEKS-cUTI

Title: A Multicenter, Double-blind, Randomized, Clinical Study to Assess the Efficacy and Safety of Intravenous S-649266 in Complicated Urinary Tract Infections With or Without Pyelonephritis or Acute Uncomplicated Pyelonephritis Caused by Gram-negative Pathogens in Hospitalized Adults in Comparison with Intravenous Imipenem/Cilastatin		
Study identifier	1409R2121	
Design	This was a Phase 2, randomised, double-blind, active-controlled, parallel-group, multicenter trial of cefiderocol compared with IMP/CS in adult subjects with cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis. Hospitalised subjects were randomised in a 2:1 ratio to receive cefiderocol or IMP/CS.	
	Duration of main phase:	The treatment phase was 7 to 14 days. Efficacy was assessed at Early assessment (EA; day 4 ± 1), End-of-treatment (EOT), Test-of-cure (TOC; 7 days ± 2 days following EOT), and Follow-up (FU; approximately 14 days ± 3 days after EOT)
Hypothesis	Non-inferiority	
Treatments groups	Cefiderocol	Cefiderocol 2 g q8h administered over 1 h for 7 to 14 days (5 days at the lowest) Numbers randomized: 303
	IMP/CS	IMP/CS 1000 mg q8h administered over 1 h for (5) 7 to 14 days (5 days at the lowest) Numbers randomized: 149
Endpoints and definitions	Primary endpoint: Composite response	Composite of microbiological eradication (defined as a reduction to $<10^4$ CFU/mL) and clinical cure per subject at TOC in the Micro-ITT population
	Microbiological eradication (CHMP adjusted)	Microbiological eradication (defined as a reduction to $<10^3$ CFU/mL) per subject at TOC in the Micro-ITT population
Database lock	22 Nov 2016	
Results and Analysis		
Analysis description	**Primary Analysis**	

Analysis population and time point description	Micro-ITT population = All randomised patients who received at least 1 dose of study drug who had a baseline Gram-negative bacterial pathogen on culture of urine or blood that causes UTI. TOC = 7 days ± 2 days following EOT		
Descriptive statistics and estimate variability	Treatment group	Cefiderocol}	IMP/CS
	Number of subjects	252	119
	Composite response (%)	183 (72.6)	65 (54.6)
	Adjusted treatment difference in % (95% CI)	18.58 (8.23, 28.92)	
	Microbiological eradication (CHMP adjusted)	173 (68.7)	64 (53.8)
	Adjusted treatment difference in % (95% CI)	15.44 (4.94; 25.94)	

Table E22. Summary of efficacy for trial CREDIBLE-CR

Title: A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens		
Study identifier	1424R2131	
Design	This was an interim analysis of an ongoing Phase 3, randomised, open-label, active-controlled, parallel-group, multicentre trial of cefiderocol compared with BAT in adult subjects with carbapenem resistant Gram-negative infections, including HAP/VAP/HCAP, cUTI and BSI/sepsis. Hospitalised subjects were randomised in a 2:1 ratio to cefiderocol or BAT.	
	Duration of main phase:	The treatment phase was 7 to 14 days. Efficacy was assessed at End-of-treatment (EOT), Test-of-cure (TOC; 7 days ± 2 days following EOT), and Follow-up (FU; approximately 14 days ± 3 days after EOT)
Hypothesis	This was an estimation trial mainly comparing the efficacy and safety of two parallel treatment regimens	
Treatments groups	Cefiderocol	Cefiderocol 2 g q8h administered over 3 h for (5 possible for cUTI only) 7 to 14 (with a possibility to extend to up to 21) days Numbers randomized: 47

	BAT	BAT, locally sourced by study sites, within the local standard of care determined by the investigator for each infection diagnosis. This consisted of 1 to 3 antibiotic agents selected specifically for the carbapenem-resistant Gram-negative pathogen. Numbers randomized: 23
Endpoints and definitions	Primary endpoint: Clinical response for HAP/VAP/HCAP and BSI/sepsis and microbiological eradication for cUTI	HAP/VAP/HCAP and BSI/sepsis: Clinical cure per subject at TOC in the CR Micro-ITT population cUTI: Microbiological eradication (defined as a reduction to $<10^3$ CFU/mL) per subject at TOC in the CR Micro-ITT population
	All-cause mortality at day 28	Mortality of any cause assessed at day 14 and 28 in the CR Micro-ITT population (overall and by clinical diagnosis)
Database lock	28 June 2019	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	CR Micro-ITT population = All randomised patients who received at least 1 dose of study treatment who had a baseline Gram-negative pathogen from an appropriate clinical specimen and whose baseline Gram-negative pathogen was carbapenem-resistant TOC = 7 days ± 2 days following EOT		
Descriptive statistics and estimate variability	Treatment group	Cefiderocol	BAT
	Number of subjects	80	38
	Clinical response for HAP/VAP/HCAP n/N' (%) (95% CI)	20/40 (50.0) (33.8, 66.2)	10/19 (52.6) (28.9, 75.6)
	Clinical response for BSI/sepsis n/N' (%) (95% CI)	10/23 (43.5) (23.2, 65.5)	6/14 (42.9) (17.7, 71.1)
	Microbiological eradication for cUTI n/N' (%) (95% CI)	9/17 (52.9) (27.8, 77.0)	1/5 (20.0) (0.5, 71.6)
	All-cause mortality at day 28 Overall n/N (%) (95% CI)	22/80 (27.5) (18.1, 38.6)	8/38 (21.1) (9.6, 37.3)

	All-cause mortality at day 28 HAP/VAP/HCAP n/N' (%) (95% CI)	13/40 (32.5) (18.6, 49.1)	3/19 (15.8) (3.4, 39.6)
	All-cause mortality at day 28 BSI/sepsis n/N' (%) (95% CI)	7/23 (30.4) (13.2, 52.9)	3/14 (21.4) (4.7, 50.8)
	All-cause mortality at day 28 cUTI n/N' (%) (95% CI)	2/17 (11.8) (1.5, 36.4)	2/5 (40.0) (5.3, 85.3)

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

Not applicable because phase 2 and 3 efficacy data were not combined.

Clinical studies in special populations

Table E23. Exposure to cefiderocol by age-group in the Phase 2 and 3 studies

	Age 65-74 (number /total number)	**Age 75-84 (number /total number)**	**Age 85+ (number /total number)**
Controlled Trials APEKS-cUTI CREDIBLE-CR APEKS-NP	 91/300 35/101 43/148	 61/300 23/101 33/148	 6/300 6/101 7/148

Supportive study

APEKS-NP

The APEKS-NP study was a Phase 3, multicentre, randomised, double-blind, parallel-group, active-controlled study to compare all-cause mortality, clinical and microbiological outcomes of treatment with cefiderocol or meropenem in adult subjects with documented HAP/VAP/HCAP caused by Gram-negative pathogens. This study was not intended to form the basis for the indication applied for. However, the results of this study were requested by the CHMP because of the imbalance in mortality noted in the interim analysis of the CREDIBLE-CR study attributable to the subset of subjects with HAP/VAP/HCAP and the concern of low ELF penetration of cefiderocol.

Methods

Approximately 300 subjects were planned to be randomised (1:1) to receive either cefiderocol 2 g administered IV over 3 hours every 8 hours (q8h), or meropenem. Randomisation was stratified using infection diagnosis (HAP/VAP/HCAP) and APACHE II score (≤ 15 and ≥ 16) as allocation factors.

Subjects with reduced renal function, augmented renal clearance, or who were on various forms of haemodialysis had their doses of cefiderocol or meropenem adjusted. Linezolid was administered for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), to maintain the study blind and, in the cefiderocol group, to provide coverage for Gram-positive bacteria. Sequential oral antibiotic (step-down) therapy was not permitted by the protocol. Systemic antibiotics, other than linezolid, meropenem, and cefiderocol, were not permitted from randomisation until TOC. Aerosolised antibiotics were not permitted from randomisation until after TOC.

The subjects´ clinical status were evaluated at Early Assessment (EA) at Day 3 to 4, End of Treatment (EOT), Test of Cure (TOC) at EOT + 7 days, Follow-up (FUP) at EOT + 14 days, and End of Study (EOS) at EOT + 28 days.

The modified intent-to-treat (mITT) population was the primary population for efficacy. The mITT population included all randomised subjects who received at least 1 dose of study drug, who either had evidence of an infection of the lower respiratory tract caused by a Gram-negative pathogen based on either a culture, Gram stain, or other diagnostic test, or a lower respiratory tract infection, but culture or other diagnostic tests did not provide a microbiological diagnosis.

The primary efficacy endpoint was all-cause mortality at Day 14 calculated as the proportion of patients who experienced mortality regardless of the cause at or before Day 14 since first infusion of study drug. The clinical and microbiological outcomes per subject, and per pathogen, at the EA, EOT, TOC and/or FUP visits were secondary endpoints.

The study design and the primary objective were based on the hypothesis that cefiderocol is noninferior to meropenem; established based on a 12.5% noninferiority margin, which was discussed and agreed with the US FDA.

Results

A total of 148 subjects treated with cefiderocol and 150 treated with meropenem comprised the ITT population. Of these 298 subjects, 292 were eligible for inclusion in the mITT population (145 in the cefiderocol group and 147 in the meropenem group). Exclusion from the mITT population was due to pneumonia caused only by Gram-positive bacteria (for 3 subjects in the cefiderocol group and 3 subjects in the meropenem group). Of the subjects included in the mITT population, a total of 123 had VAP, 119 had HAP and 50 had HCAP and were equally distributed in the 2 treatment groups.

The populations across the APEKS-NP study and patients with pneumonia in the CREDIBLE-CR study were generally similar with regard to age, gender distribution, APACHE score, creatinine clearance, and type of pneumonia with the majority of subjects in both studies requiring ventilation (74.6% in CREDIBLE-CR and 59.7% in APEKS-NP). It is noted, however, that the proportion of subjects with treatment failure was 64.2% in the CREDIBLE-CR study and 32.6% in the APEKS-NP study, and the proportion of subjects with *A. baumannii* was 55.2% in the CREDIBLE-CR study and 15.8% in the APEKS-NP study (see below).

Comparison of Demographic, Clinical and Microbiological Parameters at Baseline Between HAP/VAP/HCAP Subjects in the CREDIBLE-CR and APEKS-NP Study Populations (ITT/Safety population)

Variable	HAP/VAP/HCAP in CREDIBLE-CR (N = 67)	APEKS-NP (N = 298)
HAP, %	40.3	40.6
VAP, %	55.2	41.9
HCAP, %	4.5	17.4
Ventilated, %	74.6	59.7
Mean age, y	63.9	65.2
Male gender, %	76.1	68.8
Region, % Europe Asia-Pacific North and South America	 40.3 38.8 20.8	 66.8 29.2 4.0
CrCL < 50 mL/min, %	32.8	33.9
APACHE II score ≥16, % Mean score	56.7 17.1	48.7 16.2
Treatment failure, %	64.2	32.6
Top 4 baseline pathogens, % *A. baumannii* *K. pneumoniae* *P. aeruginosa* *E. coli*	 55.2 25.4 25.4 7.5	 15.8 30.9 16.1 13.8

APACHE II = Acute Physiology and Chronic Health Evaluation II; CrCL = creatinine clearance; HAP = hospital acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Outcomes and estimation

All-cause mortality rates by Day 14 showed that cefiderocol was noninferior to meropenem as the upper limit of the 95% confidence interval (CI) for the difference between the treatments was below 12.5% (see below).

All-cause Mortality Rates at Day 14 and 28 in the APEKS-NP Study (Modified Intent-to treat Population)

	Cefiderocol N = 145	Meropenem N = 147	Treatment Comparison		
			Difference [a]	95% CI	P-value
	n/N' (%)	n/N' (%)	(%)	[b]	
Day 14	18/145 (12.4)	17/146 (11.6)	0.8	(-6.6, 8.2)	0.0020 [c] 0.8321 [d]
Day 28	30/143 (21.0)	30/146 (20.5)	0.5	(-8.7, 9.8)	

CI = confidence interval.
N = number of subjects in the analysis set; n = number of subjects who died; N'= number of subjects with known survival status;

Day 14 and Day 28 all-cause mortality is calculated from first infusion of study drug

[a] Treatment difference (cefiderocol minus meropenem) is the adjusted estimate of the difference in the all-cause mortality rate at Day 14 and Day 28 between the 2 treatment arms based on Cochran-Mantel Haenszel weights using APACHE II score (≤15 and ≥ 16) as the stratification factor.

[b] The 95% CI (2-sided) is based on a stratified analysis using Cochran-Mantel Haenszel weights using APACHE II score (≤ 15 and ≥ 16) as the stratification factor. The CI is calculated using a normal approximation to the difference between 2 binomial proportions (Wald method).

[c] p-value for non-inferiority hypothesis.

[d] p-value for the superiority hypothesis

Clinical and microbiological outcomes at different timepoints are shown below.

Clinical Outcomes at EOT, TOC and FUP in the APEKS-NP Study (Modified Intent-to-treat Population)

Visit Clinical Outcome	Cefiderocol (N = 145) n (%)	Meropenem (N=147) n (%)	Treatment Difference (%)	95% confidence interval for difference
End of Treatment				
Clinical cure	112 (77.2)	119 (81.0)	-3.8	(-12.8, 5.1)
Clinical failure	21 (14.5)	21 (14.3)		
Indeterminate	12 (8.3)	7 (4.8)		
Test of Cure				
Clinical cure	94 (64.8)	98 (66.7)	-2.0	(-12.5, 8.5)
Clinical failure	27 (18.6)	31 (21.1)		
Indeterminate	24 (16.6)	18 (12.2)		
Follow-up				
Sustained clinical cure	84 (57.9)	85 (57.8)	-0.1	(-10.9, 10.8)
Clinical failure	27 (18.6)	31 (21.1)		
Relapse	4 (2.8)	2 (1.4)		
Indeterminate	30 (20.7)	29 (19.7)		

APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; EOT = End of Treatment; FUP = Follow-up; HAP = hospital acquired bacterial pneumonia; HCAP = healthcare-associated bacterial pneumonia; TOC = Test of Cure; VAP = ventilator-associated bacterial pneumonia

N = number of subjects in the analysis set; n = number of subjects within the clinical outcome category.

Percentage is calculated using the number of subjects in the column heading as the denominator.

Treatment difference (cefiderocol minus meropenem) is the adjusted estimate of the difference in the cure rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factors at baseline, infection type (HAP/VAP/HCAP) and APACHE II score (≤15 and ≥16).

Microbiological Outcomes at EOT, TOC and FUP in the APEKS-NP Study (Modified Intent-to-treat Population)

Visit Microbiological Outcome	Cefiderocol (N = 145) n (%)	Meropenem (N=147) n (%)	Treatment Difference (%)	95% confidence interval for difference
End of Treatment	N*=124	N*=127		
Eradication	79 (63.7)	85 (66.9)	-3.8	(-15.5, 7.9)
Persistence	18 (14.5)	19 (15.0)		
Indeterminate	27 (21.8)	23 (18.1)		
Test of Cure	N*=124	N*=127		
Eradication	59 (47.6)	61 (48.0)	-1.4	(-13.5, 10.7)
Persistence	26 (21.0)	27 (21.3)		
Indeterminate	39 (31.5)	39 (30.7)		
Follow-up	N*=124	N*=127		
Sustained eradication	54 (43.5)	49 (38.6)	3.9	(-7.9, 15.8)
Persistence	27 (21.8)	28 (22.0)		
Recurrence	1 (0.8)	2 (1.6)		
Indeterminate	42 (33.9)	48 (37.8)		

N = number of subjects in the analysis set; n = number of subjects within the microbiological outcome category.
N* = number of subjects with non-missing baseline pathogens.
Percentage is calculated using N* as the denominator for each visit.
Treatment difference (cefiderocol minus meropenem) is the adjusted estimate of the difference in the eradication rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factors at baseline, infection type (HAP/VAP/HCAP) and APACHE II score (≤15 and ≥16).

Cefiderocol treatment resulted in microbiological eradication and clinical cure against the major causative pathogens including *K. pneumoniae*, *P. aeruginosa, A. baumannii* and *E. coli* (see below).

Microbiological Eradication and Clinical Cure Rates at EOT, TOC and FUP by Baseline Gram-negative Pathogen in the APEKS-NP Study (Modified Intent-to-treat Population)

Pathogen Visit	Cefiderocol (N=145)	Meropenem (N=147)	Treatment difference (%)	95% Confidence Interval
K. pneumoniae	**N'=48**	**N'=44**		
End of Treatment				
Microbial eradication	28 (58.3)	33 (75.0)	-16.7	(-35.6, 2.3)
Clinical cure	38 (79.2)	35 (79.5)	-0.4	(-16.9, 16.2)
Test of Cure				
Microbial eradication	22 (45.8)	24 (54.5)	-8.7	(-29.1, 11.7)

Pathogen Visit	Cefiderocol (N=145)	Meropenem (N=147)	Treatment difference (%)	95% Confidence Interval
Clinical cure	31 (64.6)	29 (65.9)	-1.3	(-20.8, 18.1)
Follow-up				
Sustained microbial eradication	19 (39.6)	17 (38.6)	0.9	(-19.0, 20.9)
Sustained clinical cure	27 (56.3)	25 (56.8)	-0.6	(-20.8, 19.7)
P. aeruginosa	**N'=24**	**N'=24**		
End of Treatment				
Microbial eradication	17 (70.8)	16 (66.7)	4.2	(-22.0, 30.4)
Clinical cure	22 (91.7)	19 (79.2)	12.5	(-7.2, 32.2)
Test of cure				
Microbial eradication	9 (37.5)	11 (45.8)	-8.3	(-36.1, 19.5)
Clinical cure	16 (66.7)	17 (70.8)	-4.2	(-30.4, 22.0)
Follow-up				
Sustained microbial eradication	10 (41.7)	10 (41.7)	0.0	(-27.9, 27.9)
Sustained clinical cure	14 (58.3)	13 (54.2)	4.2	(-23.9, 32.2)
A. baumannii	**N'=23**	**N'=24**		
End of Treatment				
Microbial eradication	14 (60.9)	11 (45.8)	15.0	(-13.2, 43.2)
Clinical cure	15 (65.2)	19 (79.2)	-13.9	(-39.3, 11.4)
Test of Cure				
Microbial eradication	9 (39.1)	8 (33.3)	5.8	(-21.7, 33.2)
Clinical cure	12 (52.2)	14 (58.3)	-6.2	(-34.5, 22.2)
Follow-up				
Sustained microbial eradication	7 (30.4)	7 (29.2)	1.3	(-24.9, 27.4)
Sustained clinical cure	10 (43.5)	13 (54.2)	-10.7	(-39.1, 17.7)
E. coli.	**N'=19**	**N'=22**		
End of Treatment				
Microbial eradication	12 (63.2)	16 (72.7)	-9.6	(-38.1, 19.0)
Clinical cure	15 (78.9)	19 (86.4)	-7.4	(-30.7, 15.9)
Test of Cure				
Microbial eradication	10 (52.6)	11 (50.0)	2.6	(-28.0, 33.3)
Clinical cure	12 (63.2)	13 (59.1)	4.1	(-25.8, 33.9)
Follow-up				
Sustained microbial eradication	9 (47.4)	9 (40.9)	6.5	(-24.0, 36.9)
Sustained clinical cure	12 (63.2)	11 (50.0)	13.2	(-17.0, 43.3)

EOT = End of Treatment; FUP = Follow-up; TOC = Test of Cure

Percentage is calculated using N' as the denominator, where N' is the number of subjects with the relevant pathogen.

In summary, the APEKS-NP study showed that cefiderocol was noninferior to meropenem for all-cause mortality at Day 14. The microbiological eradication rates and clinical cure rates were generally similar for cefiderocol and meropenem at TOC, with activity against the major causative pathogens.

2.5.3. Discussion on clinical efficacy

In line with CHMP guidance for agents that are expected to address an unmet medical need the Applicant has conducted an abbreviated clinical programme to support the proposed indication *treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options*.

In the initial submission, one phase 2 study in cUTI/pyelonephritis (APEKS-cUTI) and one phase 3 study in different infection types caused by carbapenem-resistant Gram-negative pathogens (CREDIBLE-CR) were the main clinical studies. The APEKS-cUTI study was conducted in an atypical population with cUTI and therefore cannot establish the efficacy of cefiderocol for the treatment of the target carbapenem-resistant organisms. It provides a comparison of the efficacy of cefiderocol vs. an approved carbapenem and useful safety and PK data. The CREDIBLE-CR study can only be regarded as supportive of efficacy for the intended indication because of its limited size. Therefore, the possible ability of cefiderocol to meet an unmet need i.e. treatment of carbapenem-resistant organisms expressing β-lactamases, particularly Ambler Class B or D enzymes - is based mainly on in-vitro data, on nonclinical efficacy data to determine PK/PD targets and on clinical PK data indicating that relevant PK/PD targets are met with the 2 g q8h regimen when using 3-h infusions. It is important to note that these data are pivotal to the application.

During the assessment, the CHMP requested the Applicant to provide the results from a recently completed phase 3 study in HAP/VAP/HCAP (APEKS-NP). The results of this study were asked for because of the imbalance in mortality noted in the interim analysis of the CREDIBLE-CR study, which caused some concern regarding the efficacy of cefiderocol in the subset of subjects with HAP/VAP/HCAP. This potential concern was supported by the low ELF penetration of cefiderocol documented in healthy subjects.

Design and conduct of clinical studies

APEKS-cUTI

The APEKS-cUTI study included hospitalised adult subjects with cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis with evidence of pyuria and a positive urine culture that contained $\geq 10^5$ CFU/mL of a Gram-negative uropathogen likely susceptible to IMP. There was a 30% cap for acute uncomplicated pyelonephritis. The inclusion and exclusion criteria were acceptable.

Subjects were randomised to cefiderocol 2 g q8h administered over 1 h or IMP/CS 1 g q8h for (5) 7 to 14 days. The choice of comparator and treatment duration was reasonable. According to the product information for IMP/CS in EU countries it is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as *Pseudomonas aeruginosa*) and very severe infections should be treated with 1000 mg q6h. However, because of the renal elimination of IMP/CS and subsequent accumulation in urine the 1000 mg q8h IMP/CS is acceptable. Nevertheless, in this study the imipenem dose was adjusted in accordance with baseline CrCL and body weight in line with US FDA recommendations that were current when the study started but later amended. When compared to the EU SmPCs for imipenem, there was concern that the dose adjustment schema could have led to under-dosing in some subsets.

The primary efficacy endpoint was the composite of microbiological eradication and clinical response outcomes at the TOC in the Micro-ITT population. The current CHMP guidance recommends primary efficacy endpoint in cUTI studies is microbiological eradication (defined as a reduction to $<10^3$ CFU/mL) at TOC. However, the antibacterial guideline is under revision. In the draft guideline it is proposed to change the primary endpoint to a combination of clinical and microbiological (defined as a reduction to $<10^3$ CFU/mL) success rate. The Applicant has presented results also according the current CHMP recommendation.

The sample size was dimensioned to meet FDA requirements and is also acceptable to the CHMP.

Initially, approximately 250-300 subjects were to be enrolled and randomised (2:1) with the estimation of the sample size based on a non-inferiority margin of 20%. The sample size was then clarified to approximately 300 subjects when an analysis using a non-inferiority margin of 15% was incorporated (amendment 1, protocol Version 2 05 Aug 2015). Further amendments increased the sample size to increase the safety database; from 300 to 400 (amendment 2, protocol version 3 30 Nov 2015) to be able to provide the majority of subjects for the safety evaluation of the drug and again from 400 to 450 (amendment 3, protocol version 4 26 Apr 2016) to have a total of 300 subjects treated with cefiderocol. These changes were all made to meet FDA requirements.

The randomisation was stratified according to the subject´s clinical diagnosis and region where region was added with protocol amendment 1 (05 Aug 2015), i.e. 6 months after start of recruitment (the first subject´s first visit was 5 February 2015). With each increase in the sample size the expected *number* of subjects with acute uncomplicated pyelonephritis was re-calculated; the limit of 30% was however kept throughout the study.

Study treatments were dispensed and administered in a double-blinded fashion. The methodologies for these procedures were acceptable.

The statistical analysis plan was overall appropriate. Multiplicity considerations concerned only the primary endpoint and were implemented in that non-inferiority was initially to be concluded based on a NI margin of 20% and, if shown, based on a tighter margin (15%) according to a regulatory (/FDA) requirement. The primary analysis was performed on the micro-ITT population with sensitivity analyses performed on the ITT and the ME populations.

Four-hundred ninety-five subjects were screened and 452 enrolled in a 2 to 1 ratio to receive cefiderocol or IMP/CS. Over 90% of the subjects in both treatment groups completed the study and completed treatment with similar rates in both groups for reasons of study and treatment discontinuation.

Eleven subjects (10 of these were in the cefiderocol group) were removed from the analysis populations for efficacy because of GCP noncompliance at 2 study sites. Sixty-six subjects were excluded from the primary analysis population (Micro-ITT population) as they had no baseline Gram-negative uropathogen with $\geq 10^5$ CFU.

Demographic and baseline subject characteristics were generally comparable for the treatment groups, although there were somewhat more males in the cefiderocol treatment group.

Compliance and exposure to study drug and prior and concomitant exposure to other antibacterial agents were well balanced between the treatment groups although fewer concomitant antibiotics were used in the cefiderocol group.

<u>CREDIBLE-CR</u>

The CREDIBLE-CR study included hospitalised adult subjects with HAP/VAP/HCAP, cUTI and BSI/sepsis caused by a Gram-negative pathogen with evidence of carbapenem resistance. The BSI/sepsis

infection category could include subjects with other infection types e.g. ABSSSI and cIAI. Infections in the CNS and infections requiring more than 3 weeks of antibiotic treatment such as bone and joint infections and endocarditis were excluded. However, because infections of unknown origin were acceptable for inclusion in the BSI/sepsis category, infections not suitable for evaluation could anyway be included (see below). HAP/VAP/HCAP, cUTI and cIAI are infection types most likely to be caused by pathogens of interest for the sought indication. Overall the inclusion and exclusion criteria were acceptable.

The study compared cefiderocol 2 g q8h administered over 3 h and BAT (1 to 3 antibacterial agents). A single adjunctive antibacterial agent for HAP/VAP/HCAP or BSI/sepsis subjects was allowed. This was agreed by the CHMP before study initiation because investigators may not be willing to use monotherapy when MDR organisms are anticipated, especially in HAP/VAP. The recommended treatment duration was 7 to 14 days (minimum 5 days for cUTI and maximum 21 days for all infection types).

The study primarily compared the clinical outcome at TOC in subjects with HAP/VAP/HCAP or BSI/sepsis and the microbiological outcome per subject at TOC in subjects with cUTI in the CR Micro-ITT population in line with CHMP recommendations.

The sample size was driven by feasibility and not by statistical considerations. The study size was discussed and agreed during scientific advice.

Study subjects were randomised to receive cefiderocol or BAT regimen and the randomisation was stratified according to infection types with an aim to include approximately 50% HAP/VAP/HCAP and not more than 30% cUTI and remainder BSI/sepsis. The aim to avoid a deterministic allocation of treatment is appreciated.

No inferential testing was planned. The descriptive nature of the final analysis is acknowledged. The planned sample size for the entire study was 150 subjects (~100 in cefiderocol group, ~50 in BAT group).

A total of 258 subjects were screened and 152 enrolled in a 2 to 1 fashion to receive cefiderocol or BAT. A lower number of subjects in the cefiderocol group completed the study compared to the BAT group. The difference was mainly attributable to a higher number of deaths in the cefiderocol group.

Because of the limited size of the study, differences in the between group baseline demographic and diseases characteristics are noted, but these differences were in general less than 10%.

Subjects with HAP/VAP/HCAP represented approximately 50% of the subjects in both treatment groups; approximately 30% of the subjects had BSI/sepsis (25% vs 37%) and approximately 15% of the subjects had cUTI (21% vs. 13%). Among subjects within the BSI/sepsis category patients included seems generally not to have had infections in need of >3 weeks antibacterial treatment.

Almost all subjects had moderate to severe disease severity. Carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were the major pathogens in subjects overall.

In the cefiderocol group, 66/80 of subjects received cefiderocol monotherapy (14/80 received adjunctive therapy), whereas in the BAT group, 10/38 of subjects received monotherapy. In the BAT group, 25/38 of subjects received a colistin-based regimen.

The mean duration of exposure for subjects with pneumonia or BSI/sepsis were one day shorter in the cefiderocol treatment group (11.4 days) compared to for subjects in the BAT group (12.6 days). The mean duration of exposure to cefiderocol for subjects with cUTI were 11.9 days and for BAT 7.4 days.

Nearly all subjects had received prior antimicrobial therapy within 2 weeks prior to randomisation. Many subjects achieved concomitant antibacterial agents in addition to cefiderocol ± adjunctive therapy and BAT regimen. The concomitant antibacterial agents used included agents with activity against Gram-negative pathogens also including agents that could be active against CR nonsusceptible pathogens.

APEKS-NP

The APEKS-NP study was a Phase 3 study to compare all-cause mortality, clinical and microbiological outcomes of treatment with cefiderocol or meropenem in adult subjects with documented HAP/VAP/HCAP caused by Gram-negative pathogens.

Approximately 300 subjects were planned to be randomised (1:1) to receive either cefiderocol 2 g administered IV over 3 hours every 8 hours (q8h), or meropenem.

The modified intent-to-treat (mITT) population was the primary population for evaluating efficacy. The mITT population included all randomised subjects who received at least 1 dose of study drug, who either had evidence of an infection of the lower respiratory tract caused by a Gram-negative pathogen based on either a culture, Gram stain, or other diagnostic test, or a lower respiratory tract infection, but culture or other diagnostic tests did not provide a microbiological diagnosis.

The primary efficacy endpoint was all-cause mortality at Day 14 calculated as the proportion of patients who experienced mortality regardless of the cause at or before Day 14 since first infusion of study drug. The clinical and microbiological outcomes per subject, and per pathogen, at the EA, EOT, TOC and/or FUP visits were secondary endpoints.

The study design and the primary objective were based on the hypothesis that cefiderocol is noninferior to meropenem; established based on a 12.5% noninferiority margin, which was discussed and agreed with the US FDA.

A total of 148 subjects treated with cefiderocol and 150 treated with meropenem comprised the ITT population. Of these 298 subjects, 292 were eligible for inclusion in the mITT population (145 in the cefiderocol group and 147 in the meropenem group). Exclusion from the mITT population was due to pneumonia caused only by Gram-positive bacteria (for 3 subjects in the cefiderocol group and 3 subjects in the meropenem group). Of the subjects included in the mITT population, a total of 123 had VAP, 119 had HAP and 50 had HCAP and were equally distributed in the 2 treatment groups.

The populations across the APEKS-NP study and patients with pneumonia in the CREDIBLE-CR study were generally similar with regard to age, gender distribution, APACHE score, creatinine clearance, and type of pneumonia with the majority of subjects in both studies requiring ventilation (74.6% in CREDIBLE-CR and 59.7% in APEKS-NP). It is noted, however, that the proportion of subjects with treatment failure was 64.2% in the CREDIBLE-CR study and 32.6% in the APEKS-NP study, and the proportion of subjects with *A. baumannii* was 55.2% in the CREDIBLE-CR study and 15.8% in the APEKS-NP study.

Efficacy data and additional analyses

APEKS-cUTI

The response rate for the primary endpoint composite of clinical outcome and microbiological outcome at TOC in the Micro-ITT population was 72.6% of subjects in the cefiderocol group and 54.6% of subjects in the IPM/CS group. Noninferiority at the prespecified -20% and -15% margins were met. In addition, the results were consistent with superiority of cefiderocol compared with IPM/CS. Similar analyses in the ME population confirmed the results.

Using the EU-recommended primary endpoint for studies in cUTI (microbiological eradication at TOC in the Micro-ITT population) and more stringent criterion for microbial eradication ($<10^3$ CFU/mL instead of $<10^4$ CFU/mL) essentially similar results were obtained.

At baseline, 114/252 (45%) cefiderocol and 71/119 (60%) imipenem patients had dose adjustments based on baseline renal function and body weight. In this 2:1 randomisation study, the combined response rates at TOC in the cefiderocol group were lower in each dose adjustment group vs. the unadjusted dose group. However, the cefiderocol dose adjustment schema in this study was not the same as that sued in CREDIBLE-CR or APEKS-NP and is not that in the final SmPC. In the imipenem group, the two largest dose adjustment groups showed lower response rates vs. the unadjusted group. Thus, while the overall comparison gave rates of 54.2% for unadjusted vs. 50.7% for adjusted, the rates for the two largest groups (n=61 of the 71 with adjusted doses) were lower than for the unadjusted dose group (41.7% and 48.6% vs. 54.2%). Overall, the conclusion on superiority is considered unsafe. The study had 2:1 randomisation and used imipenem dose adjustments that are not in line with the revised recommendations in the US and the existing recommendations in the EU. However, the applicant did not claim an indication for treatment of cUTI. Therefore, this conclusion does not impact on the overall conclusions on the dossier.

When the response rates were separated between clinical outcome and microbiological outcome it was clear that the composite response rates in favour or the cefiderocol arm at TOC and FU was driven by higher microbiological eradication rates.

The treatment differences in the composite response rate at TOC by different subgroups were consistent with the treatment difference in the overall Micro ITT population.

CREDIBLE-CR

The clinical cure rates and microbiological eradication rates at TOC in the CR Micro-ITT population were similar for the cefiderocol and BAT treatment arms. Moreover, with regards the main pathogens studied (*A. baumannii*, *K. pneumoniae* and *P. aeruginosa*), clinical and microbiological success rates were essentially similar at TOC although some numerical differences are noted which is likely an effect of the low number of each pathogen. For example, a somewhat lower clinical cure rate at TOC against *A. baumannii* is noted for cefiderocol compared with BAT. However, this difference changes in favour of cefiderocol at follow-up.

The imbalance in mortality observed in the interim analysis remains in the full dataset. The overall all-cause mortality at day 28 was higher in the cefiderocol group than in the BAT group. However, the imbalance is evident in both the HAP/VAP/HCAP and BSI/sepsis subsets, not just in patients with pneumonia. This update vs. the interim dataset does not suggest that the mortality difference in CREDIBLE-CR is driven by poor efficacy of cefiderocol in HAP/VAP *per se*.

The difference in mortality rates between the cefiderocol and BAT treatment groups in the CREDIBLE-CR study is unexplained although there are some indications of imbalances between the treatment groups responsible for a minor part of the difference, e.g. history of septic shock among subjects with *A. baumannii* infection. However, the mortality rate in the cefiderocol group was also higher than the mortality rate in the BAT group for subjects with *A. baumannii* who did not have a history of shock. Therefore, shock does not alone explain the difference in mortality.

The CHMP considers the data point to a possible problem for cefiderocol in the treatment of *Acinetobacter* spp., with or without shock. Although there were no difference noted in mortality between the treatment groups in the APEKS-NP study with regards subjects infected with *A. baumannii*, the data from the typical HAP/VAP study population and from the UTI study cannot be used to rule out a real problem for cediferocol vs. carbapenem-resistant *Acinetobacter*. It is considered relevant to inform the prescribers of the imbalance in mortality in the CREDIBLE-CR study and

association between mortality and infection with *Acinetobacter* in the cefiderocol treatment arm. At the request of CHMP, an adequate warning mentioning the imbalance in mortality was included in section 4.4 of the Fetcroja SmPC.

APEKS-NP

The APEKS-NP study showed that cefiderocol was noninferior to meropenem for the treatment of HAP/VAP/HCAP for all-cause mortality at Day 14 (the FDA-recommended primary endpoint). The EU-recommended primary endpoint for a HAP/VAP study (HCAP should not be included) is clinical outcome at TOC using an NI-margin of -12.5%. This was just met since the clinical cure rates at TOC were 64.8% for the cefiderocol group (94/145) and 66.7% for the meropenem group (98/147), with a treatment difference of -2.0 (95% CI: -12.5, 8.5). However, the study was not sized for the primary evaluation of non-inferiority with regards this endpoint. Overall, the clinical cure rates and the microbiological eradication rates were similar for cefiderocol and meropenem at TOC, and essentially similar success rates were noted against the major causative pathogens, including *K. pneumoniae*, *P. aeruginosa*, *A. baumannii* and *E. coli*.

2.5.4. Conclusions on the clinical efficacy

Overall it is important to note that the pivotal data for the assessment of efficacy and the adequacy of the dose of Fetcroja for the intended indication are the in-vitro data, the nonclinical efficacy data to determine PK/PD targets and clinical PK data indicating that relevant PK/PD targets are met. Although the clinical programme was in line with CHMP guidance for agents with an aim to address an unmet medical need, the studies were not designed to establish the efficacy of cefiderocol for the treatment of the target carbapenem-resistant organisms and can only be regarded as supportive. This is because infections caused by carbapenem-resistant organisms were not specifically studied in the cUTI study and the CREDIBLE-CR study was too small to draw definitive conclusions on efficacy.

Efficacy data from the APEKS-NP study and from patients with pneumonia in the CREDIBLE-CR study support the use of cefiderocol for the treatment of lung infections. Therefore, with regards to efficacy, there is no need to restrict the proposed pathogen-specific indication to exclude treatment of lung infections.

The imbalance noted in mortality in the CREDIBLE-CR study is still unexplained. It is considered relevant to inform the prescribers of the imbalance in mortality in the CREDIBLE-CR study and association between mortality and infection with *Acinetobacter* in the cefiderocol treatment arm. At the request of CHMP, an adequate warning mentioning the imbalance in mortality was included in section 4.4 of the Fetcroja SmPC.

Development of resistance is regarded as efficacy concern and should be closely monitored during the post-marketing period. Any information that becomes available to the Applicant on emerging resistance, changing patterns of resistance or new mechanisms of resistance to the antibacterial agent should be notified promptly to EU regulators with a discussion of the possible implications for section 5.1 of the SmPC. The Applicant should follow up and report this issue in the Periodic Safety Update Reports.

2.6. Clinical safety

Sources of safety data

The key clinical safety data package supporting this application consists of:

- A completed pathogen-based, open-label, Phase 3 study including 152 subjects with carbapenem-resistant, Gram-negative infections comparing cefiderocol with best available therapy (BAT) (CREDIBLE-CR).
- A completed Phase 2 study in subjects with complicated urinary tract infection (cUTI) testing noninferiority of cefiderocol (n=300) versus imipenem and cilastatin (n=148) (IPM/CS) (APEKS-cUTI).
- A randomised, double-blind, Phase 3 study (Study 1615R2132, hereafter referred to as the APEKS-NP study) including 300 subjects with carbapenem-sensitive nosocomial pneumonia (hospital-acquired pneumonia [HAP]/ventilator-associated pneumonia [VAP]/healthcare-associated pneumonia [HCAP]) due to Gram-negative pathogens. APEKS-NP was requested by the CHMP because of the imbalance in mortality noted in the imbalance in mortality noted in the interim analysis of CREDIBLE-CR attributable to the subset of subjects with HAP/VAP/HCAP and the concern of low ELF penetration of cefiderocol. The study was ongoing at the 1st round of this application, the results has been briefly presented within the 2nd round.

The most directly relevant dataset for the indication and target population applied for is that from CREDIBLE-CR. However, double-blinded, direct comparison to a single, authorised monotherapy, as well as use of a faster infusion rate mean that the APEKS-cUTI dataset are still of value in the overall assessment of the safety profile, along with safety data collected in the Clinical Pharmacology studies.

The Applicant also presented pooled safety data summaries. As the study populations, target organisms and comparator regimens differed considerably between the two studies, the safety outcomes are not directly comparable. Furthermore, there was no pre-specified SAP for pooling of data from these studies. Therefore, individual study data rather than pooled data are considered here.

Additional supportive data come from 6 completed clinical pharmacology studies (also not pooled):

- Single-and multiple-ascending dose study (R2111)
- Intrapulmonary (BAL/ELF) PK study (R2112)
- Renal impairment study (R2113)
- Mass balance study (R2114)
- Drug interaction study (R2115)
- Thorough QT/QTc study (R2116)

The Compassionate Use data to date (14 patients as of 15 Aug 2018) comprise a tabulated listing of heterogeneous subjects with insufficiently detailed information. These will not be further discussed.

Patient demographics and baseline disease characteristics

Table S1. Demographics for CREDIBLE-CR and APEKS-cUTI (Safety Populations)

		CREDIBLE-CR		APEKS-cUTI	
		Cefiderocol N=101 n (%)	BAT N=49 n (%)	Cefiderocol N=300 n (%)	Imipenem/Cilastatin N=148 n (%)
Sex	Male	66 (65.3)	27 (55.1)	137 (45.7)	66 (44.6)
	Female	35 (34.7)	14 (28.6)	163 (54.3)	82 (55.4)
Age (years)	Mean	63.1	63.0	61.1	61.3
	SD	19.0	16.7	16.5	17.8
Weight (kg)	Mean	70.28	70.74	77.91	76.69
	SD	22.01	20.23	16.45	17.69

		CREDIBLE-CR		APEKS-cUTI	
		Cefiderocol N=101 n (%)	BAT N=49 n (%)	Cefiderocol N=300 n (%)	Imipenem/Cilastatin N=148 n (%)
BMI (kg/m^2)	Mean	25.46	25.32	27.56	27.22
	SD	6.91	7.25	5.22	6.59
Race	White	63 (62.4)	32 (65.3)	287 (95.7)	142 (95.9)
	Black or African American	0	0	1 (0.3)	1 (0.7)
	Asian	29 (28.7)	14 (28.6)	11 (3.7)	4 (2.7)
	Native Hawaiian or Other Pacific Islander	0	0	1 (0.3)	1 (0.7)
	Other	9 (8.9)	3 (6.1)	0	0
Creatinine clearance, mL/min [a] (renal function)	≥ 120 (ARC)	20 (19.8)	12 (24.5)	28 (9.3)	16 (10.8)
	> 80 to < 120 (normal)	18 (17.8)	10 (20.4)	124 (41.3)	47 (31.8)
	> 50 to ≤ 80 (mild)	20 (19.8)	12 (24.5)	89 (29.7)	50 (33.8)
	≥ 30 to ≤ 50 (moderate)	23 (22.8)	8 (16.3)	49 (16.3)	28 (18.9)
	< 30 (severe)	20 (19.8)	7(14.3)	8 (2.7)	7 (4.7)

		APEKS-NP	
		Cefiderocol N=148 n (%)	Imipenem/Cilastatin N=150 n (%)
Sex	Male	101 (68.2)	104 (69.3)
	Female	47 (31.8)	46 (30.7)
Age (years)	Mean	64.7	65.6
	SD	14.5	15.1
Weight (kg)	Mean	74.8	76.6
	SD	18.6	22.2
BMI (kg/m^2)	Mean	26.3	26.7
	SD	6.1	6.8
Race	White	102 (68.9)	100 (66.7)
	Black or African American	0	1 (0.7)
	Asian	44 (29.7)	44 (29.3)
	Native Hawaiian or Other Pacific Islander	0	0
	Other	2 (1.4)	4 (2.7)
Creatinine clearance, mL/min [a] (renal function)	≥ 120 (ARC)	22 (14.9)	26 (17.3)
	> 80 to < 120 (normal)	33 (22.3)	35 (23.3)
	> 50 to ≤ 80 (mild)	44 (29.7)	37 (24.7)
	≥ 30 to ≤ 50 (moderate)	29 (19.6)	32 (21.3)
	< 30 (severe)	20 (13.5)	20 (13.3)

ARC = augmented renal clearance; BAT = best available therapy; BMI = body mass index; cUTI = complicated urinary tract infection; max = maximum; min = minimum; SD = standard deviation

a Creatinine clearance is calculated using the Cockcroft-Gault formula based on data from the central laboratory.

APEKS-cUTI enrolled hospitalised male and female subjects at least 18 years of age with symptomatic cUTI with (26.8%) or without (46.9%) pyelonephritis, and uncomplicated pyelonephritis (26.3%). Most subjects (71.4%) were classified as having moderately severe disease. The baseline disease characteristics, including relative proportions of different infection types, severity of infection, duration of cUTI prior to randomisation, reasons complicating cUTI and medical history were similar between the treatment groups. The most frequently reported prior infection history was cUTI (around a third in both treatment groups). Overall, 18.7% of cefiderocol and 20.3% of IMP/CS subjects received concomitant antimicrobials (most frequently fluoroquinolones and nitrofurantoin derivatives), while 82.9% of cefiderocol and 84.0% of IMP/CS subjects received concomitant non-antimicrobial medications.

Of the subjects enrolled in the APEKS-NP, 125 (41.9%) had ventilator-associated pneumonia (VAP), 121 (40.6&) had hospital-acquired pneumonia (HAP) and 52 (17.4%) were diagnosed with healthcare-associated pneumonia (HCAP).

CREDIBLE-CR enrolled hospitalised male and female subjects at least 18 years of age with HAP/VAP/HCAP (45%), BSI/sepsis (31%) or cUTI (24%) caused by a carbapenem-resistant Gram-negative pathogen. There were slightly more cUTI patients in the cefiderocol group in the Safety Population. More subjects had severe baseline disease in the cefiderocol group. Other baseline disease characteristics, including Sequential Organ Failure Assessment Score, Clinical Pulmonary Infection Score, APACHE II score, and past medical history were similar between the treatment groups.

BAT was not defined as one single active comparator drug or regimen, but 1 to 3 antibiotic agents selected as per local standard of care. Furthermore, subjects with HAP/VAP/HCAP or BSI randomised to cefiderocol were permitted to receive a second Gram negative antibiotic (not polymyxins or cephalosporin/beta-lactam inhibitor combinations) at the discretion of the investigator, and subjects in either group with mixed Gram-positive or anaerobic infections may have received appropriate concomitant narrow spectrum antibiotics (e.g., vancomycin, linezolid, metronidazole, clindamycin). This led to a diverse range of regimens used, which further confounds the comparison of safety events.

Patient exposure

Across the clinical programme, 761 subjects have been exposed to single doses of cefiderocol from 100 mg to 4g, or multiple doses of up to 2g for up to a maximum of 21 days, including 212 healthy subjects or volunteers with renal impairment who received single doses of cefiderocol from 100 mg to 4 g or multiple doses of 1 g or 2 g q8h for 10 days, and 14 patients treated under compassionate use. A total of 435 subjects in the clinical safety and efficacy studies who received the proposed dose of 2g q8h for multiple doses, generally for 7 to 14 days.

Table S2. Duration of exposure to cefiderocol in CREDIBLE-CR (to date) and APEKS-cUTI (Safety Populations)

Duration of Exposure (days)	APEKS-cUTI N=300	APEKS-NP N=148	CREDIBLE-CR N=101	All Studies N=549
<7 days	18	18	10+5	51
7 to ≤14 days	277	97	47+14	435
>14 days	5	33	18+7	63

The safety database for the proposed therapeutic dose of 2g iv over 3h q8h in subjects with CR-organisms and limited therapeutic options comes solely from the CREDIBLE-CR study and is therefore limited (101 subjects with complete data). However, such a dataset could in principle provide sufficient safety reassurances, complemented by data in healthy volunteers and cUTI subjects, to support the application, in accordance with the limited clinical development programme agreed with CHMP at the time of Scientific Advice in view of the potential to meet an unmet clinical need. The remainder of the safety database comprises mostly subjects receiving 1 h infusions in the Clinical Pharmacology studies and in APEKS-cUTI, but it is reasonable to expect that a slower, 3 h infusion rate will not adversely affect tolerability.

Table S3. Patient exposure to cefiderocol across the clinical programme to date

Data source	Study	Study population	Dose(s)	Number of patients							
				Total (Cefiderocol)	**100 mg**	**250 mg**	**500 mg**	**1 g**	**2 g**	**3 g**	**4 g**
Placebo-controlled	Phase 1 SAD, MAD R2111 Randomised, double-blind	HV (male/female, Japanese), mean age 30.8y	SAD 100, 250, 500 mg, 1g and max 2g over 1h 3:1 vs placebo	40 (30)	6	6	6	6	6		
		HV (male, 19 Japanese and 5 Caucasian), mean age 31.9y	MAD 1g or 2g over 1h q8h x 10d 4:1 vs placebo	22 (16*)				8	8		
	Phase 1 Thorough QT R2116 Randomised, double-blind	HV (male/female, Caucasian and Black or African American) mean age	Part 1: Placebo control, SD 3g and 4g over 3h	16 (12)						6	6
Active - controlled			Part 2: Placebo control, moxifloxacin positive control, SAD 2g and 4 g over 3h	48 (44)					43		44
	Phase 2 APEKS-cUTI Randomised, double-blind	cUTI	MD 2g over 3h (or renal adjustment) q8h q8h x 7-14d IMI/CIL control	448 (300)					300		
	Phase 3 CREDIBLE-CR (micro ITT population) Randomised, open-label CR G- pathogens	HAP/VAP/HCAP	MD 2g over 3h (or renal adjustment) q8h x 7-14d ± second G- antibiotic BAT control (max 3x therapies) Gram+ adjunctive therapy both arms	59 (40)**					24		
		BSI/sepsis		27 (13) **					14		
		cUTI		22 (17) **					9		

Open studies	Phase 1 BAL/ELF R2112	HV (male, Japanese), mean age 26.3y	SD 2g over 1h	20 (20)					20		
	Phase 1 Renal impairment*** R2113	Cohort 1: Normal RF (8) Cohorts 2-4: Mild (8), mod (8), severe (6) impairment Cohort 5: ESRD on HD (8) (Male/female, Caucasian and Black or African American), mean age 54.6y	SD 1g over 1h (repeated pre- and post-HD for Cohort 5)	38 (38)				38			
	Phase 1 Mass balance R2114	HV (male), mean age 36.0y	SD [^{14}C]-cefiderocol 1g over 1h	6 (6)				6			
	Phase 1 Drug interaction R2115	HV (male/female, Caucasian and Black or African American,), mean age 36.1y	MD 2g over 3h q8h x 3 doses with: furosemide (12), metformin (13) or rosuvastatin (13)	38 (37)					37		
Compassionate use	CUP			14 (14)**							
CUP=compassionate use programme, ESRD=end stage renal disease, HD=haemodialysis, HV=healthy volunteers, IMI/CIL=imipenem/cilastatin MAD=multiple ascending dose, MD=multiple dose, SAD=single ascending dose, SD=single dose, RF=renal function, * 8 subjects receiving 1000 mg cefiderocol contaminated with iodide are excluded for purposes of assessment. **Patients for whom complete data are available as of cut-off date 15 Aug 2018. ***Renal function estimated by Cockcroft-Gault method.											

Adverse events

Table S4. Overview of AEs in APEKS-cUTI Study (Safety Populations)

Adverse Event Category	cUTI Study	
	Cefiderocol N=300 n (%)	Imipenem/Cilastatin N=148 n (%)
Treatment-emergent adverse events	122 (40.7)	76 (51.4)
Treatment-related TEAEs	27 (9.0)	17 (11.5)
Death	1 (0.3)	0
SAEs	14 (4.7)	12 (8.1)
Treatment-related SAEs	1 (0.3)	1 (0.7)
Discontinuation due to TEAEs	5 (1.7)	3 (2.0)
Discontinuation due to treatment-related TEAEs	3 (1.0)	0

BAT = best available therapy; cUTI = complicated urinary tract infection; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table S5. Overview of AEs in CREDIBLE-CR study (Safety populations)

	Cefiderocol (N = 101)		BAT (N = 49)		Total (N = 150)	
Adverse Event Category	Subjects n (%)	Events n'	Subjects n (%)	Events n'	Subjects n (%)	Events n'
TEAEs	92 (91.1)	634	47 (95.9)	311	139 (92.7)	945
Treatment-related TEAEs	15 (14.9)	27	11 (22.4)	16	26 (17.3)	43
Death	34 (33.7)	45	9 (18.4)	14	43 (28.7)	59
SAEs	50 (49.5)	92	23 (46.9)	36	73 (48.7)	128
Treatment-related SAEs	1 (1.0)	1	5 (10.2)	7	6 (4.0)	8
Discontinuation due to TEAEs	10 (9.9)	12	3 (6.1)	3	13 (8.7)	15
Discontinuation due to treatment-related TEAEs	3 (3.0)	3	2 (4.1)	2	5 (3.3)	5

BAT = best available therapy; SAEs = serious adverse events; TEAE = treatment-emergent adverse event

Percentage is calculated using the number of subjects in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit are defined as treatment-emergent.

Only in study deaths are included in this table. This is defined as a death resulting from a fatal SAE with an onset date before the End of Study visit (even if the death occurred after the end of study).

Table S6. Overview of AEs in APEKS-NP study (Safety populations)

Adverse Event Category	Cefiderocol N = 148		Meropenem N = 150		Difference of Proportion (95% Confidence Interval)
	Subjects n (%)	# of events	Subjects n (%)	# of events	
TEAEs	130 (87.8)	582	129 (86.0)	537	1.8 (-5.8, 9.5)
Treatment-related TEAEs	14 (9.5)	24	17 (11.3)	22	-1.9 (-8.8, 5.1)
SAEs leading to death	39 (26.4)	49	35 (23.3)	50	3.0 (-6.8, 12.8)
Treatment-emergent SAEs	54 (36.5)	102	45 (30.0)	96	6.5 (-4.2, 17.2)
Treatment-related SAEs	3 (2.0)	6	5 (3.3)	6	-1.3 (-5.0, 2.4)
Discontinuation due to TEAEs	12 (8.1)	18	14 (9.3)	19	-1.2 (-7.6, 5.2)
Discontinuation due to treatment-related TEAEs	2 (1.4)	4	2 (1.3)	3	0.0 (-2.6, 2.6)

TEAEs = treatment emergent adverse events; SAEs = serious adverse events
Percentage is calculated using the number of subjects in the column heading as the denominator. Adverse events that started on or after the first dose date of the study drug and up to End of Study are defined as treatment-emergent.
Confidence intervals are calculated using the Wilson score method.

2.6.1.1. Treatment Emergent Adverse Events (TEAEs)

Clinical Pharmacology studies

TEAEs occurred infrequently in Clinical Pharmacology studies, were mostly mild in severity and almost all resolved spontaneously without intervention. No severe or serious AEs were reported. There were no dose-dependent trends in the frequency or type of TEAEs observed.

Phase 2/3 studies

The frequency of TEAEs was notably higher in CREDIBLE-CR, in which almost all subjects reported at least 1 TEAE, than in APEKS-cUTI. This is consistent with more severe clinical condition of the enrolled study population. The most frequently reported TEAEs for cefiderocol across both studies belong to the Gastrointestinal Disorders and Infections and Infestations SOCs.

The overall frequency of TEAEs was slightly lower for cefiderocol than IMP/CS in APEKS-cUTI. The Preferred Terms reported were similar/overlapping between treatment groups and the absolute frequencies of most individual terms were low. Severe TEAEs were infrequent (2% cefiderocol group and 3.4% IMP/CS group). No severe TEAE Preferred Terms were reported for more than 1 subject in either treatment group. The severe TEAEs reported were anaemia, cardiorespiratory arrest, gastrointestinal haemorrhage, melaena, pneumonia, ALT increased, AST increased, gout, dyspnoea, and pleural effusion in the cefiderocol group.

In the APEKS-NP study most of the subjects in the cefiderocol group and meropenem group experienced at least 1 TEAE (87.8% [130/148] and 86.0% [129/150], respectively). Specifically, the most common TEAEs were urinary tract infection in the cefiderocol group (in 15.5% [23/148] of subjects compared with 10.7% [16/150] in the meropenem group) and hypokalaemia in the meropenem group (in 15.3% [23/150] of subjects compared with 10.8% [16/148] in the cefiderocol group).

The overall frequency of TEAEs was similar for cefiderocol and BAT in CREDIBLE-CR. Diarrhoea was the most commonly reported AE in the cefiderocol group (18.8% [19/101] of subjects), while hyperkalaemia was the most commonly reported AE in the BAT group (12.2% [6/49] of subjects). The

small study size and low absolute frequencies of most Preferred Terms means only an approximate comparison between the treatment groups is possible. Some TEAEs were reported more frequently for cefiderocol, while others were reported more frequently for BAT. This is possibly a reflection of the heterogeneous nature of the treatment(s) received in the both groups and the open-label study design, which may impact how TEAEs are reported.

The higher incidences of diarrhoea and elevated liver transaminases with cefiderocol treatment is discussed in the section on Adverse Events of Special Interest (AESIs).

The higher incidences of cardiac arrest, and pneumonia in the cefiderocol group in CREDIBLE-CR are discussed in section 4.4. Serious adverse events and deaths.

Chest pain was reported in 5.9% (6/47) of subjects in the cefiderocol group and 0 subjects in the BAT group, affecting subjects with all infection types. These events were reviewed. The majority of cases of chest pain were considered by the investigator to be noncardiovascular in nature and not related to cefiderocol. One subject had a medical history of myocardial infarction 3 months before randomisation, and the TEAE of chest pain was treated with nitroglycerin, oral isosorbide nitrate, and diltiazem. The remaining subjects experienced chest pain that recovered with no treatment and while continuing to receive the study drug or recovered after administration of nonsteroidal anti-inflammatory drugs or opioids, suggesting a noncardiovascular nature for the chest pain.

Table S7. Incidence of TEAEs Occurring in ≥ 1% Subjects Treated with Cefiderocol across CREDIBLE-CR and APEKS-cUTI, by Preferred Term (Safety Populations)

- Preferred Term	CREDIBLE-CR		APEKS-cUTI	
	Cefiderocol N=101 n (%)	BAT N=23 n (%)	Cefiderocol N=300 n (%)	IMP/CS N=148 n (%)
Subjects with any TEAEs	92 (91.1)	47 (95.9)	122 (40.7)	76 (51.4)
- Diarrhoea	19 (18.8)	6 (6.1)	13 (4.3)	9 (6.1)
- Vomiting	13 (12.9)	7 (14.3)	6 (2.0)	2 (1.4)
- Alanine aminotransferase increased	7 (6.9)	0	3 (1.0)	0
- Chest pain	6 (5.9)	0	1 (0.3)	0
- Decubitus ulcer	10 (9.9)	4 (8.2)	0	0
- Dyspnoea	7 (6.9)	2(4.1)	3 (1.0)	0
- Pyrexia	14 (13.9)	6 (12.2)	3 (1.0)	1 (0.7)
- Septic shock	13 (12.9)	7 (14.3)	0	0
- Agitation	5 (5.0)	2 (4.1)	0	0
- Anaemia	8 (7.9)	2 (4.1)	1 (0.3)	1 (0.7)
- Aspartate aminotransferase increased	8 (7.9)	1 (2.0)	1 (0.3)	0
- Constipation	8 (7.9)	3 (6.1)	10 (3.3)	6 (4.1)
- Nausea	7 (6.9)	2 (4.1)	7 (2.3)	6 (4.1)
- Abdominal pain	6 (5.9)	4 (8.2)	2 (0.7)	0
- Hypoglycaemia	4 (4.0)	2 (4.1)	1 (0.3)	1 (0.7)
- Hypokalaemia	9 8.9)	7 (14.3)	5 (1.7)	4 (2.7)
- Hypotension	8(7.9)	3 (6.1)	1 (0.3)	0
- Pleural effusion	8 (7.9)	1 (2.0)	3 (1.0)	1 (0.7)
- Abdominal pain upper	4 (4.0)	0	2 (0.7)	5 (3.4)
- Bradycardia	3 (3.0)	3 (6.1)	1 (0.3)	1 (0.7)
- Cough	3 (3.0)	1 (2.0)	7 (2.3)	1 (0.7)
- Hyperkalaemia	5(5.0)	6 (12.2)	1 (0.3)	0
- Pneumonia	7 (6.9)	1 (2.0)	2 (0.7)	2 (1.4)
- Headache	3 (3.0)	0	7 (2.3)	8 (5.4)
- Oedema peripheral	5 (5.0)	2 (4.1)	4 (1.3)	1 (0.7)
- Candiduria	2 (2.0)	1 (2.0)	3 (1.0)	2 (1.4)
- Gamma-glutamyltransferase increased	2 (2.0)	0	5 (1.7)	1 (0.7)
- Haematuria	1 (1.0)	0	3 (1.0)	2 (1.4)
- Hypertension	3 (3.0)	2 (4.1)	13 (4.3)	8 (5.4)
- Insomnia	2 (2.0)	3 (6.1)	4 (1.3)	3 (2.0)
- Nephrolithiasis	1 (1.0)	0	3 (1.0)	1 (0.7)
- Infusion site pain	2 (2.0)	1 (2.0)	9 (3.0)	5 (3.4)
- Rash	3 (3.0)	4 (8.2)	5 (1.7)	0
- Renal cyst	0	0	4 (1.3)	5 (3.4)

BAT = best available therapy; cUTI = complicated urinary tract infection; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event. Listed from highest frequency in the CREDIBLE-CR cefiderocol group.

AEs coded using MedDRA Version 19.0

Table S8. Most commonly reported TEAEs (≥5%) in the APEKS-NP study (Safety population).

PT	Cefiderocol (N = 148) n (%)	Meropenem (N = 150) n (%)	Difference of Proportion (95% Confidence Interval)
Subjects with TEAEs	130 (87.8)	129 (86.0)	1.8 (-5.8, 9.5)
Blood and lymphatic disorders	**27 (18.2)**	**28 (18.7)**	**-0.4 (-9.2, 8.4)**
Anaemia	12 (8.1)	12 (8.0)	0.1 (-6.1, 6.3)
Thrombocytopenia	2 (1.4)	8 (5.3)	-4.0 (-8.0, 0.1)
Gastrointestinal disorders	**41 (27.7)**	**36 (24.0)**	**3.7 (-6.2, 13.6)**
Diarrhoea	13 (8.8)	13 (8.7)	0.1 (-6.3, 6.5)
Infections and infestations	**60 (40.5)**	**53 (5.3)**	**5.2 (-5.8, 16.2)**
Pneumonia	11 (7.4)	8 (5.3)	2.1 (-3.4, 7.6)
Urinary tract infection	23 (15.5)	16 (10.7)	4.9 (-2.8, 12.5)
Investigations	**32 (21.6)**	**29 (19.3)**	**2.3 (-6.9, 11.4)**
Alanine aminotransferase increased	9 (6.1)	6 (4.0)	2.1 (-2.9, 7.0)
Aspartate aminotransferase increased	10 (6.8)	6 (4.0)	2.8 (-2.4, 7.9)
Hepatic enzyme increased	4 (2.7)	10 (6.7)	-4.0 (-8.7, 0.8)
Metabolism and nutrition disorders	**43 (29.1)**	**47 (31.3)**	**-2.3 (-12.7, 8.1)**
Hypoalbuminaemia	5 (3.4)	8 (5.3)	-2.0 (-6.6, 2.7)
Hypokalaemia	16 (10.8)	23 (15.3)	-4.5 (-12.2, 3.1)
Hypomagnesaemia	8 (5.4)	1 (0.7)	4.7 (0.9, 8.6)
Hyponatraemia	4 (2.7)	10 (6.7)	-4.0 (-8.7, 0.8)
Respiratory, thoracic, and mediastinal disorders	**37 (25.0)**	**34 (22.7)**	**2.3 (-7.3, 12.0)**
Pleural effusion	10 (6.8)	6 (4.0)	2.8 (-2.4, 7.9)
Skin and subcutaneous tissue disorders	**11 (7.4)**	**23 (15.3)**	**-7.9 (-15.0, -0.8)**
Decubitus ulcer	4 (2.7)	10 (6.7)	-4.0 (-8.7, -0.8)
Vascular disorders	**18 (12.2)**	**28 (18.7)**	**-6.5 (-14.7, 1.7)**
Hypotension	2 (1.4)	10 (6.7)	-5.3 (-9.7, -0.9)

AE = adverse event; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse events

Percentage is calculated using the number of subjects in the column heading as the denominator. All AEs are treatment-emergent that started on or after the first dose date of the study drug and up to 'End of Study' are included. Although a subject may have had 2 or more AEs, the subject is counted only once within an SOC category. The same subject may contribute to 2 or more PTs in the same SOC category.

Table S9. The Most Commonly Reported Severe TEAEs in CREDIBLE-CR (Safety Population)

SOC PT	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Total (N = 150) n (%)
Subjects with severe TEAEs	43 (42.6)	22 (44.9)	65 (43.3)
Cardiac disorders	**8 (7.9)**	**4 (8.2)**	**12 (8.0)**
Bradycardia	2 (2.0)	1 (2.0)	3 (2.0)
Cardiac arrest	4 (4.0)	2 (4.1)	6 (4.0)
General disorders and administration site conditions	**6 (5.9)**	**3 (6.1)**	**9 (6.0)**
Multi-organ failure	2 (2.0)	2 (4.1)	4 (2.7)
Pyrexia	3 (3.0)	0	3 (2.0)
Infections and infestations	**25 (24.8)**	**10 (20.4)**	**35 (23.3)**
Bacteraemia	2 (2.0)	0	2 (1.3)
Empyema	1 (1.0)	1 (2.0)	2 (1.3)
Enterococcal infection	2 (2.0)	0	2 (1.3)
Pneumonia	6 (5.9)	0	6 (4.0)
Sepsis	3 (3.0)	0	3 (2.0)
Septic shock	13 (12.9)	6 (12.2)	19 (12.7)
Investigations	**8 (7.9)**	**2 (4.1)**	**10 (6.7)**
Aspartate aminotransferase increased	4 (4.0)	0	4 (2.7)
Liver function test abnormal	2 (2.0)	1 (2.0)	3 (2.0)
Metabolism and nutrition disorders	**4 (4.0)**	**1 (2.0)**	**5 (3.3)**
Metabolic acidosis	3 (3.0)	1 (2.0)	4 (2.7)
Renal and urinary disorders	**6 (5.9)**	**3 (6.1)**	**9 (6.0)**
Acute kidney injury	4 (4.0)	2 (4.1)	6 (4.0)
Oliguria	2 (2.0)	0	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**8 (7.9)**	**2 (4.1)**	**10 (6.7)**
Acute respiratory failure	1 (1.0)	1 (2.0)	2 (1.3)
Pneumonia aspiration	2 (2.0)	0	2 (1.3)
Respiratory failure	3 (3.0)	0	3 (2.0)
Vascular disorders	**5 (5.0)**	**1 (2.0)**	**6 (4.0)**
Hypotension	4 (4.0)	1 (2.0)	5 (3.3)

AE = adverse event; BAT = best available therapy; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

Percentage is calculated using the number of subjects in the column heading as the denominator. AEs that started after the first dose of the study drug and up to End of Study visit are defined as treatment-emergent. Subjects experiencing more than 1 AE within each PT and SOC category are only counted once, and the most severe AEs are counted.

Table S10. Severe TEAEs Reported in ≥1 subject in the APEKS-NP study

SOC PT	Cefiderocol (N = 148) n (%)	Meropenem (N = 150) n (%)	Total (N = 298) n (%)
Subjects with severe TEAEs	56 (37.8)	45 (30.0)	101 (33.9)
Blood and lymphatic system disorders	**4 (2.7)**	**6 (4.0)**	**10 (3.4)**
Anaemia	2 (1.4)	0	2 (0.7)
Haemorrhagic anaemia	0	2 (1.3)	2 (0.7)
Iron deficiency anaemia	2 (1.4)	0	2 (0.7)
Thrombocytopenia	0	2 (1.3)	2 (0.7)
Cardiac disorders	**15 (10.1)**	**15 (10.0)**	**30 (10.1)**
Acute myocardial infarction	2 (1.4)	0	2 (0.7)
Cardiac arrest	7 (4.7)	5 (3.3)	12 (4.0)
Cardiac failure	2 (1.4)	3 (2.0)	5 (1.7)
Cardiac failure acute	0	2 (1.3)	2 (0.7)
Cardio-respiratory arrest	3 (2.0)	2 (1.3)	5 (1.7)
General disorders and administration site conditions	**7 (4.7)**	**6 (4.0)**	**13 (4.4)**
Multiple organ dysfunction syndrome	4 (2.7)	4 (2.7)	8 (2.7)
Infections and infestations	**18 (12.2)**	**16 (10.7)**	**34 (11.4)**
Pneumonia	7 (4.7)	3 (2.0)	10 (3.4)
Sepsis	4 (2.7)	3 (2.0)	7 (2.3)
Septic shock	4 (2.7)	1 (0.7)	5 (1.7)
Investigations	**5 (3.4)**	**5 (3.3)**	**10 (3.4)**
Hepatic enzyme increased	1 (0.7)	4 (2.7)	5 (1.7)
Nervous system disorders	**10 (6.8)**	**11 (7.3)**	**21 (7.0)**
Brain oedema	1 (0.7)	5 (3.3)	6 (2.0)
Cerebrovascular accident	2 (1.4)	1 (0.7)	3 (1.0)
Intracranial pressure increased	2 (1.4)	1 (0.7)	3 (1.0)
Renal and urinary disorders	**0**	**3 (2.0)**	**3 (1.0)**
Acute kidney injury	0	2 (1.3)	2 (0.7)
Respiratory, thoracic and mediastinal disorders	**18 (12.2)**	**14 (9.3)**	**32 (10.7)**
Acute respiratory failure	6 (4.1)	1 (0.7)	7 (2.3)
Pleural effusion	3 (2.0)	1 (0.7)	4 (1.3)
Pneumonia aspiration	3 (2.0)	2 (1.3)	5 (1.7)
Pulmonary artery thrombosis	3 (2.0)	3 (2.0)	6 (2.0)
Pulmonary embolism	1 (0.7)	2 (1.3)	3 (1.0)
Pulmonary oedema	3 (2.0)	0	3 (1.0)
Respiratory failure	2 (1.4)	3 (2.0)	5 (1.7)
Vascular disorders	**1 (0.7)**	**6 (4.0)**	**7 (2.3)**
Hypotension	0	3 (2.0)	3 (1.0)

AE = adverse event;
Percentage is calculated using the number of subjects in the column heading as the denominator. Subjects experiencing more than 1 AE within each PT and SOC are only counted once, and the most severe AEs are counted. Adverse events with missing severity are counted as severe.

2.6.1.2. Treatment-Related Adverse Events

Clinical Pharmacology studies

There were no trends in the frequency or type of TEAEs considered by the investigator to be treatment-related.

Phase 2/3 studies

Table S11. Treatment-related TEAEs, CREDIBLE-CR and APEKS-cUTI (Safety Populations)

	CREDIBLE-CR		APEKS-cUTI	
	Cefiderocol N=101 n (%)	BAT N=49 n (%)	Cefiderocol N=300 n (%)	IMP/CS N=148 n (%)
Subjects with treatment-related TEAEs	**15 (14.9)**	**11 (22.4)**	**27 (9.0)**	**17 (11.5)**

BAT = best available therapy; cUTI = complicated urinary tract infection; IMP/CS = imipenem/cilastatin; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event

The frequency of treatment-related TEAEs was similar between comparative treatment groups in CREDIBLE-CR and between comparative treatment groups in APEKS-cUTI. The overall frequency of treatment-related TEAEs was higher in CREDIBLE-CR. The incidence of each treatment related TEAE (Preferred Term) was low across both studies. No individual treatment-related TEAE was reported in >2 subjects in CREDIBLE-CR or >4 subjects in APEKS-cUTI.

The types of TEAEs reported by the investigators as treatment-related were generally similar in the CREDIBLE-CR and cUTI studies. The most frequently reported SOCs were Gastrointestinal disorders and Infections and infestations. Diarrhoea (2% [2/101], ALT increased, and AST increased were the most commonly reported treatment-related AEs (3% each; 3/101 subjects) in the cefiderocol group; while acute kidney injury were the most commonly reported treatment-related AE in the BAT group (8.2%; 4/49 subjects), in CREDIBLE-CR.

2.6.1.3. Adverse Events of Special Interest (AESIs)

Cefiderocol is a cephalosporin. Known effects for these drugs include *C. difficile* related adverse effects and diarrhoea, hypersensitivity including rash, seizures and epilepsy, liver-related adverse effects including liver biochemistry and clotting tests, and bone marrow suppression. These events were closely monitored during the studies. In addition, since cefiderocol is a siderophore antibiotic, potential effects on iron transport were investigated in the Phase 2/3 studies.

- *Clostridium difficile-related AEs*

In CREDIBLE-CR, the incidence of TEAEs related to *C. difficile* was low, with only 4 subjects experiencing *C. difficile*-related TEAEs (including preferred terms of *C. difficile* infection and pseudomembranous colitis), of which 3 (2.9%) treated with cefiderocol and 1 (2.0%) treated with BAT. The incidence of diarrhoea was 18.8% (19/101) of subjects in the cefiderocol group and 12.2% (6/49) of subjects in the BAT group. The majority of the TEAEs of diarrhoea were mild in severity; none was severe, and none led to discontinuation of study drug.

In APEKS-cUTI, 0.3% (1/300) of subjects in the cefiderocol group had a TEAE related to *C. difficile* compared with 3.4% (5/148, of which 2 were SAEs) of subjects in the IPM/CS group. Diarrhoea was reported for 4.3% (13/300) of subjects in the cefiderocol group compared with 6.1% (9/148) of subjects in the IPM/CS group. All TEAEs of diarrhoea were considered to be mild or moderate. Two

subjects, 1 in each treatment group had diarrhoea that was an SAE. One subject, in the cefiderocol group was discontinued due to a nonserious TEAE of diarrhoea.

In APEKS-NP, the incidence of TEAEs related to *C. difficile* was low, with 8 subjects experiencing *C. difficile*-related TEAEs (including preferred terms of *C. difficile* infection), of which 4 (2.7%) treated with cefiderocol and 4 (2.7%) treated with BAT.

C. difficile-associated diarrhoea is listed as an ADR in SmPC sections 4.4 and 4.8, which is appropriate.

- *Hypersensitivity and rash*

Mild and moderate TEAEs relating to rash were reported very infrequently in the Clinical Pharmacology studies. All resolved spontaneously without intervention. One subject with moderate renal impairment in the renal impairment Study R2113 reported a TEAE of moderate urticaria that was considered by the investigator to be related to the study drug and that led to discontinuation of the study drug and premature withdrawal from the study.

No SAEs related to rash/hypersensitivity were reported in the either CREDIBLE-CR, APEKS-NP or APEKS-cUTI. The high frequency of hypersensitivity seen in CREDIBLE-CR is perhaps unsurprising, given the multiple medications received by these clinically unwell subjects, including in many cases multiple antibiotics. Given this is a known class risk, a causal relationship is a possibility for some events.

Hypersensitivity reactions, including warnings regarding previous hypersensitivity to other beta-lactam antibiotics, are listed as an ADR in SmPC sections 4.3, 4.4 and 4.8, which is appropriate.

Table S12. Subjects with TEAEs by Standard MedDRA Query Hypersensitivity and Preferred Term, across CREDIBLE-CR and APEKS-cUTI (Safety Populations)

	CREDIBLE-CR Study		cUTI Study	
Standard MedDRA Queries - Preferred Term	**Cefiderocol N=101 n (%)**	**BAT N=49 n (%)**	**Cefiderocol N=300 n (%)**	**Imipenem/Cilastatin N=148 n (%)**
Hypersensitivity	11 (10.9)	7 (14.3)	8 (2.7)	2 (1.4)
- Rash	3 (3.0)	4 (8.2)	5 (1.7)	0
- Eczema	2 (2.0)	0	0	1 (0.7)
- Drug eruption	1 (1.0)	0	0	0
- Drug hypersensitivity	1 (1.0)	0	1 (0.3)	0
- Rash generalised	1 (2.1)	0	0	0
- Rash macular	0	0	1 (0.3)	0
- Rash maculo-papular	0	0	1 (0.3)	0
- Skin necrosis	1 (1.0)	0	0	0
- Heparin-induced thrombocytopenia	1 (1.0)	0	0	0
- Dermatitis contact	0	1 (2.0)	0	0
- Lip oedema	0	0	0	1 (0.7)
- Shock	1 (1.0)	2 (4.1)	0	0

BAT = best available therapy; cUTI = complicated urinary tract infection; MedDRA = Medical Dictionary for Regulatory Activities

- *Seizures*

In CREDIBLE-CR, in the cefiderocol group, 1 subject experienced 3 mild TEAEs of seizure. The subject had hypoglycaemia associated with haemodialysis, which was considered as the cause of seizures. In the BAT group, 1 subject experienced a treatment-related SAE of status epilepticus.

In APEKS-cUTI, in the cefiderocol treatment group, 1 subject with a medical history of epilepsy had a moderate TEAE of epilepsy.

- *Liver function*

In CREDIBLE-CR, ALT increased was reported in 6.9% (7/101) of subjects in the cefiderocol group (affecting subjects with all infection types) and 0 subjects in the BAT group. Other TEAEs reported were AST increased 7.9% (8/101),and blood ALP increased 2.0% (2/101); and hepatic cirrhosis, hepatic failure, hepatic function abnormal, hepatitis, GGT increased, INR increased and liver function test abnormal for 1 subject each in the cefiderocol group (affecting subjects with all infection types), all vs 0 subjects in the BAT group. Underlying disease or concomitant medication existed as confounding factors or alternative aetiology was suggested by the Applicant for most of the subjects, although the events for 2 subjects were considered related to cefiderocol by the investigators.

In APEKS-cUTI, liver events were reported for 0.7% (2/300) subjects treated with cefiderocol and 0.7% (1/148) of subject treated with IPM/CS.

Cephalosporins have been reported to affect liver function. Effects on liver enzymes are listed as an ADR in SmPC section 4.8, which is appropriate.

- *Bone marrow suppression*

In CREDIBLE-CR, as per the interim CSR, the most commonly reported TEAE that could suggest bone marrow suppression was anaemia (7.9% [8/101] of subjects in the cefiderocol group and 4.1% [2/49] of subjects in the BAT group). All other TEAEs that could suggest bone marrow suppression were reported for ≤ 2 subjects in each treatment group and were similar between treatment groups. None of these TEAEs led to discontinuation of study treatment. Severe infection itself can affect bone marrow function, which complicates conclusions regarding causality. However, given the known class effect of bone marrow suppression, non-clinical findings of decreased red cell parameters, and frequency of this category of TEAEs in CREDIBLE-CR, a causal relationship remains a possibility. Transient decrease in haemoglobin was noted in cefiderocol treated subjects in both CREDIBLE-CR and APEKS-NP studies.

In APEKS-cUTI, reported TEAEs included anaemia (1 subject in each group), haemorrhagic anaemia (1 cefiderocol), iron deficiency anaemia (1 cefiderocol), and haematocrit decreased (1 IPM/CS).

- *Iron homeostasis*

TEAEs related to iron homeostasis were very infrequent across the Phase 2/3 studies. Overall, there is no indication from the Phase 2/3 safety data that cefiderocol systemically impacts iron chemistry values in the target population at therapeutic doses. However, one subject in CREDIBLE-CR experienced deranged iron chemistry values following an incorrect dose of cefiderocol,).

Serious adverse event/deaths/other significant events

Clinical Pharmacology studies

No SAEs or deaths were reported in the Clinical Pharmacology studies.

Phase 2/3 studies

Table S13. Incidence of Serious Adverse Events across APEKS-cUTI (Safety Populations)

System Organ Class - Preferred Term	cUTI Study Cefiderocol N=300 n (%)	 Imipenem Cilastatin N=148 n (%)
Subjects with SAEs	14 (4.7)	12 (8.1)
Blood and lymphatic system disorders	2 (0.7)	0
- Anaemia	1 (0.3)	0
- Febrile neutropenia	0	0
- Haemorrhagic anaemia	1 (0.3)	0
Cardiac disorders	3 (1.0)	1 (0.7)
- Cardiac arrest	0	0
- Bradycardia	0	0
- Cardiac failure	1 (0.3)	1 (0.7)
- Cardiac failure acute	1 (0.3)	0
- Cardiac failure congestive	0	0
- Cardio-respiratory arrest	1 (0.3)	0
- Myocardial infarction	0	0
- Myocardial ischaemia	1 (0.3)	0
- Pulseless electrical activity	0	0
Congenital, familial and genetic disorders	0	1 (0.7)
- Congenital ureteric anomaly	0	1 (0.7)
Gastrointestinal disorders	2 (0.7)	2 (1.4)
- Diarrhoea	1 (0.3)	1 (0.7)
- Duodenal ulcer	1 (0.3)	0
- Pancreatitis	0	0
- Upper gastrointestinal haemorrhage	1 (0.3)	0
- Lower gastrointestinal haemorrhage	0	1 (0.7)
General disorders and administration site conditions	1 (0.3)	0
- Pyrexia	1 (0.3)	0
- Chills	0	0
- Multi-organ failure	0	0
- General physical health deterioration	0	0
Hepatobiliary disorders	1 (0.3)	0
- Gallbladder pain	1 (0.3)	0
- Hepatic failure	0	0
- Hepatitis	0	0
Infections and infestations	5 (1.7)	6 (4.1)
- Septic shock	0	0
- Pneumonia	1 (0.3)	0
- Bacteraemia	0	0
- Renal abscess	1 (0.3)	0
- Enterococcal infection	0	0
- Ascariasis	1 (0.3)	0
- Cellulitis	1 (0.3)	0
- Clostridium difficile colitis	1 (0.3)	2 (1.4)
- Systemic candida	0	0
- Urinary tract infection	1 (0.3)	0
- Urosepsis	0	0
- Bacterial infection	0	0
- Pneumonia bacterial	0	0
- Abscess	0	1 (0.7)
- Meningitis	0	0

System Organ Class - Preferred Term	cUTI Study Cefiderocol N=300 n (%)	 Imipenem/ Cilastatin N=148 n (%)
- Necrotising fasciitis	0	0
- Prostatic abscess	0	1 (0.7)
- Pyelonephritis	0	1 (0.7)
- Device related infection	0	1 (0.7)
Injury, poisoning and procedural complications	0	2 (1.4)
- Alcohol poisoning	0	1 (0.7)
- Gastrointestinal injury	0	1 (0.7)
Investigations	1 (0.3)	1 (0.7)
- Blood creatine phosphokinase increased	1 (0.3)	0
- Liver function test abnormal	0	0
- Haematocrit decreased	0	1 (0.7)
- Hepatic enzyme increased	0	0
Metabolism and nutrition disorders	0	0
- Metabolic acidosis	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0
- Lung neoplasm malignant	0	0
Nervous system disorders	0	1 (0.7)
- Dizziness	0	0
- Hypoaesthesia	0	0
- Paraesthesia	0	0
- Quadriplegia	0	0
- Status epilepticus	0	0
- Ischaemic stroke	0	1 (0.7)

System Organ Class - Preferred Term	cUTI Study Cefiderocol N=300 n (%)	 Imipenem/ Cilastatin N=148 n (%)

Renal and urinary disorders	3 (1.0)	2 (1.4)
- Anuria	0	0
- Nephrolithiasis	0	0
- Oliguria	0	0
- Urinary tract obstruction	1 (0.3)	0
- Acute kidney injury	0	1 (0.7)
- Obstructive nephropathy	1 (0.3)	0
- Ureterolithiasis	1 (0.3)	0
- Hydronephrosis	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	0
- Acute respiratory failure	0	0
- Pneumonia aspiration	0	0
- Respiratory failure	0	0
Surgical and medical procedures	1 (0.3)	0
- Urethrotomy	1 (0.3)	0
Vascular disorders	0	1 (0.7)
- Hypotension	0	0
- Deep vein thrombosis	0	1 (0.7)
Infections and infestations	1 (0.3)	1 (0.7)
- Clostridium difficile colitis	1 (0.3)	1 (0.7)
Nervous system disorders	0	0
- Status epilepticus	0	0

Table S14. CREDIBLE-CR Study: SAEs – Safety Population

SOC PT	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)
Subjects with SAEs	50 (49.5)	23 (46.9)
Blood and lymphatic system disorders	**1 (1.0)**	**1 (2.0)**
Anaemia	0	1 (2.0)
Febrile neutropenia	1 (1.0)	0
Cardiac disorders	**6 (5.9)**	**4 (8.2)**
Bradycardia	1 (1.0)	1 (2.0)
Cardiac arrest	4 (4.0)	2 (4.1)
Cardiac failure congestive	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
Pulseless electrical activity	0	1 (2.0)
Gastrointestinal disorders	**5 (5.0)**	**0**
Abdominal pain	1 (1.0)	0
Abdominal pain upper	1 (1.0)	0
Gastrointestinal haemorrhage	1 (1.0)	0
Intestinal ischaemia	1 (1.0)	0
Lower gastrointestinal haemorrhage	1 (1.0)	0
Pancreatitis	1 (1.0)	0
Small intestinal obstruction	1 (1.0)	0
General disorders and administration site conditions	**7 (6.9)**	**3 (6.1)**
Chills	1 (1.0)	0
General physical health deterioration	0	1 (2.0)
Multi-organ failure	2 (2.0)	2 (4.1)
Pyrexia	3 (3.0)	0
Sudden death	1 (1.0)	0
Hepatobiliary disorders	**3 (3.0)**	**0**
Chronic hepatic failure	1 (1.0)	0
Hepatic failure	1 (1.0)	0
Hepatitis	1 (1.0)	0
Immune system disorders	**0**	**1 (2.0)**
Anaphylactic reaction	0	1 (2.0)
Infections and infestations	**29 (28.7)**	**11 (22.4)**
Bacteraemia	3 (3.0)	0
Bacterial infection	1 (1.0)	0
Device related infection	0	1 (2.0)
Empyema	1 (1.0)	1 (2.0)
Endocarditis	0	1 (2.0)

SOC PT	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Total (N = 150) n (%)
Enterococcal bacteraemia	1 (1.0)	0	1 (0.7)
Enterococcal infection	2 (2.0)	0	2 (1.3)
Meningitis	0	1 (2.0)	1 (0.7)
Necrotising fasciitis	0	1 (2.0)	1 (0.7)
Osteomyelitis	1 (1.0)	0	1 (0.7)
Osteomyelitis acute	0	1 (2.0)	1 (0.7)
Pneumonia	5 (5.0)	1 (2.0)	6 (4.0)
Pneumonia bacterial	1 (1.0)	0	1 (0.7)
Renal abscess	1 (1.0)	0	1 (0.7)
Sepsis	3 (3.0)	0	3 (2.0)
Septic shock	12 (11.9)	6 (12.2)	18 (12.0)
Systemic candida	1 (1.0)	0	1 (0.7)
Urinary tract infection	1 (1.0)	0	1 (0.7)
Urosepsis	1 (1.0)	0	1 (0.7)
Investigations	**5 (5.0)**	**3 (6.1)**	**8 (5.3)**
Liver function test abnormal	4 (4.0)	3 (6.1)	7 (4.7)
Transaminases increased	1 (1.0)	0	1 (0.7)
Metabolism and nutrition disorders	**3 (3.0)**	**1 (2.0)**	**4 (2.7)**
Hyponatraemia	1 (1.0)	0	1 (0.7)
Metabolic acidosis	2 (2.0)	1 (2.0)	3 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.0)**	**0**	**1 (0.7)**
Lung neoplasm malignant	1 (1.0)	0	1 (0.7)
Nervous system disorders	**3 (3.0)**	**2 (4.1)**	**5 (3.3)**
Dizziness	1 (1.0)	0	1 (0.7)
Hypoaesthesia	1 (1.0)	0	1 (0.7)
Neurological decompensation	1 (1.0)	0	1 (0.7)
Paraesthesia	1 (1.0)	0	1 (0.7)
Quadriplegia	0	1 (2.0)	1 (0.7)
Status epilepticus	0	1 (2.0)	1 (0.7)
Renal and urinary disorders	**6 (5.9)**	**2 (4.1)**	**8 (5.3)**
Acute kidney injury	3 (3.0)	2 (4.1)	5 (3.3)
Anuria	1 (1.0)	0	1 (0.7)
Nephrolithiasis	1 (1.0)	0	1 (0.7)
Oliguria	2 (2.0)	0	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**7 (6.9)**	**2 (4.1)**	**9 (6.0)**
Acute respiratory failure	1 (1.0)	1 (2.0)	2 (1.3)
Chronic obstructive pulmonary disease	1 (1.0)	0	1 (0.7)
Obstructive airways disorder	1 (1.0)	0	1 (0.7)
Pneumonia aspiration	2 (2.0)	0	2 (1.3)
Respiratory arrest	0	1 (2.0)	1 (0.7)
Respiratory failure	2 (2.0)	0	2 (1.3)
Vascular disorders	**2 (2.0)**	**2 (4.1)**	**4 (2.7)**
Hypotension	2 (2.0)	1 (2.0)	3 (2.0)

SOC PT	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Total (N = 150) n (%)
Shock	1 (1.0)	1 (2.0)	2 (1.3)

BAT = best available therapy; PT = preferred term; SAEs = serious adverse events; SOC = system organ class

Percentage is calculated using the number of subjects in the column heading as the denominator. AEs that started after the first dose of the study drug and up to End of Study visit are defined as treatment-emergent. Although a subject may have had 2 or more AEs, the subject is counted only once within a SOC category. The same subject may contribute to 2 or more PTs in the same SOC category.

Table S15. APEKS-NP Study: SAEs – Safety Population

SOC PT	Cefiderocol (N = 148) n (%)	Meropenem (N = 150) n (%)
Subjects with SAEs	54 (36.5)	45 (30.0)
Blood and lymphatic system disorders	**2 (1.4)**	**6 (4.0)**
Coagulopathy	1 (0.7)	2 (1.3)
Disseminated intravascular coagulation	0	1 (0.7)
Haemorrhagic anaemia	0	2 (1.3)
Thrombocytopenia	1 (0.7)	2 (1.3)
Cardiac disorders	**16 (10.8)**	**15 (10.0)**
Acute myocardial infarction	2 (1.4)	0
Cardiac arrest	7 (4.7)	5 (3.3)
Cardiac failure	2 (1.4)	3 (2.0)
Cardiac failure acute	0	2 (1.3)
Cardiac failure congestive	0	1 (0.7)
Cardio-respiratory arrest	3 (2.0)	2 (1.3)
Cardiogenic shock	0	1 (0.7)
Cardiopulmonary failure	0	1 (0.7)
Cardiovascular disorder	0	1 (0.7)
Cardiovascular insufficiency	1 (0.7)	1 (0.7)
Left ventricular dysfunction	2 (1.4)	0
Myocardial infarction	1 (0.7)	0
Gastrointestinal disorders	**4 (2.7)**	**2 (1.3)**
Abdominal wall haematoma	1 (0.7)	0
Acute abdomen	0	1 (0.7)
Gastric haemorrhage	1 (0.7)	0
Gastrointestinal haemorrhage	0	1 (0.7)
Intestinal infarction	1 (0.7)	0
Intestinal ischaemia	1 (0.7)	0
General disorders and administration site conditions	**7 (4.7)**	**6 (4.0)**
Death	1 (0.7)	1 (0.7)
General physical health deterioration	1 (0.7)	0
Multiple organ dysfunction syndrome	4 (2.7)	4 (2.7)

SOC PT	Cefiderocol (N = 148) n (%)	Meropenem (N = 150) n (%)
Sudden death	1 (0.7)	0
Systemic inflammatory response syndrome	0	1 (0.7)
Hepatobiliary disorders	**1 (0.7)**	**2 (1.3)**
Cholecystitis acute	0	1 (0.7)
Hepatic function abnormal	0	1 (0.7)
Hepatocellular injury	1 (0.7)	0
Infections and infestations	**17 (11.5)**	**14 (9.3)**
Acinetobacter bacteraemia	0	1 (0.7)
Bacteraemia	1 (0.7)	0
Bacterial sepsis	1 (0.7)	0
Brain abscess	0	1 (0.7)
Herpes zoster	1 (0.7)	0
Lung infection	1 (0.7)	0
Meningitis	0	1 (0.7)
Meningoencephalitis bacterial	0	1 (0.7)
Pneumonia	6 (4.1)	3 (2.0)
Pneumonia bacterial	1 (0.7)	0
Pneumonia necrotising	0	1 (0.7)
Pseudomonas infection	0	1 (0.7)
Sepsis	3 (2.0)	2 (1.3)
Septic encephalopathy	0	1 (0.7)
Septic shock	4 (2.7)	1 (0.7)
Spinal cord infection	1 (0.7)	0
Systemic candida	0	1 (0.7)
Urinary tract infection	1 (0.7)	2 (1.3)
Injury, poisoning and procedural complications	**1 (0.7)**	**1 (0.7)**
Splenic rupture	0	1 (0.7)
Subarachnoid haemorrhage	1 (0.7)	0
Investigations	**6 (4.1)**	**8 (5.3)**
Alanine aminotransferase increased	1 (0.7)	0
Aspartate aminotransferase increased	1 (0.7)	1 (0.7)
Blood pressure increased	1 (0.7)	0
Hepatic enzyme increased	1 (0.7)	5 (3.3)
Liver function test abnormal	0	1 (0.7)
Liver function test increased	2 (1.4)	0
Transaminases increased	1 (0.7)	1 (0.7)
Metabolism and nutrition disorders	**1 (0.7)**	**2 (1.3)**
Hyperkalaemia	0	1 (0.7)
Hypovolaemia	0	1 (0.7)
Lactic acidosis	1 (0.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.7)**	**0**
Lung cancer metastatic	1 (0.7)	0

SOC PT	Cefiderocol (N = 148) n (%)	Meropenem (N = 150) n (%)
Nervous system disorders	**9 (6.1)**	**11 (7.3)**
Autonomic nervous system imbalance	1 (0.7)	0
Brain injury	0	1 (0.7)
Brain oedema	1 (0.7)	5 (3.3)
Cerebral ischaemia	1 (0.7)	0
Cerebrovascular accident	2 (1.4)	1 (0.7)
Encephalopathy	0	1 (0.7)
Hypoxic-ischaemic encephalopathy	1 (0.7)	0
Intracranial pressure increased	2 (1.4)	1 (0.7)
Lacunar stroke	0	1 (0.7)
Metabolic encephalopathy	1 (0.7)	1 (0.7)
Status epilepticus	1 (0.7)	0
Stroke in evolution	1 (0.7)	0
Renal and urinary disorders	**1 (0.7)**	**3 (2.0)**
Acute kidney injury	1 (0.7)	3 (2.0)
Respiratory, thoracic and mediastinal disorders	**17 (11.5)**	**15 (10.0)**
Acute respiratory distress syndrome	1 (0.7)	0
Acute respiratory failure	6 (4.1)	1 (0.7)
Bronchopleural fistula	0	1 (0.7)
Chronic obstructive pulmonary disease	0	1 (0.7)
Pleural effusion	1 (0.7)	1 (0.7)
Pneumonia aspiration	3 (2.0)	2 (1.3)
Pneumothorax	0	1 (0.7)
Pneumothorax spontaneous	1 (0.7)	0
Pulmonary artery thrombosis	3 (2.0)	3 (2.0)
Pulmonary congestion	0	1 (0.7)
Pulmonary embolism	1 (0.7)	1 (0.7)
Pulmonary hypertension	1 (0.7)	0
Pulmonary oedema	2 (1.4)	0
Respiratory distress	0	1 (0.7)
Respiratory failure	2 (1.4)	3 (2.0)
Stridor	1 (0.7)	0
Skin and subcutaneous tissue disorders	**1 (0.7)**	**0**
Diabetic foot	1 (0.7)	0
Surgical and medical procedures	**1 (0.7)**	**0**
Leg amputation	1 (0.7)	0
Vascular disorders	**1 (0.7)**	**3 (2.0)**
Femoral artery embolism	0	1 (0.7)
Hypotension	0	1 (0.7)
Hypovolaemic shock	0	1 (0.7)
Peripheral vascular disorder	1 (0.7)	0
Shock haemorrhagic	0	1 (0.7)

AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class
Percentage is calculated using the number of subjects in the column heading as the denominator. All AEs are treatment-emergent that started on or after the first dose date of the study drug and up to End of Study are included. Although a subject may have had 2 or more AEs, the subject is counted only once within an SOC category. The same subject may contribute to 2 or more PTs in the same SOC category.
Confidence intervals are calculated using the Wilson score method.

Fewer SAEs were reported with cefiderocol than IMP/CS in APEKS-cUTI and APEKS-NP. Individual Preferred Terms were generally reported by one or a few subjects, therefore robust comparison of the groups is limited. All specific SAEs were reported for 1 or 2 subjects in a treatment group, and no notable differences between groups were observed for any preferred term. The most frequently reported SAE in APEKS-cUTI was *C. difficile* colitis, affecting 1/300 (0.3%) in the cefiderocol group and 2/148 (1.4%) in the IMP/CS group.

The frequency of serious AEs was notably higher in CREDIBLE-CR, which is consistent with more severe clinical condition of the enrolled study population. The overall rate of SAEs was approximately similar between the cefiderocol group (49.5% [50/101] of subjects) and the BAT group (46.9% [23/49] of subjects), where the final data shown a similar frequency of septic shock (11.9% [12/101] of subjects) and BAT (12.2% [6/49] of subjects). However, the higher incidences specifically of cardiac arrest (4.0% [4/101] subjects in the cefiderocol group and two subjects in the BAT group), and pneumonia (5.0% [5/101] subjects in the cefiderocol group and one subjects in the BAT group) in the cefiderocol group in CREDIBLE-CR are further discussed below in relation to a higher rate of fatal SAEs in the cefiderocol group.

2.6.1.4. Deaths

APEKS-cUTI

One death, in a subject treated with cefiderocol, was reported in APEKS-cUTI. On Day 7 of cefiderocol treatment, the subject, a 76-year-old white male with a complex past medical history had an SAE of cardio-respiratory arrest of unknown cause, that was not considered by the investigator to be related to study drug. Cardiopulmonary resuscitation was unsuccessful, and the subject died on the same day. The subject had not previously reported any TEAEs since starting study medication.

APEKS-NP

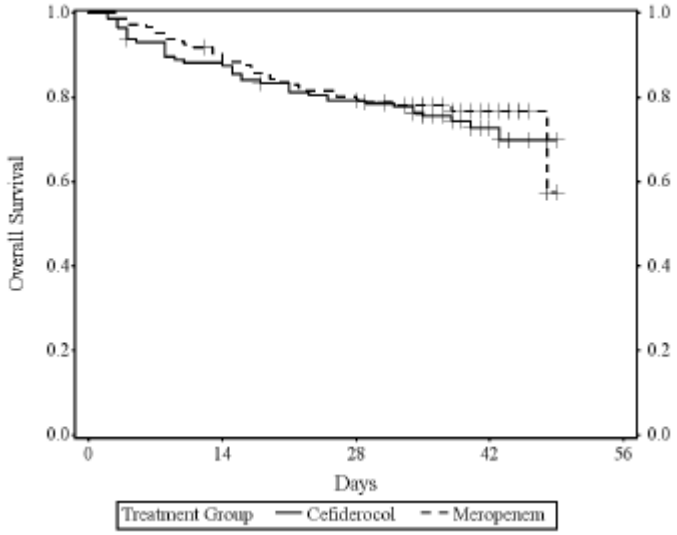
The primary objective of this study was to compare all-cause mortality between the 2 study treatments at Day 14 after start of study drug therapy in the mITT population. Cefiderocol was non-inferior to meropenem as the difference between treatment was 0.8% with 95% CI of -6.6, 8.2%. All-cause mortality rates for the mITT population at Day 14 were 12.4% (18/145) for cefiderocol and 11.6% (17/146) for meropenem. In the safety population, there were 74 subjects who experienced SAEs with a fatal outcome in the study, 39 (26.4%) subjects in the cefiderocol group and 35 (23.3%) subjects in the meropenem group. Overall, the frequency of SAEs leading to death was 49 events in 39/148 (26.4%) subjects in the cefiderocol group and 50 events in 35/150 (23.3%) in the meropenem group.

Table S16. All-cause Mortality Rate at Day 14 and Day 28 after Start of Study Drug Therapy (Sensitivity Analysis) Intent-to-treat Population

				---Treatment Comparison [a] ---	
Survival Status	Cefiderocol (N = 148) n/N' (%)	Meropenem (N = 150) n/N' (%)	Total (N = 298) n/N' (%)	Difference (%)	95% CI [b]
Day 14 ACM	19/148 (12.8)	17/149 (11.4)	36/297 (12.1)	1.4	(-6.0, 8.7)
Day 28 ACM	31/146 (21.2)	30/149 (20.1)	61/295 (20.7)	1.1	(-8.0, 10.3)

Day 14 ACM = all-cause mortality at Day 14 since first infusion of study drug; Day 28 ACM = all-cause mortality at Day 28 since first infusion of study drug; APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; N = number of subjects in the analysis set; n = number of subjects who died; N' = number of subjects with known survival status.
[a] Treatment difference (cefiderocol minus meropenem) is the adjusted estimate of the difference in the all-cause mortality rate at Day 14 and Day 28 between the 2 treatment arms based on Cochran-Mantel Haenszel weights using APACHE II score (<= 15 and >= 16) as the stratification factor.
[b] The 95% CI (2-sided) is based on a stratified analysis using Cochran-Mantel Haenszel weights using APACHE II score (<= 15 and >= 16) as the stratification factor. The CI is calculated using a normal approximation to the difference between 2 binomial proportions (Wald method).

Table S17. Survival Time up to End of Study (modified Intent-to-Treat Population



CREDIBLE-CR

In the interim report (15 Aug 2018) the mortality analysis showed that a total of 27 subjects died of which 21 were treated with cefiderocol and 6 of them treated with BAT. This imbalance in mortality rate was also observed when the final data of the study was analysed, where a total of 43 subjects experienced SAEs with a fatal outcome with onset before the End of Study; 34 (33.7% of 101 subjects) in the cefiderocol group and 9 (18.4% of 49 subjects) in the BAT group. In the final data set for CREDIBLE-CR, 50 subjects are known to have died, 36 of 101 (35.6%) treated with cefiderocol and 14 of 49 (28.6%) treated with BAT. The applicant claims that 7 of the subjects (2 from the cefiderocol group and 5 from the BAT group) died after study completion and these were not collected in a systematic way and detailed mortality data for these subjects is not included in the study database. The 7 subjects were: 2AA001 (died on Day 89, cause of death not available) and 3HK002 (died due to urosepsis) in the cefiderocol group, and 3HN001 (died on Day 43 due to sepsis), 3HJ001 (died due to septic shock), 3HJ004 (died on Day 108 due to cardiopulmonary arrest), 3HM003 (sudden cardiac death), and 3FG010 (died Day 53 due to septic shock and cardiac arrest) in the BAT group.

In contrast to the interim report where the imbalance was mainly noted in the HAP/VAP/HCAP groups, the imbalance in mortality was seen for subjects with BSI/sepsis (36.7% for cefiderocol and 17.6% for BAT) as well as those with HAP/VAP/HCAP (42.2% for cefiderocol versus 18.2% for BAT) in the final dataset.

Table S18. Summary for All-Cause Mortality in the Study (ITT-Population)

Infection Site All-cause Mortality Rate	Cefiderocol (N = 101) n/N (%)	95% CI	BAT (N = 49) n/N (%)	95% CI
HAP/VAP/HCAP	N' = 45		N' = 22	
Day 14	11/45 (24.4)	(12.9, 39.5)	3/22 (13.6)	(2.9, 34.9)
Day 28	14/45 (31.1)	(18.2, 46.6)	4/22 (18.2)	(5.2, 40.3)
Through EOS	19/45 (42.2)	(27.7, 57.8)	4/22 (18.2)	(5.2, 40.3)
BSI/Sepsis	N' = 30		N' = 17	
Day 14	5/30 (16.7)	(5.6, 34.7)	1/17 (5.9)	(0.1, 28.7)
Day 28	7/30 (23.3)	(9.9, 42.3)	3/17 (17.6)	(3.8, 43.4)
Through EOS	11/30 (36.7)	(19.9, 56.1)	3/17 (17.6)	(3.8, 43.4)
cUTI	N' = 26		N' = 10	
Day 14	3/26 (11.5)	(2.4, 30.2)	2/10 (20.0)	(2.5, 55.6)
Day 28	4/26 (15.4)	(4.4, 34.9)	2/10 (20.0)	(2.5, 55.6)
Through EOS	4/26 (15.4)	(4.4, 34.9)	2/10 (20.0)	(2.5, 55.6)
HAP/VAP/HCAP + BSI/Sepsis	N' = 75		N' = 39	
Day 14	16/75 (21.3)	(12.7, 32.3)	4/39 (10.3)	(2.9, 24.2)
Day 28	21/75 (28.0)	(18.2, 39.6)	7/39 (17.9)	(7.5, 33.5)
Through EOS	30/75 (40.0)	(28.9, 52.0)	7/39 (17.9)	(7.5, 33.5)
Overall	N' = 101		N' = 49	
Day 14	19/101 (18.8)	(11.7, 27.8)	6/49 (12.2)	(4.6, 24.8)
Day 28	25/101 (24.8)	(16.7, 34.3)	9/49 (18.4)	(8.8, 32.0)
Through EOS	34/101 (33.7)	(24.6, 43.8)	9/49 (18.4)	(8.8, 32.0)

BAT = best available therapy; BSI = bloodstream infection; CI = confidence interval; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare associated pneumonia; VAP = ventilator-associated pneumonia

Percentage is calculated using N as the denominator where N is the number of subjects who had the specified infection site and continued the study or expired at each time point. The 95% CI is calculated using Clopper-Pearson method.

Table S19. Subjects with Adverse Events Leading to Death by System Organ Class and Preferred Term Safety Population

System Organ Class Preferred Term	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Total (N = 150) n (%)
Subjects with AEs leading to death	34 (33.7)	9 (18.4)	43 (28.7)
Cardiac disorders	6 (5.9)	3 (6.1)	9 (6.0)
Bradycardia	0	1 (2.0)	1 (0.7)
Cardiac arrest	4 (4.0)	2 (4.1)	6 (4.0)
Cardiac failure congestive	1 (1.0)	0	1 (0.7)
Myocardial infarction	1 (1.0)	0	1 (0.7)
General disorders and administration site conditions	3 (3.0)	3 (6.1)	6 (4.0)
General physical health deterioration	0	1 (2.0)	1 (0.7)
Multi-organ failure	2 (2.0)	2 (4.1)	4 (2.7)
Sudden death	1 (1.0)	0	1 (0.7)
Hepatobiliary disorders	2 (2.0)	0	2 (1.3)
Chronic hepatic failure	1 (1.0)	0	1 (0.7)
Hepatic failure	1 (1.0)	0	1 (0.7)
Infections and infestations	21 (20.8)	3 (6.1)	24 (16.0)
Bacteraemia	2 (2.0)	0	2 (1.3)
Device related infection	0	1 (2.0)	1 (0.7)
Pneumonia	5 (5.0)	0	5 (3.3)
Pneumonia bacterial	1 (1.0)	0	1 (0.7)
Sepsis	3 (3.0)	0	3 (2.0)
Septic shock	11 (10.9)	3 (6.1)	14 (9.3)
Metabolism and nutrition disorders	1 (1.0)	1 (2.0)	2 (1.3)
Hyponatraemia	1 (1.0)	0	1 (0.7)
Metabolic acidosis	0	1 (2.0)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0	1 (0.7)
Lung neoplasm malignant	1 (1.0)	0	1 (0.7)
Renal and urinary disorders	3 (3.0)	1 (2.0)	4 (2.7)
Acute kidney injury	1 (1.0)	1 (2.0)	2 (1.3)
Anuria	1 (1.0)	0	1 (0.7)
Oliguria	2 (2.0)	0	2 (1.3)
Respiratory, thoracic and mediastinal disorders	4 (4.0)	2 (4.1)	6 (4.0)
Acute respiratory failure	0	1 (2.0)	1 (0.7)
Obstructive airways disorder	1 (1.0)	0	1 (0.7)
Pneumonia aspiration	1 (1.0)	0	1 (0.7)
Respiratory arrest	0	1 (2.0)	1 (0.7)
Respiratory failure	2 (2.0)	0	2 (1.3)
Vascular disorders	1 (1.0)	0	1 (0.7)
Hypotension	1 (1.0)	0	1 (0.7)
Shock	1 (1.0)	0	1 (0.7)

AEs = adverse events; BAT = best available therapy

Percentage is calculated using the number of subjects in the column heading as the denominator. Adverse events that started after the first dose of the study drug and up to End of Study visit are defined as treatment-emergent. Although a subject may have had 2 or more adverse events, the subject is counted only once within a System Organ Class category. The same subject may contribute to 2 or more Preferred Terms in the same System Organ Class category.

One subject receive cefiderocol after completion of BAT; this subject is included under BAT in this table.

The most common SAE leading to death by preferred term was septic shock, reported in 10.9% (11/101) in the cefiderocol group compared with 6.1% (3/49) in the BAT group. Other SAEs leading to death that were reported in ≥2 subjects in either treatment group and that were reported more frequently in the cefiderocol group than in the BAT group were pneumonia (5.0% [5/101] vs. 0% of subjects), sepsis (3.0% [3/101] vs. 0% of subjects) and bacteraemia, oliguria and respiratory failure (each reported in 2.0% [2/101] vs. 0% of subjects).

Six of the 7 subjects who died of pneumonia/pneumonia bacterial/pneumonia aspiration had pneumonia as diagnosis for inclusion in the study.

Host and pathogen factors

The impact of potentially relevant host and pathogen factors on mortality has been further investigated. All deaths in the CREDIBLE-CR final dataset and in the APEKS-NP study have been investigated for the following potentially relevant host and pathogen factors: age, sex, race, region, diagnosis, renal function at baseline, hepatic impairment (CREDIBLE-CR only), Acute Physiology and Chronic Health Evaluation (APACHE) II score at baseline, baseline pathogen and MIC, medical history, clinical outcome, microbiological outcome, and treatment duration. In addition, as the CREDIBLE-CR study was an open-label study, all deaths in this study were reviewed by a blinded adjudication committee who were asked to determine cause of death as attributable to the Gram-negative infection for which the subject was enrolled in the study or attributable to some alternative reason.

Table S20. Comparison of Demographic, Clinical and Microbiological Parameters at Baseline Between HAP/VAP/HCAP Subjects in the CREDIBLE-CR and APEKS-NP Study Populations (ITT/Safety Population)

Variable	HAP/VAP/HCAP in CREDIBLE-CR (N = 67)	APEKS-NP (N = 298)
HAP, %	40.3	40.6
VAP, %	55.2	41.9
HCAP, %	4.5	17.4
Ventilated, %	74.6	59.7
Mean age, y	63.9	65.2
Male gender, %	76.1	68.8
Region, % Europe Asia-Pacific North and South America	 40.3 38.8 20.8	 66.8 29.2 4.0
CrCL < 50 mL/min, %	32.8	33.9
APACHE II score ≥16, % Mean score	56.7 17.1	48.7 16.2
Treatment failure, %	64.2	32.6
Top 4 baseline pathogens, % *A. baumannii* *K. pneumoniae* *P. aeruginosa* *E. coli*	 55.2 25.4 25.4 7.5	 15.8 30.9 16.1 13.8

APACHE II = Acute Physiology and Chronic Health Evaluation II; CrCL = creatinine clearance; HAP = hospital acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Table S21. CREDIBLE-CR: Summary for All-cause Mortality Overall by Subgroups (ITT Population)

All-cause Mortality Subgroup	Cefiderocol (N=101) n/N' (%)	BAT (N=49) n/N' (%)
Overall	34/101 (33.7)	9/49 (18.4)
Age group		
< 65 years	10/37 (27.0)	3/27 (11.1)
>= 65 years	24/64 (37.5)	6/22 (27.3)
Gender		
Male	23/66 (34.8)	7/35 (20.0)
Female	11/35 (31.4)	2/14 (14.3)
Race		
White	18/63 (28.6)	6/32 (18.8)
Asian	14/29 (48.3)	3/14 (21.4)
Other	2/9 (22.2)	0/3 (0.0)
Baseline CR pathogen group		
Enterobacteriaceae	7/29 (24.1)	3/11 (27.3)
Nonfermenters	22/49 (44.9)	5/25 (20.0)
Mixed	1/2 (50.0)	0/2 (0.0)
Total APACHE II score group		
<= 15	13/55 (23.6)	5/27 (18.5)
>= 16	21/46 (45.7)	4/22 (18.2)
Region		
North America	0/6 (0.0)	0/3 (0.0)
South America	1/9 (11.1)	0/4 (0.0)
Europe	19/57 (33.3)	6/28 (21.4)
Asia-Pacific	14/29 (48.3)	3/14 (21.4)
Ventilation at Baseline		
Yes	24/50 (48.0)	7/26 (26.9)
No	10/51 (19.6)	2/23 (8.7)
ICU at Baseline		
Yes	22/57 (38.6)	6/21 (28.6)
No	12/44 (27.3)	3/28 (10.7)
Iron at Baseline		
Low	26/77 (33.8)	7/28 (25.0)
Normal	5/14 (35.7)	1/15 (6.7)
Total CCI at Baseline		

All-cause Mortality Subgroup	Cefiderocol (N=101) n/N' (%)	BAT (N=49) n/N' (%)
<= 5	10/52 (19.2)	2/24 (8.3)
>= 6	24/49 (49.0)	7/25 (28.0)
Severity		
Mild	1/5 (20.0)	0/4 (0.0)
Moderate	14/41 (34.1)	3/22 (13.6)
Severe	19/55 (34.5)	6/23 (26.1)
SOFA		
<= 6	16/67 (23.9)	2/32 (6.3)
>= 7	18/33 (54.5)	7/17 (41.2)
CPIS		
<= 5	13/30 (43.3)	4/16 (25.0)
>= 6	5/14 (35.7)	0/5 (0.0)
Creatinine clearance renal grading group		
>= 120 mL/min (ARC)	3/20 (15.0)	2/12 (16.7)
> 80 mL/min to < 120 mL/min (normal)	4/18 (22.2)	1/10 (10.0)
> 50 mL/min to 80 mL/min (mild)	9/20 (45.0)	2/12 (16.7)
30 mL/min to 50 mL/min (moderate)	10/23 (43.5)	2/8 (25.0)
< 30 mL/min (severe)	8/20 (40.0)	2/7 (28.6)
Cancer		
Yes	12/24 (50.0)	2/13 (15.4)
No	22/77 (28.6)	7/36 (19.4)

APACHE II = Acute Physiology and Chronic Health Evaluation II; BAT = best available therapy; BSI = bloodstream infection; CCI = Charlson co-morbidity index; CPIS = clinical pulmonary infection score; cUTI = complicated urinary tract infection; CR = carbapenem-resistant; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; ICU = intensive care unit; SOFA = sequential organ failure assessment; VAP = ventilator-associated pneumonia

Table S22. CREDIBLE-CR: All-cause Mortality by Baseline Pathogen (Micro-ITT Population)

Mortality Pathogen	Cefiderocol (N=86) n/N' (%)	BAT (N=44) n/N' (%)
ACINETOBACTER BAUMANNII	19/39 (48.7)	3/17 (17.6)
KLEBSIELLA PNEUMONIAE	8/34 (23.5)	4/16 (25.0)
PSEUDOMONAS AERUGINOSA	6/17 (35.3)	2/12 (16.7)
ESCHERICHIA COLI	1/6 (16.7)	0/3 (0.0)
STENOTROPHOMONAS MALTOPHILIA	4/5 (80.0)	---
ACINETOBACTER NOSOCOMIALIS	2/2 (100.0)	---
ENTEROBACTER CLOACAE	1/2 (50.0)	---
KLEBSIELLA VARIICOLA	0/1 (0.0)	0/1 (0.0)
ACINETOBACTER RADIORESISTENS	0/1 (0.0)	---
CHRYSEOBACTERIUM INDOLOGENES	1/1 (100.0)	---
KLEBSIELLA OXYTOCA	1/1 (100.0)	---
SERRATIA MARCESCENS	0/1 (0.0)	---
ENTEROBACTER ASBURIAE	---	1/1 (100.0)
MORGANELLA MORGANII	---	0/1 (0.0)
PROVIDENCIA STUARTII	---	0/1 (0.0)

BAT = best available therapy

Micro-Intent-to-treat population only includes subjects with a baseline Gram-negative pathogen

Includes data from mixed infections

Among the subjects treated with cefiderocol 42/101 (41.6%) subjects in the cefiderocol group and 17/49 (34.7%) subjects in the BAT group had infection with *Acinetobacter spp*. There were 29 subjects in the cefiderocol group and 10 subjects in the BAT group with HAP/VAP/HCAP, and 12 subjects in the cefiderocol group and 7 subjects in the BSI sepsis group with *Acinetobacter spp*. infection; there was only 1 subject (in the cefiderocol group) with cUTI who had *Acinetobacter spp*. Overall for subjects with *Acinetobacter spp*., the 28-day mortality was 38.1% in the cefiderocol group and 17.6% in the BAT group, and at the end of study was 50.0% in the cefiderocol group compared with 17.6% in the BAT group. For subjects without *Acinetobacter spp*., the mortality rates were similar in the 2 groups (15.3% for cefiderocol and 18.8% for BAT for 28-day mortality; 22.0% for cefiderocol and 18.8% for BAT at end of study). Results were similar for HAP/VAP/HCAP and for BSI/sepsis.

Table S23. CREDIBLE-CR: Summary of All-cause Mortality for Subjects with and without Acinetobacter spp. (safety population)

	With Acinetobacter				Without Acinetobacter			
Infection Site All-cause Mortality Rate	Cefiderocol (N = 42) n/N (%)	95% CI	BAT (N = 17) n/N (%)	95% CI	Cefiderocol (N = 59) n/N (%)	95% CI	BAT (N = 32) n/N (%)	95% CI
HAP/VAP/HCAP	N = 29		N = 10		N = 16		N = 12	
Day 14	9/29 (31.0)	(15.3, 50.8)	2/10 (20.0)	(2.5, 55.6)	2/16 (12.5)	(1.6, 38.3)	1/12 (8.3)	(0.2, 38.5)
Day 28	11/29 (37.9)	(20.7, 57.7)	2/10 (20.0)	(2.5, 55.6)	3/16 (18.8)	(4.0, 45.6)	2/12 (16.7)	(2.1, 48.4)
Through EOS	15/29 (51.7)	(32.5, 70.6)	2/10 (20.0)	(2.5, 55.6)	4/16 (25.0)	(7.3, 52.4)	2/12 (16.7)	(2.1, 48.4)
BSI/Sepsis	N = 12		N = 7		N = 18		N = 10	
Day 14	3/12 (25.0)	(5.5, 57.2)	1/7 (14.3)	(0.4, 57.9)	2/18 (11.1)	(1.4, 34.7)	0/10 (0.0)	(0.0, 30.8)
Day 28	5/12 (41.7)	(15.2, 72.3)	1/7 (14.3)	(0.4, 57.9)	2/18 (11.1)	(1.4, 34.7)	2/10 (20.0)	(2.5, 55.6)
Through EOS	6/12 (50.0)	(21.1, 78.9)	1/7 (14.3)	(0.4, 57.9)	5/18 (27.8)	(9.7, 53.5)	2/10 (20.0)	(2.5, 55.6)
cUTI	N = 1		N = 0		N = 25		N = 10	
Day 14	0/1 (0.0)	(0.0, 97.5)	---	---	3/25 (12.0)	(2.5, 31.2)	2/10 (20.0)	(2.5, 55.6)
Day 28	0/1 (0.0)	(0.0, 97.5)	---	---	4/25 (16.0)	(4.5, 36.1)	2/10 (20.0)	(2.5, 55.6)
Through EOS	0/1 (0.0)	(0.0, 97.5)	---	---	4/25 (16.0)	(4.5, 36.1)	2/10 (20.0)	(2.5, 55.6)
Overall	N = 42		N = 17		N = 59		N = 32	
Day 14	12/42 (28.6)	(15.7, 44.6)	3/17 (17.6)	(3.8, 43.4)	7/59 (11.9)	(4.9, 22.9)	3/32 (9.4)	(2.0, 25.0)
Day 28	16/42 (38.1)	(23.6, 54.4)	3/17 (17.6)	(3.8, 43.4)	9/59 (15.3)	(7.2, 27.0)	6/32 (18.8)	(7.2, 36.4)
Through EOS	21/42 (50.0)	(34.2, 65.8)	3/17 (17.6)	(3.8, 43.4)	13/59 (22.0)	(12.3, 34.7)	6/32 (18.8)	(7.2, 36.4)

BAT = best available therapy; BSI = bloodstream infection; CI = confidence interval; cUTI = complicated urinary tract infection; EOS = end of study; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Percentage is calculated using N as the denominator where N is the number of subjects who had the specified infection site and continued the study or expired at each time point. The 95% CI is calculated using the Clopper-Pearson method

Laboratory findings

Clinical Pharmacology studies

No notable trends in laboratory parameters were observed amongst the infrequent occurrences of abnormal values in the Clinical Pharmacology studies.

Phase 2/3 studies

- *Haematology*

In CREDIBLE-CR a slightly greater percentage of subjects in the cefiderocol group than in the BAT group had a decrease in haemoglobin ≥ 1.5 g/dL (27.8% [27/101] versus 24.5%12/49], respectively). In APEKS-NP study a higher proportion of subjects with decreases ≥ 1.5 g/dL in haemoglobin at the end of treatment was observed for the cefiderocol groups (29.4%) compared to meropenem (21.8%). Cefiderocol subjects in CREDIBLE-CR also experienced anaemia as a TEAE (8 [7.9%]) more frequently than BAT (2 [4.1%]).

Table S24. APEKS-NP: Subjects with Haemoglobin Decrease ≥1.5 g/dl Post Baseline (Safety Population)

		Cefiderocol N=148 n (%)	Meropenem N=150 n (%)
Haemoglobin decrease ≥ 1.5 g/dL postbaseline	Early Assessment	N=143 29 (20.3)	N=143 24 (16.8)
	End of Treatment	N=126 37 (29.4)	N=142 31 (21.8)
	Test of Cure	N=116 31 (26.7)	N=121 30 (24.8)
	Follow-up	N=102 28 (27.5)	N=106 27 (25.5)

Table S25. Incidence of Anaemia Treatment-emergent Adverse Events in Phase 2/3 Studies

Preferred Term	cUTI Study		CREDIBLE-CR Study		APEKS-NP Study	
	Cefiderocol N=300 n (%)	Imipenem/ Cilastatin N=148 n (%)	Cefiderocol N=101 n (%)	BAT N=49 n (%)	Cefiderocol N=148 n (%)	Meropenem N=150 n (%)
Anaemia	1 (0.3)	1 (0.7)	8 (7.9)	2 (4.1)	12 (8.1)	12 (8.0)
Anaemia of chronic disease	0	0	1 (1.0)	1 (2.0)	2 (1.4)	0
Haemorrhagic anaemia	1 (0.3)	0	0	0	0	2 (1.3)
Iron deficiency anaemia	1 (0.3)	0	0	0	3 (2.0)	0
Normochromic normocytic anaemia	0	0	1 (1.0)	0	1 (0.7_	0
Nephrogenic anaemia	0	0	0	0	0	1 (0.7)
Blood iron decreased	0	0	1 (1.0)	0	0	0
Haemoglobin decreased	0	0	1 (1.0)	0	1 (0.7)	0
Haematocrit decreased	0	1 (0.7)	0	0	0	0
Serum ferritin increased	0	0	1 (1.0)	0	0	0
Transferrin decreased	0	0	1 (1.0)	0	0	0
Transferrin saturation decreased	0	0	2 (2.0)	0	0	0
Red blood cell count decreased	0	0	0	0	1 (0.7)	0

BAT = best available therapy

Adverse events are coded using MedDRA Version 19.0.

Table S26. Subjects with Laboratory Test Predefined Category Outliers Postbaseline (Safety Population)

Parameter (Unit) Category	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)
BUN (mg/dL)	N' = 80	N' = 42
INC >= 50% and value > ULN	19 (23.8)	11 (26.2)
Serum creatinine (mg/dL)	N' = 98	N' = 49
INC >= 0.3	36 (36.7)	19 (38.8)
ALP (U/L)	N' = 94	N' = 47
INC >= 50% and value > ULN	31 (33.0)	18 (38.3)
Hemoglobin (g/dL)	N' = 97	N' = 49
DEC >= 1.5	27 (27.8)	12 (24.5)
Platelet count (10^3/uL)	N' = 96	N' = 49
DEC >= 25% and value < LLN	28 (29.2)	12 (24.5)
INC >= 100% and value > ULN	6 (6.3)	3 (6.1)
WBC count (10^3/uL)	N' = 94	N' = 49
DEC >= 50% and value < LLN	5 (5.3)	3 (6.1)
INC >= 20% and value > ULN	38 (40.4)	18 (36.7)

ALP = alkaline phosphatase; BAT = best available therapy; BUN = blood urea nitrogen; DEC = decrease from baseline; INC = increase from baseline; LLN = lower limit of normal; ULN = upper limit of normal; WBC = white blood cell

In APEKS-cUTI, no notable differences between groups in mean changes from baseline for haematology parameters were observed.

- *Renal chemistry*

Overall, the clinical data do not suggest cefiderocol-related nephrotoxicity.

- *Liver chemistry*

Table S27. Subjects with Abnormal Liver Chemistry Values Meeting Predefined Outlier Limits Postbaseline, across CREDIBLE-CR and APEKS-cUTI (Safety Populations)

	CREDIBLE-CR Study		cUTI Study	
Parameter (Unit) **Category**	**Cefiderocol (N = 101)** **n (%)**	**BAT (N = 49)** **n (%)**	**Cefiderocol (N = 300)** **n (%)**	**IPM/CS (N = 148)** **n (%)**
AST (U/L)				
Value > 3 × ULN	20 (20.8)	7 (14.6)	3 (1.0)	1 (0.7)
Value > 5 × ULN	11 (11.5)	7 (14.6)	2 (0.7)	0
Value > 10 × ULN	6 (6.3)	1 (2.1)	1 (0.2)	0
Value > 20 × ULN	4 (4.2)	0	0	0
ALT (U/L)				
Value > 3 × ULN	16 (16.3)	4 (8.3)	4 (1.3)	1 (0.7)
Value > 5 × ULN	5 (5.1)	3 (6.3)	1 (0.3)	1 (0.7)
Value > 10 × ULN	1 (1.0)	2 (4.2)	1 (0.3)	1 (0.7)
Value > 20 × ULN	0	0	0	0
AST (U/L) or ALT (U/L)				
Value > 3 × ULN	25 (26.0)	8(16.7)	4 (1.3)	1 (0.7)
Value > 5 × ULN	12 (12.5)	3 (6.3)	2 (0.7)	1 (0.7)
Value > 10 × ULN	6 (6.3)	3 (6.3)	1 (0.3)	1 (0.7)
Value > 20 × ULN	4 (4.2)	0	0	0
Total bilirubin (µmol/L)				
Value > 2 × ULN	14 (15.1)	6(12.5)	0	0
INC ≥ 50% and value > ULN	9 (9.7)	6 (12.5)	0	0

	CREDIBLE-CR Study		cUTI Study	
Parameter (Unit) Category	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Cefiderocol (N = 300) n (%)	IPM/CS (N = 148) n (%)
PT-INR				
Value > 1.5	21 (21.6)	10 (21.3)	20 (6.7)	3 (2.0)
(ALT and/or AST > 3 × ULN) and				
(Total bilirubin > 2 × ULN or PT-INR > 1.5)	12 (13.2)	4 (8.7)	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAT = best available therapy; cUTI = complicated urinary tract infection; INC = increase from baseline; IPM/CS = imipenem/cilastatin; PT-INR = prothrombin time-international normalised ratio; ULN = upper limit of normal

Percentage was calculated using the number of subjects with valid postbaseline value as the denominator.

Table S28. APEKS-NP Study: Subjects with Laboratory Test Values Meeting Predefined Category Outliers at End of Treatment – Safety Population

Parameter (Unit) Category	Cefiderocol (N = 148) n (%)	Meropenem (N = 150) n (%)
AST (U/L)	N' = 125	N' = 137
Value > 3 x ULN	9 (7.2)	11 (8.0)
Value > 5 x ULN	6 (4.8)	7 (5.1)
Value > 10 x ULN	3 (2.4)	4 (2.9)
Value > 20 x ULN	1 (0.8)	3 (2.2)
ALT (U/L)	N' = 125	N' = 138
Value > 3 x ULN	10 (8.0)	12 (8.7)
Value > 5 x ULN	4 (3.2)	7 (5.1)
Value > 10 x ULN	3 (2.4)	3 (2.2)
Value > 20 x ULN	1 (0.8)	1 (0.7)
AST (U/L) or ALT (U/L)	N' = 125	N' = 138
Value > 3 x ULN	14 (11.2)	18 (13.0)
Value > 5 x ULN	7 (5.6)	9 (6.5)
Value > 10 x ULN	3 (2.4)	4 (2.9)
Value > 20 x ULN	1 (0.8)	3 (2.2)
Total bilirubin (µmol/L)	N' = 125	N' = 137
Value > 2 x ULN	3 (2.4)	5 (3.6)
INC >= 50% and value > ULN	6 (4.8)	12 (8.8)
PT-INR	N' = 125	N' = 133
Value > 1.5	13 (10.4)	17 (12.8)
ALT or AST > 3 x ULN and	N' = 125	N' = 138
Total bilirubin > 2 x ULN or PT-INR > 1.5	4 (3.2)	7 (5.1)
BUN (mmol/L)	N' = 122	N' = 137
INC >= 50% and value > ULN	9 (7.4)	17 (12.4)
Serum creatinine (mg/dL)	N' = 126	N' = 140
INC >= 0.3	11 (8.7)	10 (7.1)
ALP (U/L)	N' = 122	N' = 135
INC >= 50% and value > ULN	21 (17.2)	25 (18.5)
Haemoglobin (g/dL)	N' = 126	N' = 142
DEC >= 1.5	37 (29.4)	31 (21.8)

Platelet count (10^9/L)	N' = 126	N' = 141
DEC >= 25% and value < LLN	12 (9.5)	13 (9.2)
INC >= 100% and value > ULN	10 (7.9)	12 (8.5)
WBC count (10^9/L)	N' = 126	N' = 142
DEC >= 50% and value < LLN	0	3 (2.1)
INC >= 20% and value > ULN	12 (9.5)	20 (14.1)

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DEC = decrease from baseline; INC = increase from baseline; LLN = lower limit of normal;
PT-INR = prothrombin time-international normalized ratio; ULN = upper limit of normal; WBC = white blood cell
Percentage is calculated using N' as the denominator, where N' is the number of subjects with valid end of treatment measurements.
Baseline is defined as the last measurement prior to receipt of the first infusion of study drug.
The summary is based on local laboratory assessments.

The incidence of elevated liver enzymes was higher for cefiderocol in CREDIBLE-CR and is reflected in the higher reporting rate of liver-related TEAEs in this group (see also section on adverse events of special interest). Changes in liver enzymes were generally mild or moderate severity and recovered when treatment with cefiderocol was discontinued. These effects are listed as ADRs in SmPC section 4.8. Review of biochemical data and relevant clinical data did not identify any subjects who met the criteria for Hy's law in either CREDIBLE-CR or APEKS-cUTI.

The imbalance between the 2 treatment groups in the incidence of PT-INR >1.5 in APEKS-cUTI is largely explained by the use of concomitant anticoagulant therapy in 15/20 cefiderocol-treated subjects who met this criterion and 2/3 IMP/CS-treated subjects who met the same criterion. Excluding such subjects, the number of non-anticoagulant associated events are 5 (1.67%) for cefiderocol and 1 (0.68%) for IMP/CS.

- *Vital signs*

Overall, the clinical data do not suggest any trends or systematic effect of cefiderocol on vital signs.

- *Electrocardiogram*

Findings from the non-clinical programme included QTc prolongation in monkeys (NOEL 300 mg/kg/d, safety margin 8x). There were no treatment-related or dose-dependent trends in ECG measurements in the Clinical Pharmacology studies. Results of a well-conducted Thorough QT/QTc Study R2116 indicate that cefiderocol does not prolong QT at supratherapeutic doses up to 4g over 3h (corresponding to Cmax and exposure at least double that expected for the proposed therapeutic dose). Thus, it is concluded that the non-clinical findings at extremely high doses are unlikely to be relevant to clinical use of the approved dose.

In CREDIBLE-CR, ECG measurements were only routinely made at Screening for safety assessments. The limited data available did not suggest an effect of cefiderocol on ECGs. In the Cardiac Disorders SOC, the incidence of TEAEs (bradycardia: 3.0% and 6.1%, respectively; atrial fibrillation: 2.0% and 2.0%, respectively; tachycardia: 1.0% and 4.1% respectively and atrial flutter and sinus tachycardia were each reported in 1 subject in the BAT group and no subjects in the cefiderocol group) did not suggest an effect of cefiderocol associated with cardiac disorders.

In APEKS-cUTI, following DSMB concerns that ECG data appeared to be outside physiological limits, copies of all ECGs were obtained and sent to an independent cardiologist who was asked to perform a blinded reading and reinterpretation of all available ECGs. The parameters derived from manual centralised reading by an independent cardiologist were considered the reliable dataset. The data did not indicate systematic QT prolongation with cefiderocol.

Safety in special populations

- *Race*

The impact of potentially relevant host factors such as race and gender were evaluated further with respect to the imbalance in mortality. Even though the frequency of mortality was slightly higher in the Asian population in the CREDIBLE-CR, the sample size is limited, and this difference was not seen in APEKS-NP.

- *Renal impairment*

In the renal impairment Study R2113, no other type of dialysis than intermittent haemodialysis was studied.

Subjects with creatinine clearance <21 mL/min, oliguria (<20 mL/hour over 24h) or receiving haemodialysis, peritoneal dialysis or haemofiltration were not eligible for enrolment in APEKS-cUTI. Over half of subjects had some degree of renal impairment, although very few had severe impairment (8 (2.7%) cefiderocol, 7 (4.7%) IMP/CS) and none had augmented renal clearance. Cefiderocol dosing was adjusted for bodyweight and creatinine clearance (calculated from Cockcroft-Gault equation), but this did not include augmented renal clearance or renal replacement therapy.

Subjects on peritoneal dialysis were not eligible for enrolment in CREDIBLE-CR. The majority of subjects had altered renal function (either augmented or impaired). Greater proportions of subjects in the cefiderocol group had moderate or severe renal impairment (moderate 22.8% vs 16.3%; severe 19.8% vs 14.3%). Cefiderocol dosing was adjusted for creatinine clearance and BSA-adjusted creatinine clearance (calculated from Cockcroft-Gault and MDRD equations), including augmented renal clearance and renal replacement therapy.

There was no notable trend in the overall frequency of TEAEs with regard to renal function in either individual study. Of the fatal SAEs reported in the cefiderocol group in CREDIBLE-CR, the 3 events of cardiac arrest occurred in subjects with moderate (2) or severe renal impairment (1), while the 3 events of pneumonia occurred in subjects with mild (2) or moderate (1) renal impairment and the 6 events of septic shock were distributed across the full spectrum of renal impairment.

- *Hepatic impairment*

No dedicated studies in subjects with hepatic impairment have been conducted for cefiderocol, given that the primary route of elimination is renal excretion of unchanged drug. Subjects with AST, ALT, ALP or total bilirubin >3x ILN were not eligible for enrolment in APEKS-cUTI, however similar exclusions were not applied in CREDIBLE-CR.

No dose adjustment for hepatic impairment is proposed by the Applicant, as cefiderocol PK is not expected to be affected.

- *Pregnancy and lactation*

No pregnancies with cefiderocol have been reported up to the data cut-off date for this submission of 15 Aug 2018. The safety of cefiderocol in pregnancy and lactation, and effects on human fertility, are not known and as such this is considered Missing Information. Conclusions from the pre-clinical data and the lack of human data need to be adequately reflected in the SmPC.

- *Age and gender*

The mean age of subjects enrolled in both CREDIBLE-CR and APEKS-cUTI was >60 years, reflecting the incidence of the respective indications in the older population. Therefore, the extent of exposure of

older subjects as a proportion of subjects enrolled across the Phase 2/3 studies is reasonable. Approximately equal numbers of male and female subjects were enrolled across the Phase 2/3 studies.

TEAE data per study categorised by age and gender, and listed by SOC and PT, presented in the Applicant's Integrated Summary of Safety, indicate no notable trends with age or gender in the respective studies in the total frequency of TEAEs. Absolute numbers in the oldest age categories and for individual Preferred Terms make more granular assessment difficult, but no safety signal for any individual Preferred Term for cefiderocol treatment is noted. In CREDIBLE-CR, 37% of the subjects were at the age 18 to <65 and 64% were ≥65 years of age.

Table S29. Exposure to Cefiderocol by Age group and gender in APEKS-cUTI (Safety Populations)

Age (years)	cUTI Study		
	Male	Female	Total
18 to 64	42	100	142
65 to 74	60	31	91
75 to 84	30	31	61
>= 85	5	1	6
Total	137	163	300

Table S30. Exposure by age group in APEKS-NP

Demographic Characteristics Statistic/Category	Cefiderocol (N = 148)	Meropenem (N = 150)	Total (N = 298)
Age (years)			
N	148	150	298
Mean	64.7	65.6	65.2
Standard deviation	14.5	15.1	14.8
Median	67.0	68.0	67.0
Minimum	18	20	18
Maximum	91	94	94
Age group (n, %)			
< 65 years	65 (43.9)	58 (38.7)	123 (41.3)
>= 65 years	83 (56.1)	92 (61.3)	175 (58.7)
< 75 years	108 (73.0)	103 (68.7)	211 (70.8)
>= 75 years	40 (27.0)	47 (31.3)	87 (29.2)

Safety related to drug-drug interactions and other interactions

No safety concerns relating to drug-drug interactions or other interactions are noted from the clinical programme to date.

Discontinuation due to adverse events

Clinical Pharmacology studies

Of the 236 subjects included in the size clinical pharmacology studies, 3 subjects discontinued study treatment prematurely due to AEs (moderate pyrexia, moderate urticaria, mild hepatic enzymes elevated).

Phase 2/3 studies

In CREDIBLE-CR, a greater percentage of subjects in cefiderocol group (9.9% [10/101]) than in the BAT group (6.1% [3/49]) experienced TEAEs leading to discontinuation of study treatment. The difference is largely due to the higher mortality rate in the cefiderocol group. Septic shock leading to discontinuation occurred in 4 subjects in the cefiderocol group and 0 subjects in the BAT group; both events were SAEs. No other TEAEs leading to discontinuation of study treatment occurred in more than 1 subject.

Reasons for discontinuation from CREDIBLE-CR study (including after successful completion of study treatment) included lost to follow up (0.7% (1/150), 1 subject was in the cefiderocol group), withdrawal by subject (2.0% [3/150], 1 subject in cefiderocol group and 2 in the BAT), and death (overall 25.7% (39/150), 29.7% [30/101] in the cefiderocol group and 17.6% [9/49] in the BAT group).

In APEKS-cUTI, 1.7% (5/300) of subjects in the cefiderocol group and 2.0% (3/148) of subjects in the IPM/CS group had TEAEs leading to discontinuation from treatment or premature withdrawal from the study. No TEAE that led to discontinuation was reported in > 1 subject.

In the APEKS-NP, 27.3% (82/298) discontinued the study. Reasons included withdrawal by subject 1.7% (5/298) 2 subjects in cefiderocol group and 3 in the meropenem, and death 24.3% (overall 73/298, 26.4% [39/148] in the cefiderocol group and 22.4% [34/150] in the meropenem group).

2.6.2. Discussion on clinical safety

The safety database for cefiderocol is based on one completed phase 2 trial (APEKS-cUTI) and two completed phase 3 trials (CREDIBLE-CR and APEKS-NP). APEKS-cUTI included subjects with complicated urinary tract infection (cUTI) testing noninferiority of cefiderocol (n=300) versus imipenem and cilastatin (n=148) (IPM/CS). CREDIBLE-CR included subjects with carbapenem-resistant, Gram-negative infections and compared cefiderocol (n=101) with best available therapy(n=49) (BAT). APEKS-NP was requested by the CHMP because of the imbalance in mortality noted in the imbalance in mortality noted in the interim analysis of CREDIBLE-CR attributable to the subset of subjects with HAP/VAP/HCAP and the concern of low ELF penetration of cefiderocol. The study included carbapenem-sensitive HAP/VAP/HCAP subjects treated with cefiderocol (n=148) and meropenem (n=150). All subjects treated with cefiderocol received the recommended dose of 2 g q8h.

A thorough QT/QTc study conducted in healthy volunteers indicates no clinically significant effect of cefiderocol on the QT interval in humans at supratherapeutic doses up to 4g over 3 hours, and this is supported by ECG findings from APEKS-cUTI.

Within both individual CREDIBLE-CR, APEKS-NP and APEKS-cUTI studies, the overall incidence of TEAEs, severe TEAEs and SAEs was similar to the comparator group. The most frequently reported TEAEs for cefiderocol across clinical studies belong to the Gastrointestinal Disorders and Infections and Infestations SOCs. The frequency of TEAEs, severe TEAEs and SAEs was (not unexpectedly) highest in CREDIBLE-CR, which enrolled the most clinically unwell study population and in which most subjects (92%) reported at least 1 TEAE, 38.6% reported a severe TEAE and 42.6% reported an SAE.

The most frequently reported individual Preferred Terms for cefiderocol in CREDIBLE-CR were diarrhoea, vomiting, ALT increased, chest pain, decubitus ulcer, dyspnoea, pyrexia, septic shock, agitation, anaemia, AST increased, constipation and nausea, all reported in >10% of subjects receiving cefiderocol. The small study size, heterogeneity of treatments received in each treatment group and low absolute frequencies of most Preferred Terms means only an approximate comparison between the treatment groups in CREDIBLE-CR is possible.

The most frequently reported individual Preferred Terms for cefiderocol in APEKS-cUTI were ALT increased, AST increased, CK increased, WBC increased, diarrhoea, pyrexia and rash, all reported in >10% of subjects receiving cefiderocol.

The adverse effects of cephalosporins are well known and these events were monitored closely as AESIs in the clinical studies. These adverse effects included *C. difficile*-related diarrhoea, rash/hypersensitivity, seizures/epilepsy, liver-related adverse effects including liver biochemistry and clotting tests, and bone marrow suppression. All of these known class effects were reported, though at low frequency, in the Phase 2/3 studies, with no unexpected findings. Liver chemistry effects were generally mild or moderate and reversible, and no subject met the criteria for Hy's law. *C. difficile*-associated diarrhoea, hypersensitivity, seizures (class effect) and effects on hepatic enzymes are described in SmPC sections 4.4 and 4.8, which is appropriate.

The most notable safety finding is the higher incidences of fatal SAEs, of cardiac arrest, septic shock and pneumonia in the cefiderocol group in CREDIBLE-CR, which are reflected in a higher total mortality rate in the cefiderocol group. It was noted that there was no imbalance in mortality rate in the APEKS-NP study. In total, 43 subjects experienced SAEs with a fatal outcome with onset before the End of Study; 34 (33.7% of 101 subjects) in the cefiderocol group and 9 (18.4% of 49 subjects) in the BAT group. The most notable difference in SAEs leading to death between the two treatment groups was septic shock (10.9% [11/101] cefiderocol group vs 6.1% [3/49] BAT). The imbalance was seen for subjects with BSI/sepsis as well as those with HAP/VAP/HCAP. To investigate the imbalance in mortality further, the impact of potentially relevant host and pathogen factors on mortality has been further evaluated. At that analysis, a higher rate of *Acinetobacter spp* infections was noted in the cefiderocol group compared to the BAT group. Overall for subjects with *Acinetobacter spp*., the 28-day mortality was 38.1% in the cefiderocol group and 17.6% in the BAT group, and at the end of study was 50.0% in the cefiderocol group compared with 17.6% in the BAT group.

The difference in mortality rates between the cefiderocol and BAT treatment groups in the CREDIBLE-CR study is unexplained although there are some indications of imbalances between the treatment groups responsible for a minor part of the difference, e.g. history of septic shock among subjects with *A. baumannii* infection. However, the mortality rate in the cefiderocol group was also higher than the mortality rate in the BAT group for subjects with *A. baumannii* who did not have a history of shock. Therefore, shock does not alone explain the difference in mortality.

The possibility that this is an efficacy problem is raised and discussed in the section of clinical efficacy. There is no indication of a specific safety issue with respect to causes of death. Furthermore, data from the cUTI and HAP/VAP setting are reassuring in this regard.

2.6.3. Conclusions on the clinical safety

With the exception of the unexplained imbalance in mortality rate observed in CREDIBLE-CR, the safety profile of cefiderocol is as what can be expected for cephalosporines.

2.7. Risk Management Plan

This product does not have any safety concerns in the RMP. Therefore, no additional pharmacovigilance activities or additional risk minimisation measures are in place.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.13 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.11.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points. The PRAC agreed that the Data Lock Point for the first PSUR is 14 November 2020.

2.9. New Active Substance

The applicant compared the structure of cefiderocol with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers cefiderocol to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

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

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD group accepted the request for minimum particulars for the vial label, including the short term for the pharmaceutical form. According to the outcome the applicant had been requested, depending on the space, to include the statement 'Dilute before use' or "For IV use after reconstitution and dilution" on the vial label, as well as the statement "for single use only". However, due to the limited space none of the above statements could fit without significantly compromising the readability of the vial label.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fetcroja (cefiderocol) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Fetcroja is proposed by the Applicant to be indicated for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options.

Multi drug resistant (MDR) Gram-negative organisms such as carbapenem-resistant Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* play an increasing role as pathogens in various types of infection most importantly hospital-acquired including ventilator-associated pneumonia (HAP/VAP), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) but also other types of infections can be caused by these pathogens.

3.1.2. Available therapies and unmet medical need

Beta-lactam antibacterial agents are commonly used to manage infections when they involve Gram-negative pathogens. Increasing resistance to beta-lactams, including the carbapenems, has led to some organisms being effectively untreatable or treatable only with resource to colistin with or without other agents to which they remain at least partly susceptible. A few antibacterial agents addressing carbapenem-resistance have been made available during the past years but none of them are active against class B beta-lactamases and have no or limited activity against class D beta-lactamases. The European Centre for Disease Prevention and Control (ECDC) estimate that nearly 700,000 infections and 33,000 deaths in the EU and European Economic Area (EEA) in 2015 are a consequence of MDR bacterial infection (Cassini et al. 2019). The burden had increased since 2007. Carbapenem-resistance (CR) in *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter* spp. contributed significantly to the number of estimated deaths whereas the numbers of deaths estimated to be caused by infections caused by CR *Escherichia coli* was lower. In 2013 to 2014, the *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillinase-48 (OXA-48) was the most widely disseminated carbapenemases across Europe (Grundmann et al. 2017). Metallo-beta-lactamases such as New-Dehli metallo-betalactamase (NDM) and Verona integron-encoded metallo-β-lactamase (VIM) were detected to a lesser extent. In summary, there remains an unmet medical need for additional antibacterial agents addressing carbapenem-resistance in Gram-negative organisms.

3.1.3. Main clinical studies

APEKS-cUTI was a phase 2, randomised, double-blind, multicentre study of cefiderocol compared with imipenem/cilastatin (IMP/CS) in hospitalised adult subjects with cUTI/acute pyelonephritis caused by Gram-negative pathogens. There was no requirement in this study that the infections should be caused by carbapenem-resistant pathogens. This study was not designed to support an indication for treatment of cUTI.

CREDIBLE-CR was a phase 3, randomised, open-label, multicentre study of cefiderocol compared with best available therapy (BAT) in adult subjects for the treatment of severe infections (HAP/VAP/HCAP, cUTI and BSI/sepsis) caused by carbapenem-resistant Gram-negative pathogens. The study can only be regarded as supportive of efficacy for the intended indication because of its limited size.

APEKS-NP was a phase 3, randomised, double-blind, multicentre study of cefiderocol compared with meropenem in hospitalised adult subjects with HAP/VP/HCAP caused by Gram-negative pathogens. In line with the APEKS-cUTI study, there was no requirement in this study that the infections should be caused by carbapenem-resistant pathogens. This study was not intended to form the basis for the indication applied for. However, the results of this study were requested by the CHMP because of the imbalance in mortality noted in the interim analysis of the CREDIBLE-CR study in the subset of subjects with HAP/VAP/HCAP, and the concern of low ELF penetration of cefiderocol. This study was not designed to support an indication for treatment of HAP/VAP.

The possible ability of cefiderocol to meet an unmet need i.e. treatment of carbapenem-resistant organisms expressing β-lactamases, particularly Ambler Class B or D enzymes, is based mainly on in-vitro data, on nonclinical efficacy data to determine PK/PD targets and on clinical PK data indicating that relevant PK/PD targets are met with the 2 g q8h regimen when using 3h infusions. It is important to note that these data are pivotal to the application.

3.2. Favourable effects

In the APEKS-cUTI study the results for the composite endpoint of microbiological eradication and clinical cure per subject at TOC in the Micro-ITT population were 72.6% (n/N; 183/252) in the cefiderocol group and 54.6% (n/N; 65/119) in the IMP/CS group. The adjusted treatment difference was 18.6% (95% CI, 8.2, 28.9). Noninferiority at the prespecified -20% and -15% margins were met. Using the EU-recommended primary endpoint for studies in cUTI (microbiological eradication at TOC in the Micro-ITT population) and more stringent criterion for microbiological eradication ($<10^3$ CFU/mL instead of $<10^4$ CFU/mL) essentially similar results were obtained.

In the CREDIBLE-CR study clinical cure per subject (for subjects with HAP/VAP/HCAP and BSI/Sepsis) and microbiological eradication per subject (for subjects with cUTI) at TOC in the CR Micro-ITT population were evaluated. The clinical cure rate for subjects with HAP/VAP/HCAP were 50.0% (n/N', 20/40; 95% CI, 33.8, 66.2) in the cefiderocol group and 52.6% ((n/N', 10/19; 95% CI, 28.9, 75.6) in the BAT group. The clinical cure rate for subjects with BSI/sepsis were 43.5% (n/N', 10/23; 95% CI, 23.2, 65.5) in the cefiderocol group and 42.9% ((n/N', 6/14; 95% CI, 17.7, 71.1) in the BAT group. The microbiological eradication rate for subjects with cUTI were 52.9% (n/N', 9/17; 95% CI, 27.8, 77.0) in the cefiderocol group and 20.0% (n/N', 1/5; 95% CI, 0.5, 71.6) in the BAT group.

In the APEKS-NP study noninferiority of cefiderocol compared with meropenem was demonstrated for the treatment of HAP/VAP/HCAP for all-cause mortality at Day 14 (the FDA-recommended primary endpoint). The EU-recommended primary endpoint for a HAP/VAP study (HCAP should not be included) is clinical outcome at TOC using an NI-margin of -12.5%. This was just met since the clinical cure rates at TOC were 64.8% for the cefiderocol group (n/N', 94/145) and 66.7% for the meropenem group (n/N', 98/147), with a treatment difference of -2.0 (95% CI: -12.5, 8.5). However, the study was not sized for the primary evaluation of non-inferiority with regards this endpoint.

Based on plasma probability of target attainment (PTA) simulations using relevant PDTs (up to 100% *f*T>MIC), derived from neutropenic murine thigh and lung model studies against major target pathogens, the doses of cefiderocol in different renal function categories are satisfactory (PTA >90%) for the treatment of infections caused by pathogens having MICs up to 2 mg/L. These PTA simulations suggests that the dose is sufficient to cover the majority of target pathogens.

3.3. Uncertainties and limitations about favourable effects

Since the sample size in the CREDIBLE-CR study is limited, it does not form a basis for concluding on the efficacy of Fetcroja for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options. Moreover, the APEKS-cUTI and APEKS-NP studies cannot either support the efficacy evaluation for the intended indication, although the studies lend support of the efficacy of cefiderocol for the treatment of cUTI and HAP/VAP/HCAP caused by carbapenem-susceptible organisms.

As this application relies on a limited clinical programme, the PK/PD package, including in vitro data, determination of a non-clinical PK/PD target and PTA simulations using clinical PK data, are pivotal to the application.

As noted above, based on plasma PTA simulations, the doses of cefiderocol in different renal function categories are satisfactory for the treatment of infections caused by pathogens having MICs up to 2 mg/L. An adequate dose for the treatment of infections caused by pathogens with MICs of up to 2 mg/L will include most species within the spectrum of cefiderocol. When only carbapenemase-producing pathogens are considered, which are the main targets for cefiderocol, the MIC_{90s} are somewhat higher, in general 4 mg/L and highest (8 mg/L) for the subsets of NDM-producing Enterobacteriaceae and OXA-24/40-like carbapenemase-producing *A. baumannii*. Therefore, PK-PD analyses predict that a minor subset of target organisms with high MIC values may not be treatable with cefiderocol at the recommended doses.

The imbalance in mortality observed in the interim analysis of the CREDIBLE-CR study is maintained in the full dataset. However, the imbalance is evident in both the HAP/VAP/HCAP and BSI/sepsis subsets, not just in HAP/VAP/HCAP patients. This update vs. the interim dataset does not suggest that the mortality difference in CREDIBLE-CR is driven by poor efficacy of cefiderocol in HAP/VAP *per se.* As mentioned above, the non-inferiority of cefiderocol compared with meropenem in the APEKS-NP study lend further support that cefiderocol could be used for the treatment of infections in the lungs within the proposed pathogen-specific indication.

The difference in mortality rates between the cefiderocol and BAT treatment groups in the CREDIBLE-CR study is unexplained, although there are some indications of imbalances between the treatment groups responsible for a minor part of the difference, e.g. history of septic shock among subjects with *A. baumannii* infection. However, the mortality rate in the cefiderocol group was also higher than the mortality rate in the BAT group for subjects with *A. baumannii* who did not have a history of shock. Therefore, shock does not alone explain the difference in mortality.

The data indicate to a potential problem for cefiderocol in the treatment of *Acinetobacter* spp., with or without shock. Although there were no difference noted in mortality between the treatment groups in the APEKS-NP study with regards subjects infected with *A. baumannii*, the data from the typical HAP/VAP study population and from the cUTI study cannot provide reassurance with respect to a real efficacy problem for cediferocol vs. carbapenem-resistant *Acinetobacter*.

3.4. Unfavourable effects

In subjects with cUTI, cefiderocol demonstrated a comparable safety profile to an authorised active comparator, imipenem-cilastatin. Severe or serious AEs were infrequent (2% and 4.7% respectively). The most frequently reported individual Preferred Terms for cefiderocol in APEKS-cUTI were ALT increased, AST increased, CK increased, WBC increased, diarrhoea, pyrexia and rash, all reported in >10% of subjects receiving cefiderocol.

In subjects with CR-infections, the overall incidence of TEAEs, severe TEAEs and SAEs was similar between cefiderocol and BAT. Most subjects (94%) reported at least 1 TEAE, 37% reported a severe TEAE and 47% reported an SAE. The most frequently reported individual Preferred Terms for cefiderocol in CREDIBLE-CR were diarrhoea, vomiting, ALT increased, chest pain, decubitus ulcer, dyspnoea, pyrexia, septic shock, agitation, anaemia, AST increased, constipation and nausea, all reported in >10% of subjects receiving cefiderocol. There was no relevant difference for the reported TEAEs in subjects included the APEKS-NP study compared to CREDIBLE-CR.

The most notable safety finding is the higher incidences of fatal SAEs in the cefiderocol group, specifically septic shock (10.9% [11/101] of subjects) and BAT (6.1% [3/49] of subjects) and pneumonia (5.0% [5/101] subjects in the cefiderocol group and no subjects in the BAT group). These are reflected in a higher total mortality rate in the cefiderocol group. In total, 43 subjects in the CREDIBLE-CR study died, of which 33.7% (34/101) were treated with cefiderocol and 18.4% (9/49) were treated with BAT.

For the APEKS-NP study no imbalance in mortality rate was observed.

Known adverse effects of cephalosporins (*C. difficile*-related diarrhoea, rash/hypersensitivity, seizures/epilepsy, liver-related adverse effects including liver biochemistry and clotting tests, and bone marrow suppression) were reported infrequently, in both CREDIBLE-CR and APEKS-cUTI.

3.5. Uncertainties and limitations about unfavourable effects

The imbalance in mortality rates observed in CREDIBLE-CR is still unexplained. Even though septic shock was the more commonly reported SAE resulting in death among the subjects treated with cefiderocol compared to BAT, this difference is not sufficient to explain the imbalance in mortality. The causes of death in the CREDIBLE-CR study varied and included worsening and/or complications of infection and underlying conditions. Thus, no specific safety problem has been identified as causative of this observed imbalance and it seems more likely that the underlying cause is related to the efficacy of cefiderocol in certain types of host-pathogen settings. Some uncertainty on whether the different mortality estimates reflect a safety issue for cefiderocol remains.

3.6. Effects Table

Table BR1. Effects Table for Fetcroja for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Composite of microbiological eradication and clinical cure	Composite of microbiological eradication and clinical cure per subject at TOC in the Micro-ITT population	% (n/N)	Cefiderocol 72.6% (183/252)	IMP/CS 54.6% (65/119)	Adjusted treatment difference 18.6% (95% CI, 8.2, 28.9) i.e. NI was met at prespecified margins. Uncertainties: The study did not specifically include subjects infected with target pathogens.	APEKS-cUTI study
Clinical cure	HAP/VAP/HCAP Clinical cure per subject at TOC in the CR Micro-ITT population	% n/N' 95% CI	Cefiderocol 50.0% (20/40) (33.8, 66.2)	BAT 52.6% (10/19) (28.9, 75.6)	Too small sample size to conclude on efficacy of Fetcroja and to justify the dose for the intended indication	CREDIBLE-CR study
Clinical cure	BSI/Sepsis Clinical cure per subject at TOC in the CR Micro-ITT population	% n/N' 95% CI	Cefiderocol 43.5% (10/23) (23.2, 65.5)	BAT 42.9% (6/14) (17.7, 71.1)	Too small sample size to conclude on efficacy of Fetcroja and to justify the dose for the intended indication	CREDIBLE-CR study
Microbiological eradication	cUTI Microbiological eradication per subject at TOC in the CR Micro-ITT population	% n/N' 95% CI	Cefiderocol 52.9% (9/17) (27.8, 77.0)	BAT 20.0% 1/5 0.5, 71.6	Too small sample size to conclude on efficacy of Fetcroja and to justify the dose for the intended indication	CREDIBLE-CR study

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Clinical cure	HAP/VAP/HCAP Clinical cure per subject at TOC in the mITT population	% n/N'	Cefiderocol 64.8% 94/145	Meropenem 66.7% 98/147	Treatment difference -2.0% (95% CI, -12.5, 8.5) Supports the use of cefiderocol for the treatment of lung infections. Uncertainties: HCAP should not be included in a study intended for a standalone indication of HAP/VAP. The study did not specifically include subjects infected with target pathogens.	APEKS-NP study
Dose justification	Probability of target attainment of cefiderocol against target pathogens at the proposed susceptibility breakpoint based on PTA simulations using a non-clinical PK/PD target and clinical PK data				Based on plasma PTA simulations, the doses of cefiderocol in different renal function categories are sufficient for the treatment of infections caused by pathogens having MICs up to 2 mg/L. and simulations for ELF suggest the dose is sufficient when MICs are up to 1 mg/L.	Section of Clinical pharmacodynamics
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
All-cause mortality (end of study)	Incidence (ITT Population)	n/N % (95 % CI)	Cefiderocol 34/101 33.7% (24.6, 43.8)	BAT 9/49 18.4% (8.8, 32.0)	No causal explanation found	CREDIBLE-CR
All-cause mortality (at D28)	Incidence (ITT Population)		Cefiderocol 25/101 24.8% (16.7, 34.3)	BAT 9/49 18.4% (8.8, 32.0)		
TEAEs ≥10% Diarrhoea Vomiting ALT increase Chest pain Decub. ulcer Dyspnoea Pyrexia Septic Shock Agitation Anaemia AST increase Constipation Nausea	Incidence	%	Cefiderocol 18.8 12.9 6.9 5.9 9.9 6.9 13.9 12.9 5.0 7.9 7.9 7.9 6.9	BAT 6.1 14.3 0 0 8.2 4.1 12.2 14.3 4.1 4.1 2.0 6.1 4.1		CREDIBLE-CR

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite recent advances in the development of antibacterial agents, there is still an unmet need of antibacterial agents with an acceptable safety profile that are active against carbapenem-resistant Gram-negative organisms especially against organism producing Class B and Class D carbapenemases. The microbiology data indicate that cefiderocol is active against important Gram-negative organisms including Enterobacteriaceae, *P. aeruginosa*, *A. baumannii* and *S. maltophilia* and stable to all classes of beta-lactamases. Cefiderocol seems moreover not adversely affected by efflux pumps or loss of outer membrane porins. Therefore, Fetcroja could provide useful alternative for the treatment of most infections due to carbapenem-resistant aerobic Gram-negative bacteria.

Even though non-inferiority of cefiderocol compared with IMP/CS was met in the APEKS-cUTI and APEKS-NP studies, the efficacy of cefiderocol for the intended indication was not established in these studies because the target organisms of the indication was not specifically studied. Moreover, the sample size of the CREDIBLE-CR study conducted in subjects infected with target pathogens was too small to conclude on the efficacy of cefiderocol and to justify the dose.

Because of the limited size of the clinical programme, a robust PK/PD package to support the adequacy of the dose cefiderocol is pivotal. Based on plasma PTA simulations, the doses of cefiderocol in different renal function categories are sufficient for the treatment of infections caused by pathogens

having MICs up to 2 mg/L. An adequate dose for the treatment of infections caused by pathogens with MICs of up to 2 mg/L will include most species within the spectrum of cefiderocol.

There were initial concerns that the dose may be insufficient, especially for the treatment of infections in the lungs because of the low ELF penetration. The imbalance in mortality observed in the interim analysis of the CREDIBLE-CR study remains in the final dataset and is evident in both the HAP/VAP/HCAP and BSI/sepsis subsets. This update vs. the interim dataset does not suggest that the mortality difference in CREDIBLE-CR is driven by poor efficacy of cefiderocol in HAP/VAP *per se.* As commented above, the non-inferiority of cefiderocol compared with meropenem in the APEKS-NP study lend further support that cefiderocol could be used for the treatment of infections in the lungs within the proposed pathogen-specific indication.

The imbalance noted in mortality in the CREDIBLE-CR study is still unexplained. The data indicate to a potential problem for cefiderocol in the treatment of *Acinetobacter* spp., with or without shock. Although there were no difference noted in mortality between the treatment groups in the APEKS-NP study with regards subjects infected with *A. baumannii*, the data from the typical HAP/VAP study population and from the UTI study are not relevant to rule out a real problem for cefiderocol vs. *Acinetobacter*. It is considered crucial to inform the prescribers of the imbalance in mortality in the CREDIBLE-CR study and association between mortality and infection with *Acinetobacter* in the cefiderocol treatment arm.

In clinical studies, the overall safety profile of cefiderocol was similar to that of the relevant active comparator (IMP/CS in cUTI and BAT in CR Gram-negative infections), with the notable exception of a currently unexplained numerical imbalance in all-cause mortality between treatment groups in CREDIBLE-CR. A similar imbalance was not observed between treatment groups amongst cUTI patients in APEKS-cUTI. Furthermore, no imbalance in mortality was observed in the APEKS-NP study.

3.7.2. Balance of benefits and risks

The overall nonclinical and clinical data support the ability of cefiderocol to address an unmet need. The balance of benefits and risks is considered positive.

3.8. Conclusions

The overall B/R of Fetcroja is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Fetcroja is not similar to Cayston, TOBI Podhaler, Bronchitol, Kalydeco and Symkevi within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fetcroja is favourable in the following indication:

Fetcroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (see sections 4.2, 4.4 and 5.1).

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that cefiderocol is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.