28 April 2016
EMA/CHMP/377887/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zavicefta

International non-proprietary name: ceftazidime / avibactam

Procedure No. EMEA/H/C/004027/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

%*f*T>MIC	Percent of dose interval in which free drug concentration exceeds the minimum inhibitory concentration of the drug for a specific organism or group of organisms
APACHE	Acute Physiology and Chronic Health Evaluation
ARC	Augmented renal clearance
AUC	Area under the plasma concentration time curve
BAT	Best available therapy
BMI	Body mass index
CDAD	*Clostridium difficile* associated diarrhea
CE	Clinically evaluable
CEP	Certificate of Suitability of the EP
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CL	Total body clearance of drug from plasma
CLSI	Clinical Laboratory Standards Institute
C_{max}	Maximum plasma drug concentration
CQA	Critical Quality Attribute
C_T	Critical threshold concentration
CrCL	Creatinine clearance
cSSTI	Complicated skin and soft tissue infections
cUTI	Complicated urinary tract infection
CXL	Ceftaroline fosamil + avibactam
CYP	Cytochrome P450
DBC	Double-blind controlled
DCO	Data cut-off
DDI	Drug-drug interaction
ECDC	European Centre for Disease Prevention and Control
ED_{50}	50% effective dose
EDQM	European Directorate for the Quality of Medicines
ELF	Epithelial lining fluid
eME	Extended microbiologically evaluable
EOIV	End of IV therapy
EOT	End of therapy
EP	European Pharmacopoeia
ESBL	Extended spectrum β-lactamase
ESRD	End stage renal disease
EU	European Union
FED	Factorial Experimental Design
FMEA	Failure mode effects and criticality analysis
*f*T>C_T	Time plasma concentration of free drug meets or exceeds threshold concentration
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GMP	Good Manufacturing Practice
GVS	Gravimetric Vapour Sorption
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
IV	Intravenous
KF	Karl Fischer titration
KPC	*Klebsiella pneumoniae* carbapenemase
LDPE	Low Density Polyethylene
LFU	Late follow-up
MDR	Multi-drug resistant, i.e., acquired non-susceptibility to at least one agent in three or more antimicrobial categories

ME	Microbiologically evaluable
MIC	Minimum inhibitory concentration
MITT	Modified intention to treat
mMITT	Microbiologically modified intention to treat
MRIB	Moderate renal impairment at baseline
MS	Mass Spectrometry
MTZ	Metronidazole
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NP	Nosocomial Pneumonia
OAT	Organic anion transporter
PACMP	Post-approval change management protocol
PAR	Proven Acceptable Range
PCS	Potentially clinically significant
Ph. Eur.	European Pharmacopoeia
PTA	Probability of PK/PD target attainment
QbD	Quality by design
QTPP	Quality target product profile
q8h, q12h, q24h, q48h	Every 8, 12, 24, 48 hours, respectively
r	Correlation coefficient
ROW	Rest of World (outside of North America)
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System organ class
SXRD	Single crystal X-Ray diffraction
t½	Terminal elimination half-life
TOC	Test of cure
TSE	Transmissible Spongiform Encephalopathy
VAP	Ventilator associated pneumonia
V_c / V_{ss}	Apparent volume of distribution - of the central compartment / at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 24 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zavicefta, 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 22 May 2014.

The applicant applied for the following indication Zavicefta is indicated for the treatment of the following infections in adults:

- Complicated Intra-Abdominal Infection (cIAI)
- Complicated Urinary Tract Infection (cUTI), including pyelonephritis
- Nosocomial pneumonia, including ventilator associated pneumonia (VAP)
- Infections due to aerobic Gram-negative organisms in patients with limited treatment options.

Consideration should be given to official guidance on the appropriate use of antibacterial agents. For treatment of cIAI use in combination with metronidazole.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that the constituent of Zavicefta, avibactam sodium, was considered to be a new active substance.

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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0052/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0052/2015 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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indications.

New active Substance status

The applicant requested the active substance, avibactam sodium, contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 January 2012, 16 February 2012, 25 April 2014. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Ceftazidime-avibactam (AVYCAZ) has been given a Marketing Authorisation in United States on 25 February 2015.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 24 March 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 July 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2015.
- PRAC Rapporteur's Assessment Report was circulated on 29 August 2015.
- Updated PRAC Rapporteur's Assessment Report was circulated on 9 September 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2015.
- PRAC Rapporteur's Assessment Report was circulated on 27 January 2016.
    - The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2016.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2016.
- During the meeting on 28 April 2016, 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 Zavicefta.

2. Scientific discussion

2.1. Introduction

This application concerns a fixed drug combination product (FDC) presented for clinical use in vials containing ceftazidime 2 g and avibactam 0.5 g (CAZ-AVI), to be reconstituted and diluted for thrice daily infusions, each over 2 h in 100 mL volumes. The rationale for the FDC rests on the activity of ceftazidime (CAZ) against a wide range of aerobic Gram-negative pathogenic bacteria and the ability of avibactam (AVI), a non-β-lactam β-lactamase inhibitor, to protect CAZ from hydrolysis by a wide range of serine β-lactamases. Importantly, the range of inhibition of AVI includes class A ESBLs and carbapenemases (e.g. KPCs), class C β-lactamases and some class D oxacillinases and carbapenemases.

Ceftazidime was first licensed in the EU during the 1980s for a wide range of indications. An Article 30 procedure was completed during 2012. The development of AVI was initially undertaken by Novexel, which was later acquired by AstraZeneca. AstraZeneca and Forest Laboratories then entered into an agreement to co-develop CAZ-AVI. AstraZeneca has responsibility for CAZ-AVI in the EU.

2.1.1. Problem statement

β-lactamases are a major cause of resistance to beta-lactam antibacterial agents in infections caused by Gram-negative pathogens. Many of these enzymes are carried on transferable elements (i.e. plasmids), which facilitate rapid transmission of resistance within and across bacterial species. This characteristic, coupled with the fact that infections caused by β-lactam resistant pathogens are already widespread in the hospital and community setting, means that continued proliferation of treatment-resistance can be expected (Carlet *et al* 2012).

The microbiology of serious infections varies depending on the host, type of infection, and the location (geographic location and hospital vs outpatient) where the infection was acquired. However, certain pathogens are clearly predisposed to acquire and spread resistance. *Enterobacteriaceae* (particularly *Escherichia coli* and *K. pneumoniae*) and *Pseudomonas aeruginosa* are commonly associated with β-lactamase-mediated resistance irrespective of the site of infection (Morrissey *et al* 2013; Jones 2010; Giske *et al* 2008; Boucher *et al* 2009). *Acinetobacter spp.,* particularly *A. baumannii,* are also commonly associated with resistance to β-lactams; although these species acquire β-lactamases, they are also intrinsically resistant to many β-lactams due to their selective ability to exclude various molecules from penetrating their outer membrane (ECDC 2012).

In the 2012 European Centre for Disease Prevention and Control (ECDC) microbiological surveillance report, 11.8% of *E. coli* isolates and 25.7% of *K. pneumoniae* isolates were resistant to 3rd generation cephalosporins. In both cases this represents a statistically significant increase from the same figures in 2009 (EU/EEA means: 8.2% and 21.5%, respectively [ECDC 2012]).

Resistance to extended-spectrum cephalosporins has been developing over two decades. It is most often caused by ESBLs, but may also be conferred by plasmid-mediated or chromosomally hyper-produced AmpC-type enzymes. Plasmids that encode ESBL genes often carry other resistance genes too, meaning that ESBL producing pathogens are commonly resistant to other classes (MacVane *et al* 2014). Thus, increasing resistance to cephalosporins conferred by ESBLs has coincided with increasing combined resistance to other antimicrobial groups. In the 2012 ECDC surveillance report, 4.4% of *E. coli* isolates and 18.5% of *K. pneumoniae* isolates possessed combined resistance to cephalosporins, aminoglycoside and fluoroquinolones; combined resistance rates were as high as 16.1% and 59.9%, respectively, in individual EU countries. This pattern of increasing resistance has significantly limited

treatment options in patients with suspected ESBL infections and often only carbapenems remain suitable for empiric use.

Carbapenemases are another increasingly common mechanism for resistance to β-lactams among the *Enterobacteriaceae*; these cause resistance to carbapenems as well as other β-lactams (Nordmann 2014). There are serine-based enzymes (mainly Ambler class A) and metallo- (also referred to as zinc) based enzymes. The most prevalent group of serine enzymes have been described as "KPCs" because they were first encountered in *K. pneumoniae,* however, the genes that code for these enzymes are spread amongst *Enterobacteriaceae* (Nordmann 2014).

ECDC surveillance data for healthcare associated infections across Europe reported that overall 7.6% of *Enterobacteriaceae* were non-susceptible to carbapenems (ECDC 2013). The highest rates of carbapenem resistance are routinely found in Greece, where 60.5% of *K. pneumoniae* isolates from hospitals have been reported to be resistant to carbapenems. Across Europe, there has been a statistically significant increase in EU/EEA population-weighted mean percentage of carbapenem-resistant *K. pneumoniae* from 3.2% in 2009 to 6.2% in 2012. Carbapenem resistance is generally associated with combined resistance to cephalosporins, aminoglycosides and fluoroquinolones (ECDC 2012). It is also increasingly evident that carbapenem-resistance can be conferred through other mechanisms besides carbapenemases (e.g. AmpC enzymes and pathogens that possess an ESBL in combination with mechanisms that limit carbapenem entry into the cell [Huang *et al* 2013; Lopez-Camacho *et al* 2014; Robert *et al* 2014]).

2.1.2. About the product

Ceftazidime-avibactam (CAZ-AVI; CAZ104) is a β-lactam/β-lactamase fixed drug combination (FDC) of:

- Avibactam (NXL104; AVE1330A) is a novel non-β-lactam β-lactamase inhibitor with a spectrum of activity encompassing β-lactamases of class A and class C, including ESBLs and serine-based carbapenemases (KPCs). It also inhibits some class D β-lactamases (e.g. OXA-48 type carbapenemase). Avibactam has no inhibitory effect on class B metallo-β-lactamases.
- Ceftazidime is a cephalosporin that is approved in the EU for the treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), nosocomial pneumonia (NP) and a range of other infections. It has no appreciable antibacterial activity against Gram-positive pathogens, with the exception of some streptococci, or anaerobes.

The proposed indications for adults are:

- Complicated Intra-Abdominal Infection (cIAI)
- Complicated Urinary Tract Infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia including ventilator associated pneumonia (VAP)
- Infections due to aerobic Gram-negative organisms in patients with limited treatment options

The proposed posology is:

Posology

The recommended intravenous dose regimen for patients with creatinine clearance >51 mL/min is shown by infection type.

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated IAI[2,3]	2 g/0.5 g	Every 8 hours	2 hours	5-14 days
Complicated UTI, including pyelonephritis[3]	2 g/0.5 g	Every 8 hours	2 hours	5-10 days[4]
Hospital-acquired pneumonia, including VAP[3]	2 g/0.5 g	Every 8 hours	2 hours	7-14 days
Infections due to aerobic Gram-negative organisms in patients with limited treatment options2,3	2 g/0.5 g	Every 8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]

[1] CrCL estimated using the Cockcroft-Gault formula
[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process
[3] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process
[4] The total duration shown may include intravenous Zavicefta followed by appropriate oral therapy
[5] There is very limited experience with the use of Zavicefta for more than 14 days

It is recommended that Zavicefta should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see section 4.4).

Special populations

Elderly

No dosage adjustment is considered necessary in elderly patients (see section 5.2).

Renal impairment

In patients with mild renal impairment (estimated creatinine clearance CrCL 50-> 80 mL/min) no dose adjustment is necessary (see section 5.2).

The following dose adjustments are recommended in patients with estimated CrCL ≤ 50 mL/min (see sections 4.4 and 5.2).

Estimated CrCL (mL/min)[2]	Dose regimen[1]	Frequency	Infusion time
31-50	1 g/0.25 g	Every 8 hours	2 hours
16-30	0.75 g/0.1875 g	Every 12 hours	2 hours
6-15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD on haemodialysis[4]	0.75 g/0.1875 g	Every 48 hours	2 hours

[1] CrCL estimated using the Cockcroft-Gault formula
[2] Dose recommendations are based on pharmacokinetic modelling
[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). Dosing of Zavicefta on haemodialysis days should occur after completion of haemodialysis.

Haemodialysis

Both ceftazidime and avibactam are haemodialyzable; thus, Zavicefta should be administered after haemodialysis on haemodialysis days (see Table 2).

Haemofiltration

There is insufficient data to make specific dosage adjustment recommendations for patients undergoing continuous veno-venous haemofiltration.

Peritoneal dialysis

There is insufficient data to make specific dosage adjustment recommendations for patients undergoing peritoneal dialysis.

Hepatic impairment

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

Paediatric population

Safety and efficacy in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Zavicefta is administered by intravenous infusion over 120 minutes in an infusion volume of 100 mL (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration (see section 6.6).

Class D OXA β-lactamases are also increasingly reported in *Enterobacteriaceae*. Amongst these, OXA-48 is of particular concern due to its carbapenem-hydrolysing activity. OXA-48 has recently started to spread in Europe and the Middle East (Potron *et al* 2013). Many OXA-48 expressing strains of bacteria are susceptible to ceftazidime, which is relatively stable to hydrolysis by OXA-48 itself, but OXA-48 strains can co-express ESBLs and narrow spectrum β-lactamases with ceftazidime hydrolysing activity.

Pseudomonas aeruginosa is a major cause of infection in hospitalised patients. Resistance can be intrinsic (e.g. chromosomally-encoded β-lactamases) or acquired (including serine- and metallo-β-lactamases), and is often mediated by interplay of various mechanisms that lead to resistance to β-lactams, aminoglycosides and fluoroquinolones. Carbapenem resistance is common in the EU (population-adjusted mean percentage of 17.1% [range 3.2% to 51.2%]: ECDC 2012). Combined resistance is also common: in the 2012 ECDC surveillance report, 13.8% of the isolates were resistant to at least 3 antimicrobial groups and 5.8% of the isolates were resistant to all 5 antimicrobial classes under surveillance (ECDC 2012). Of particular relevance is mutational derepression of the chromosomally coded AmpC β-lactamase, which can confer resistance to cephalosporins that are active against *P. aeruginosa.* This beta-lactamase is not inhibited by existing inhibitors such as tazobactam. Furthermore, acquisition of plasmid-mediated resistance genes coding for various β-lactamases and aminoglycoside-modifying enzymes can confer resistance to various β-lactams, including carbapenems, and aminoglycosides (ECDC 2012). Metallo-β-lactamases are the most common carbapenemases

identified in *P. aeruginosa*, however, the Ambler class A β-lactamase KPC has also been reported (Cuzon et al 2011).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam as active substances.

The only other ingredient is sodium carbonate (anhydrous).

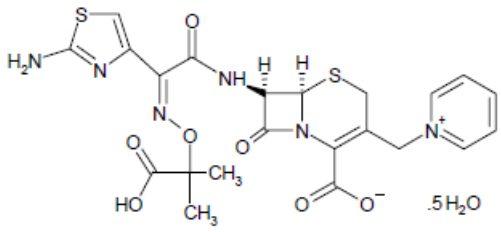
The product is available in a 20 ml glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap as described in section 6.5 of the SmPC.

2.2.2. Active substance

Ceftazidime pentahydrate

General information

The chemical name of ceftazidime pentahydrate is (*Z*)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-(1-carboxy-1-methylethyloxyimino)acetylamino]-3-(1-pyridiniumylmethyl)-3-cephem-4-carboxylate pentahydrate corresponding to the molecular formula $C_{22}H_{22}N_6O_7S_2.5H_2O$. It has a relative molecular mass of 636.7 g/mol and the following structure:



The active substance is a white to almost white crystalline powder, slightly soluble in water and non-hygroscopic.

The active substance exhibits stereoisomerism due to the presence of two chiral centres. Polymorphism has not been observed for active substance.

As there is a monograph for ceftazidime pentahydrate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the non-sterile ceftazidime pentahydrate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information for the non-sterile ceftazidime pentahydrate has been assessed by the EDQM before issuing the Certificate of Suitability.

Sterilisation of ceftazidime pentahydrate is described. Sterile ceftazidime pentahydrate is further processed aseptically with sodium carbonate to yield to a sterile ceftazidime carbonate blend. Details have been provided on process validation.

The active substance is packaged in a sterilised Low Density Polyethylene (LDPE) inner bag. This provides a sterile barrier and contains a nitrogen headspace. The first bag is in an outer sterilised laminate bag of aluminium coupled with LDPE, nylon and polyester. This provides a gas, moisture and light barrier, which maintains a nitrogen headspace. The two sealed bags are then enclosed in a third, outer bag which is used for general handling protection only. The LDPE inner product contact bag conforms to the requirements of Ph. Eur. 3.1.4 “Polyethylene without additives for containers for preparations for parenteral use and for ophthalmic preparations”.

Specification

The specifications for sterile ceftazidime pentahydrate comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set in compliance with the CEP for aqueous degradation products (HPLC) and residual solvents (GC). Additional specifications have been also for set for bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

Non-compendial methods have been adequately validated and described according to ICH Q2.

The relevant information for reference standards has been assessed by the EDQM before issuing the Certificate of Suitability.

Batch analysis data on three batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

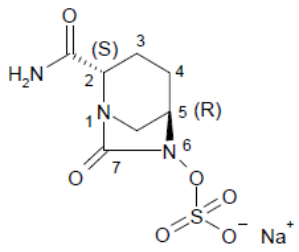
According to the CEP, a retest period of 18 months is applicable if the non-sterile ceftazidime pentahydrate is stored at a temperature between 2 °C and 8 °C in a LPDE bag under nitrogen in an aluminium laminated bag placed in a sealed sterilised aluminium laminated bag.

Sterile ceftazidime pentahydrate is not isolated during the manufacturing process. No hold time nor retest period is applied to sterile ceftazidime pentahydrate which is immediately blended in-line to make the finished product intermediate, sterile ceftazidime carbonate blend.

Avibactam sodium

General information

Avibactam sodium is a new active substance. The chemical name of avibactam sodium is sodium[(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl]sulfate corresponding to the molecular formula $C_7H_{10}N_3O_6SNa$. It has a relative molecular mass of 287.23 g/mol and the following structure:



The active substance is a white to pale yellow anhydrous hygroscopic crystalline powder, freely soluble in water.

The active substance exhibits stereoisomerism due to the presence of three chiral centres (at the 1, the 2- and 5-positions). Stereoisomeric purity at C2 and C5 is controlled in the specification of the starting material. The stereochemistry at the bridgehead nitrogen (the 1-position) is dictated by the stereochemistry at the 5-position bridgehead carbon. The specification for avibactam sodium contains a limit for the enantiomer.

Polymorphism has been observed for the active substance. Several polymorphic forms have been identified. The active substance can also be amorphous. The manufacturing process consistently produces the same polymorphic form. Polymorphism is controlled by the manufacturing process of the active substance. Pivotal stability studies have shown that the polymorphic form produced does not convert to any other form under the proposed storage conditions.

Manufacture, characterisation and process controls

The active substance is synthesized in four main steps using a well-defined starting material with acceptable specifications. Initially, a major objection was raised requesting re-definition of the starting material in order to ensure that critical steps of the manufacturing process were described in the dossier and carried out under GMP. In order to address these concerns, the applicant provided a detailed discussion of the origin, fate and purge of impurities upstream of the starting material, as well as a description of the synthetic process of the starting material including solvents, reagents and catalysts. It was demonstrated that impurities in the starting material are all efficiently purged and do not have the potential to impact the active substance quality. Control of stereoisomeric impurities has been demonstrated and there are no concerns in relation to elemental or mutagenic impurities.

Rework of avibactam sodium may be performed. A detailed description of reworking steps has been provided and is considered acceptable.

The active substance is sterilised using sterile filtration followed by sterile crystallisation. Process details and process validation data have been provided.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Impurity tracking studies were carried out to understand the fate and purge of impurities present in the intermediates. It has been demonstrated that the impurity limits set in the intermediates' specifications are sufficient to ensure they are purged to acceptable levels in isolated avibactam sodium.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. A single polymorphic form has been produced in all late-stage development batches for clinical use, amorphous material having been used for the manufacture of finished product used in pre-clinical, and phase I and II clinical studies. The manufacturing route in early development used the same intermediates and the same starting material. For the commercial manufacturing route, an additional isolation point was introduced, and the processing stages between two intermediates were redeveloped. These changes improved the operability and processing and also the quality of the avibactam sodium produced.

Development of the control strategy for the manufacture of avibactam sodium has used a science and risk based approach

• Critical Quality Attributes (CQAs) for avibactam sodium were determined, following the principles defined in ICH Q11.

• A risk-based approach was used to identify knowledge gaps and risks to the CQAs for avibactam sodium. Development work was then focused on the reduction of the identified risks.

• Risk assessments in relation to scale-up have been performed for each of the manufacturing stages. There are no significant risks to the quality of avibactam with respect to scale up factors.

Appropriate ranges have been set for the parameters within each process so that operation within the parameter ranges ensures the quality of the intermediate products, and avibactam sodium.

Additionally, a control strategy has been developed summarising the critical processing and analytical steps, which ensures that all the CQAs for avibactam sodium are consistently met.

A post-approval change management protocol (PACMP) to add a site for the manufacture and quality control of avibactam sodium was agreed.

The chemical structure of the active substance has been confirmed by MS, NMR and FT-IR. In addition, solid state NMR and Gravimetric Vapour Sorption (GVS) analysis have been carried out. Single crystal X-Ray diffraction (SXRD) has been used to determine the crystal structure of the active substance and confirm the absolute configuration around the chiral carbon atoms. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. A thorough assessment of the active substance manufacturing route has been performed in accordance with ICH M7. Three impurities were found to be mutagenic. Studies showed that these impurities were fully purged.

The active substance is packaged in a sterilised LDPE inner bag. This provides a sterile barrier and contains a nitrogen headspace. The first bag is in an outer sterilised laminate bag of aluminium coupled with LDPE, nylon and polyester. This provides a gas, moisture and light barrier, which maintains a nitrogen headspace. The two sealed bags are then enclosed in a third, outer bag which is used for general handling protection only. The LDPE inner product contact bag conforms to the requirements of Ph. Eur. 3.1.4 “Polyethylene without additives for containers for preparations for parenteral use and for ophthalmic preparations”.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), enantiomeric impurity (chiral HPLC), residual solvents (GC), water content (KF), sodium (flame photometry), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

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

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 assay and impurities testing has been presented.

Batch analysis data for ten production scale batches of the active substance manufactured using the proposed commercial manufacturing route were provided. The results were within the specifications and consistent from batch to batch. Supportive batch analysis data was provided for batches manufactured with previous manufacturing routes used during development.

Stability

Stability data was provided for three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 36 months under long term conditions at 5 ºC and 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

Batches were tested for assay, organic impurities (including enantiomer), water content, sterility, bacterial endotoxins and polymorphic identity. The analytical methods are the same as described for release.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Based on the stability data available, no significant change was observed and all tested parameters were within the specifications. Avibactam sodium is not photosensitive.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored at 25°C or below in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a sterile, pyrogen-free, and white to pale yellow powder in 20 mL sterile pyrogen free vials.

The excipient used is a well-known pharmaceutical ingredient and its 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.

Ceftazidime has poor oral bioavailability and pre-clinical investigations showed that neither ceftazidime nor avibactam could achieve efficacious plasma concentrations when dosed *via* the oral route, so parenteral administration was required. Both components are highly soluble in water but long-term stability was not sufficient to allow development of an aqueous solution. Therefore, a solid dosage form for reconstitution prior to administration was sought. A powder formulation made by co-lyophilising both active substances was also found to be unstable.

For phase 1 and 2 clinical studies, avibactam and ceftazidime (FORTAZ/FORTUM) were supplied in separate vials for reconstitution and co-administration as a single infusion solution.

A formulation containing 2000 mg of ceftazidime and 500 mg of avibactam was selected for the phase 3 and commercial formulation. In order to assure the accuracy and efficiency of the reconstitution stage, to reduce the complexity of the infusion preparation and to decrease the potential for dosing or administration errors, a combination product containing avibactam sodium and ceftazidime carbonate blend was developed.

The bioavailability of the finished product prepared by using separate vials for co-administration, as a single infusion is considered to be equivalent to that of an infusion produced from a single vial containing all the components taking into account that for both phase 1/2 formulation and phase 3/commercial formulation, the finished product is presented as an aqueous solution at the point of administration.

Manufacturing process development used science and risk based approaches, following the principles of ICH Q8 'Pharmaceutical Development' and Q9 'Quality Risk Management'.

A number of finished product characteristics were determined to ensure that the commercial formulation would meet the requirements stated in the quality target product profile (QTPP) defined as: an acceptable reconstitution time in suitable IV diluents, an adequate tonicity of the infusion solution, a minimum shelf-life at launch of at least 2 years at controlled room temperature, an acceptable in-use profile consistent with intended use and typical pharmacy handling, compliance of the finished product with EP requirements for uniformity of dosage unit and stability.

Critical Quality Attributes (CQAs) were defined as those aspects affecting product purity, strength, active substance release and stability.

Terminal sterilisation by either thermal treatment or irradiation was not a viable option for this product due to the level of degradation that occurred using either method. Development options for the required combination product were limited to commercially scalable aseptic processes.

The product is manufactured through filling of both sterile ceftazidime carbonate blend and avibactam sodium. This method was used to manufacture finished product from avibactam sodium and the ceftazidime carbonate blend for phase 3 clinical studies and is the proposed commercial manufacturing process.

Headspace gas was investigated. Results of stability studies confirmed that the headspace gas composition selected was appropriate for the finished product.

An overfill is used in order to ensure that the entire contents of the reconstituted vial can be accurately removed. This has been justified.

A risk-based approach was used to identify knowledge gaps and risk to the CQAs. Failure Mode, Effects and Criticality Analysis (FMECA) was the main tool used for risk assessment throughout the development process. Each potential failure mode was scored in terms of probability, severity and detectability. The main process stages identified to potentially impact on CQAs are the vial filling and stoppering stages.

The potential failure modes were investigated in development studies involving nine batches, covering a range of batch sizes, different batches of ceftazidime carbonate blend and avibactam sodium and involving changes in equipment configuration. These batches were utilised for clinical and stability studies.

Knowledge obtained during the pharmaceutical development has been used to define an overall finished product control strategy.

The control strategy includes input material controls, process parameter controls, in-process controls and finished product testing in order to ensure delivery of the required product quality attributes.

The primary packaging is a 20 mL glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap. The material complies with Ph. Eur. requirements. 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 six main steps: mixing of sterile sodium carbonate (anhydrous) with sterile ceftazidime, aseptic vial filling with sterile ceftazidime carbonate blend and sterile

avibactam sodium, gas overlay in the vial headspace, stoppering, crimping, bulk packaging. The process is considered to be a standard manufacturing process taking into account the experience of the manufacturer.

The sterile ceftazidime carbonate blend is considered to be a finished product intermediate and its specifications include appropriate tests: appearance, identity (HPLC), appearance of aqueous solution, pH (Ph. Eur.), sodium carbonate content (flame photometry), assay (HPLC), impurities (HPLC), pyridine content (HPLC), loss on drying (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, description on reconstitution, reconstitution time, pH (Ph. Eur.), identification (HLPC, UV), ceftazidime and avibactam assay (HPLC), degradation products (HPLC), pyridine content (HPLC), uniformity of dosage unit (Ph. Eur.), particulate matter (Ph. Eur.), water content (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

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.

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

Stability of the product

Stability data was provided for three pilot scale batches of finished product stored in both the upright and inverted orientation under long term conditions for 24 months at 25 ºC / 60% RH and 30 ºC / 75% RH and for 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

An additional batch of finished product was placed on stability to support clinical studies. This batch has been manufactured using a non-sterile process. The purpose of this stability study was to generate supporting data at a stressed condition of 50°C for 1 month.

The tests performed at each time point are appearance, description on reconstitution, reconstitution time, pH, assay of ceftazidime and avibactam, ceftazidime and avibactam degradation products, pyridine content and sub-visible particulate matter. Water content, sterility and bacterial endotoxins were performed at initial, annual and final time points only.

After 2 years at 25°C/60% RH and 30°C/75% RH, small increases in pyridine content and unspecified ceftazidime impurities content were observed. All tests gave results below the specification limit. For ceftazidime assay, a decrease was observed but results comply with specifications.

After 6 months at 40 °C/75% RH, an increase in pyridine content was observed. A small increase in unspecified ceftazidime impurities content was also noted. The levels of these impurities did not exceed the specification limit.

Based on available stability data, all results comply with specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results demonstrated that the finished product is light sensitive.

Compatibility of finished product with infusion solutions was investigated. The data demonstrated the compatibility of the finished product with all combinations of dextrose and sodium chloride containing up to 5% dextrose and up to 0.9% sodium chloride and with lactated Ringer's solution when stored for 24 hours at 2°C to 8°C, followed by 12 hours at room temperature.

Stability data were also provided on:

- Three batches of bulk sterile ceftazidime carbonate blend finished product intermediate stored at 2°C to 8°C under a nitrogen headspace in sterile LDPE container closure system for 24 months after blending.
- One batch of finished product manufactured using a 20 month old batch of ceftazidime carbonate blend.

Based on available stability data, the holding time for finished product intermediate was considered acceptable. The proposed start of shelf life for the finished product, defined as the point of vial filling when the two active substances are filled into the vial, was considered acceptable.

The proposed shelf-life of 36 months when stored in the original package in order to protect from light as stated in the SmPC (section 6.3) is acceptable.

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. For the synthesis of avibactam sodium, the choice of the starting material was justified by providing further information on its route of synthesis and a detailed discussion of the fate and purge of impurities. The applicant has applied QbD principles in the development of avibactam sodium and in the development of the finished product and their manufacturing processes. However, design spaces were not claimed for either.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

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Ceftazidime is a known active substance and CHMP agreed that the available non-clinical data on ceftazidime are acceptable and that no new data need to be generated.

A comprehensive nonclinical testing program for the new active substance avibactam has been conducted.

Safety margins are calculated based on total plasma levels in healthy volunteers given 500 mg avibactam and 2000 mg ceftazidime every 8 hours, 120 minute infusion (study ID D4280C00011). Clinical AUC(0-tau) values have been multiplied by three for comparison to AUC(0-24h) values in toxicology studies. All pivotal studies with avibactam alone and in combination with ceftazidime were conducted in accordance with GLP standards.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of *in vitro* and *in vivo* studies were conducted to determine the activity of avibactam, alone and in combination with ceftazidime. These studies characterised the primary pharmacological mechanism of action, potential for resistance, mechanisms of resistance, bactericidal activity, and potential for synergy as well as spectrum of antibacterial activity. More than 10,500 contemporary isolates collected from hospitalised patients across 15 European Union countries in 2012 were tested for ceftazidime-avibactam susceptibility.

Ceftazidime-avibactam is active against ceftazidime-resistant, and many carbapenem-resistant clinical isolates of *Enterobacteriaceae* and *P. aeruginosa*. It also has *in vitro* antibacterial activity against *Haemophilus influenzae* (MIC_{90} = 0.06 mg/L), and *Moraxella catarrhalis* (MIC_{90} = 0.012 mg/L), whereas *Acinetobacter* spp. are generally not susceptible. In susceptible Gram-positive bacteria, the activity of ceftazidime-avibactam is similar to that of ceftazidime alone e.g. *Streptococcus pyogenes* (MIC_{90} = 0.25 mg/L), *Streptococcus agalactiae* (MIC_{90} = 1 mg/L) and penicillin-susceptible *Streptococcus pneumoniae* (MIC_{90} = 8 mg/L). The MIC_{90} of ceftazidime-avibactam against methicillin-susceptible *Staphylococcus aureus* ranged from 8 to 16 mg/L. In penicillin-non-susceptible *S. pneumoniae* or methicillin-resistant *S. aureus*, which use alterations to essential penicillin binding proteins (PBPs) rather than enzymatic degradation of β-lactams to mediate resistance to ceftazidime, avibactam does not restore the activity of ceftazidime. Similarly, β-lactam-resistant *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria* spp. are also resistant to both ceftazidime and ceftazidime-avibactam.

In time-kill studies against ceftazidime-resistant strains, ceftazidime-avibactam was generally bactericidal for the first 6 h, however by 24 h, various levels of re-growth had occurred. The same regimen, however, was shown to provide killing activity over 24 h in neutropenic mouse thigh and lung infection models against contemporary β-lactamase producing *P. aeruginosa*. Furthermore, the efficacy of ceftazidime-avibactam, dosed at 2000 mg ceftazidime + 500 mg avibactam as a 120-minute IV infusion, q8h, was demonstrated in a pivotal Phase 3 clinical trial (RECLAIM).

The animal models and PK/PD show that avibactam does not adversely affect the antibacterial activity of ceftazidime against Gram-negative or Gram-positive bacteria *in vivo*. Moreover, the data suggests that avibactam restores the activity of ceftazidime *in vivo* and the animal efficacy studies also indicate that ceftazidime- avibactam penetrates into the site of infection in the murine peritoneal cavity, kidney, thigh, and lung, and the cerebrospinal fluid in a rabbit meningitis model.

The *in vivo* study assessing the efficacy of ceftazidime-avibactam in a model of pyelonephritis in the neutropenic mouse was conducted prior to the current reference method of testing the susceptibility to ceftazidime-avibactam was established. Ceftazidime and avibactam were co-diluted in the fixed 4:1 ratio, whereas the reference method now established is to dilute ceftazidime while maintaining the concentration of avibactam fixed at 4 mg/L. However, suitable efficacy was demonstrated on this study and given the extent of clinical data available with ceftazidime-avibactam this was deemed acceptable by CHMP, which considered that this has no relevance for clinical safety.

In the i*n vivo* study assessing the efficacy of ceftazidime-avibactam in a rabbit model of meningitis, the Applicant claimed that the ceftazidime exposure in the CSF represented about 43% of plasma AUC and that the penetration of avibactam exposure in CSF resulted in approximately 38% of the plasma AUC. This claim could not be verified, as the AUC data were not been provided in the final study report. The exposure and subsequent efficacy, however, could be confirmed by mean ceftazidime and avibactam concentration data in both plasma and CSF and from subsequent decreases in bacterial counts in cerebrospinal fluid.

CHMP agreed that from a non-clinical perspective the *in vitro* and *in vivo* primary pharmacology data suitably support this MA application.

Secondary pharmacodynamic studies

No significant activity (defined as >50% inhibition) was detected in receptor/enzyme screens of avibactam at a single concentration of 100 µg/mL. At 1000 µM, avibactam also had no significant inhibitory activity against several mammalian serine proteases during an assessment to determine if there was any avibactam inhibition that might be analogous to its β-lactamase inhibition mechanism. Finally, avibactam had no significant activity at plasmin or thrombin proteases while an IC50 of 1.49 mM was defined for chymotrypsin. This suggests little potential for inducing off-target activity in humans at the clinical dose [human mean free Cmax = 13 µg/mL (49 µM)]. No tests have been conducted with ceftazidime, which is considered acceptable.

Safety pharmacology programme

A full package of safety pharmacology was completed for avibactam alone, which is in accordance with the CHMP guideline CPMP/ICH/539/00 (ICH Topic S7A). Since avibactam was shown not to adversely affect the antibacterial activity of ceftazidime and there are no safety concerns for avibactam, it was agreed by CHMP that combination safety pharmacology studies with ceftazidime-avibactam are not required.

In a rat CNS study in which animals were given 30-minute IV doses of up to 1000 mg/kg, reduced muscle tone, slight miosis, and decreased reactivity to touch were observed in some avibactam-treated animals, together with gastrointestinal changes (defecation/diarrhoea) at 1000 mg/kg. The Applicant argues that the reduced muscle tone, slight miosis, and decreased reactivity to touch were not considered to be test-article related as the incidence was low. Whilst it is agreed that there was a low incidence of animals affected, decreased muscle tone was observed at all doses and reactivity to touch was observed at the mid and high doses (300 and 1000 mg/kg, respectively). No safety concerns for vital signs have been noted in clinical studies. GI effects have been reported clinically.

At up to 300 µM, avibactam was found to weakly block the hERG channel (3.9 ± 2.5%, 15.5 ± 4.6%, and 20.7 ± 6.4%, at 30, 100, and 300 µM, respectively), but an IC50 value could not be defined. There were, however, no effects in the hERG assay tested in transfected human embryonic kidney (HEK293) cells at concentrations of up to 1000 µM in a subsequent GLP study. There were no new safety concerns identified from clinical ECG, hERG and thorough QT studies and therefore CHMP agreed that the effects seen in the initial non-GLP safety pharmacology study are unlikely to translate into patients.

Intravenous administration of avibactam did not produce any adverse effects on arterial blood pressure, heart rate or the ECG intervals, rhythm or waveform morphology in the dog at doses up to 1000 mg/kg (Cmax = 3474 µg/mL; AUC(0 t) = 3646 µg.h/mL). Likewise, at up to 1000 mg/kg in the rat, there were also no effects on respiratory rate, tidal volume, or minute volume (Cmax = 1234 µg/mL; AUC(0-t) = 788 µg.h/mL) or on urinary volume, urinary pH and potassium and creatinine excretion. There was, however, a dose-dependent increase in sodium excretion that was statistically significant at the nominal dose of 1000 mg/kg. As there were no significant increases in urinary sodium reported clinically, CHMP agreed that this finding is unlikely to pose a clinical risk. The Cmax values are approximately 248- and 88-fold (dog and rat, respectively) greater than the exposure data from healthy subjects receiving 500mg avibactam/2000mg ceftazidime on clinical study D4280C00011 Part B, Treatment C (Day 4).

Avibactam induced a statistically significant delay in mean intestinal transit at 2000 mg/kg via the oral route in the rat (54.5% versus 71.9% in control group). The Cmax and corresponding AUC(0-t) values were as follows: Cmax: 83.3 µg/mL; AUC(0-t): 114 µg/mL.h. The Cmax value is approximately 6-fold higher than the exposure data from healthy subjects receiving 500mg avibactam/2000mg ceftazidime on clinical study D4280C00011 Part B, Treatment C (Day 4). CHMP agreed that this had low relevance for the clinical situation where avibactam, in combination with ceftazidime, led to incidences of GI disorders, of which nausea, vomiting, and diarrhoea were the most common adverse events recorded. These findings were expected, as they are also documented on the ceftazidime PI.

Pharmacodynamic drug interactions

The effect of combining ceftazidime-avibactam with other antimicrobial agents that might be co-administered to an infected patient was assessed using the checkerboard method and determining the fractional inhibitory concentrations (FICs) and FIC indices (FICIs). The extent of interaction was determined between ceftazidime or ceftazidime-avibactam and colistin, levofloxacin, linezolid, tigecycline, tobramycin and vancomycin. Twenty-seven isolates were tested, including 3 *E. cloacae*, 5 *E. coli*, 7 *K. pneumoniae*, 6 *P. aeruginosa*, 3 *S. aureus* and 3 *E. faecalis*. No antibacterial antagonism was observed between ceftazidime-avibactam and antibacterial agents of other drug classes.

In another study, avibactam was also investigated for interactions or antagonistic effects of ceftazidime against penicillinase positive and negative strains of MSSA. Again, there was no antagonistic effect of avibactam inhibiting ceftazidime against either penicillinase positive or negative strains of MSSA.

To rule out the potential for interaction between ceftazidime or ceftazidime-avibactam with metronidazole during co-dosing in the intraabdominal clinical trials, studies were performed against target *Enterobacteriaceae* species grown under both aerobic and anaerobic conditions. Metronidazole lacked any activity against several strains of *E. coli* and *K. pneumoniae* under anaerobic conditions. Using the checkerboard method, interactions between ceftazidime-avibactam and metronidazole were investigated under both aerobic and anaerobic conditions against isolates of E. coli and K. pneumoniae expressing a variety of β-lactamases. No interactions were observed between ceftazidime or ceftazidime-avibactam and metronidazole for any of the isolates tested. It could therefore be concluded that metronidazole is likely to have no effect on the activity of ceftazidime-avibactam

against *Enterobacteriaceae* growing under aerobic or anaerobic conditions and that any efficacy observed in studies of intra-abdominal infections caused by these target pathogens is due to the activity of ceftazidime-avibactam alone.

2.3.3. Pharmacokinetics

Ceftazidime

In humans, ceftazidime has a half-life of approximately 1.9 hours following iv administration. In rat and dog, the half-life is reported to be 21 and 49 minutes, respectively. In rat and rabbit, the distribution of ceftazidime after iv or im administration was highest in kidney and liver. Distribution to the respiratory tract and brain occurs to a limited extent, similar to findings in studies conducted with avibactam in combination with ceftazidime. No data on placental or milk transfer for ceftazidime have been presented by the applicant. Cephalosporins, including ceftazidime, are however known to cross the placenta in humans, but there is no evidence of teratogenic or embryotoxic effects available from animals or humans to date. Cephalosporins are generally considered safe during pregnancy. Similar to avibactam, ceftazidime is also excreted in human milk, but in low quantities not expected to have any adverse effect on breastfed infants. Similar to avibactam, Ceftazidime binds poorly to human plasma protein, is not metabolised, and is excreted renally.

Avibactam, and avibactam in combination with ceftazidime

Slightly decreased exposures to avibactam were observed in the dog following 13 weeks of repeat IV dosing when compared to 4 weeks of dosing via the same route. Given the extensive clinical exposure data available and the fact that avibactam showed no significant inhibition of cytochrome P450 enzymes or UGT1A1 and no CYP induction potential within the clinically relevant exposure range, no further non-clinical investigations are required.

Avibactam demonstrated approximately ≤ 22.1% binding to animal plasma proteins (mouse, rat, rabbit and dog) and ranged from 5.7% to 8.2% in human plasma proteins. The use of anticoagulants with avibactam had no effect on plasma protein binding as avibactam was <20% bound across different species. The ratio of *ex vivo* blood/plasma partitioning of unchanged avibactam was 0.69 in the rat and 0.64 to 0.71 in the dog. The *in vitro* human white blood cell partitioning coefficient of avibactam was <10%, suggesting that avibactam has low penetration into blood cells.

Placental transfer of avibactam was evident in both the rat and rabbit, with elimination being faster from maternal circulation than from systemic tissues, including the foetus. Avibactam exposure in rat milk appeared approximately dose-proportional and avibactam concentrations were lower in milk than in plasma 0.5 h after the end of infusion. Very low levels of avibactam (3000-6000 fold lower than in maternal plasma) were detected in weaning pups. The lack of data on avibactam excretion in human milk has been adequately addressed in the Zavicefta SmPC (section 4.6).

In the single IV dose tissue distribution studies, the terminal half-life of radioactivity in rat plasma was estimated at approximately 42 hours. The radioactive half-life in most of the organs analysed was similar to that observed in plasma, except for non-pigmented skin (72 hours) and fat (76 hours).

Avibactam was rapidly excreted in urine in all non-clinical species via glomerular filtration, accounting for approximately 82% of the infused dose. Faecal excretion accounted for approximately 17%, 4.6% and 0.6% of the dose in the rat, dog and rabbit, respectively. Biliary excretion *in vivo* was not evaluated as the major route of elimination of avibactam is via urine.

Avibactam (but not ceftazidime) is also eliminated by transport (via OAT1 and OAT3) across the renal epithelium; therefore drugs that induce or inhibit the OAT1 and/or OAT3 transporters may affect

avibactam blood concentrations. Section 4.5 of the Zavicefta SmPC advises that CAZ-AVI should not be co-administered with probenecid or other drugs which induce or inhibit OAT1 and/or OAT3.

In studies assessing the transporter inhibition and substrate potential of avibactam, inhibition of OAT1 and OAT3 by avibactam occurred only at exposures in excess of those seen clinically and therefore this is unlikely to have clinical relevance.

Avibactam did not have any inhibitory properties or time dependent inhibition of human CYP activities (CYP1A2, 2A6, 2B6, 2C8, 2C19, 2D6, 2E1 and 3A4/5) at concentrations up to 200 µM. There was no time-dependent inhibition of CYP2C9 activity, but inhibition (29%) was recorded at the highest concentration of 200 µM, which is approximately 4-fold higher than human free C_{max} (49 µM). An additional study conducted at concentrations ranging from 1.0 to 5000 µM indicated that avibactam did not inhibit CYP2C9 activity at concentrations below 5000 µM (1326 µg/mL), which is approximately >100-fold the C_{max} at the intended human dose. These data suggest that avibactam has minimal potential for P450-dependent drug-drug interactions in humans at clinically relevant concentrations.

CHMP noted that the applicant did not discuss the transporter inhibitor constant (Ki) values in terms of the unbound free fraction. However, a study assessing the ability of avibactam to inhibit CYP2C9 in human liver microsomes showed that avibactam had an inhibition rate of 36% at 5 mM (highest concentration tested), with an estimated Ki value as 11 mM (based on the inhibition at the highest concentration only). Since avibactam has been shown not to have any inhibition potential within the clinically relevant exposure range, CHMP agreed that no further studies are required.

No PK drug-drug interactions were observed between avibactam and ceftazidime following single or repeat IV administration to rats and dogs for up to 28 days. Ceftazidime did not interact with the active uptake of avibactam into the proximal tubular cells in the kidney in an *in vitro* HEK cell model.

A known degradation product (metabolite M1), was detected in the formulation used to metabolically profile rat and dog excreta (study no. A051246). Avibactam decarbonyl (M1) has been toxicologically qualified up to a minimum of 0.7% in the 28 day intravenous study in the beagle dog and at 0.67% in the 13 week rat study, which exceeds the toxicological qualification threshold of 0.2%. The final drug product specification for M1 has a limit of NMT 0.5%, which is within the limit of toxicological qualification.

2.3.4. Toxicology

The nonclinical safety evaluation program for avibactam included toxicity studies of up to 3 months duration in rats and dogs, genetic toxicology, reproductive toxicology (male and female fertility in rats, embryo-foetal development in the rat and rabbit, and pre-and post-natal development in the rat), immunotoxicology, local tolerance studies and an *in vitro* phototoxicity study.

Ceftazidime is a marketed antibiotic with an established nonclinical and clinical safety profile that is as expected for a β-lactam agent. A summary of the nonclinical studies performed on ceftazidime by the Sponsors for the original marketing application is reported in the literature (Capel-Edwards et al, *Journal of Antimicrobial Chemotherapy* (1981)). Based on the knowledge of the ceftazidime safety profile and the absence of any nonclinical safety concerns for avibactam, combination genetic toxicology and reproductive toxicology studies have not been conducted. However, in accordance with ICH M3(R2), general toxicity studies using the combination at the intended clinical ratio have been conducted. Further, a juvenile toxicity study has also been conducted with the combination.

Single dose toxicity

Treatment with avibactam at 2000 mg/kg following a single 30 minute infusion via the tail vein in the mouse and rat was associated with haematomas and/or crusts on the tail. No deaths occurred with either species. In the mouse, no other associated test article-related effects were observed. In the rat, reduced body weight gain was observed in males during the first week of the study. The minimum lethal IV dose of avibactam was therefore deemed to be >2000 mg/kg in both the mouse and rat. No single-dose toxicity studies were conducted with avibactam in combination with ceftazidime. This is considered acceptable by CHMP, in view of the findings with avibactam, and the known safety profile of ceftazidime.

Repeat dose toxicity

Repeat-dose rat and dog toxicity studies have been conducted with avibactam, and with avibactam in combination with ceftazidime. No additional studies were conducted with ceftazidime alone, and this was considered acceptable by CHMP.

Repeat dose toxicology studies were conducted in rats and dogs of up to 4 and 13 weeks in duration via the IV route of administration with avibactam. In addition, studies of up to 4 weeks duration were conducted in the same species with avibactam and ceftazidime alone or in combination with one another in a 4:1 ratio (ceftazidime:avibactam). Doses of up to 1200 mg/kg/day avibactam and 2000 mg/kg/day ceftazidime were given to animals. In the combination studies doses of 0/0, 0/500, 2000/0, 666/167 and 2000/500 mg/kg/day CAZ-AVI were given to rats and doses of 0/0, 1000/0, 500/125 and 1000/250 mg/kg/day CAZ-AVI were given to the dogs.

In the pivotal 4-week GLP studies with avibactam (167, 500, 1000 or 1200 mg/kg/day), male rats treated with 1200 mg/kg/day were euthanized early due to local tolerance issues at the injection site. Three premature deaths also occurred (1 at each lower dose level) that were attributed to stress in the restraining tube. The main finding was lesions on the tail (injection sites), including haematoma, dryness, wounds, shortened tail, blackish colour and scabs, predominantly at ≥1000 mg/kg/day with some recovery. This correlated with the test article-related microscopic observations in and around the injection sites at all doses. Decreased body weight gain was seen in males at 1200 mg/kg/day and in females at 1000 mg/kg/day, with no corresponding food consumption effects. Slight increases in fibrinogen in males at 1200 mg/kg/day and decreased inorganic phosphorus in both sexes at 1000 mg/kg/day were deemed to be of limited toxicological importance. The NOEL was 167 mg/kg/day (based on injection site effects).

In the 4-week dog study, there were no major test article-related toxicological findings at 250, 500 or 1000 mg/kg/day avibactam. Sporadic emesis was noted in 2 animals of each sex at 1000 mg/kg/day and in 1 female at 500 mg/kg/day, which was deemed to be of limited toxicological importance. At necropsy, lesions were noted at the injection sites, comprising haemorrhage, subacute inflammatory lesions, collagen degeneration and dermal/subcutis fibrosis in the vein and adjacent subcutis lesions. The incidence and severity of the lesions was slightly greater at 1000 mg/kg/day. The NOEL was 500 mg/kg/day.

The 13-week IV rat study with avibactam (65, 125 or 250 mg/kg/day) resulted in poor clinical condition of the animals, which led to early mortality in all groups, including controls. Abscesses were observed in one or more organs, including controls, which were attributed to the dosing procedure. One male animal at 65 mg/kg/day had a malignant lymphomatous infiltration in the liver, spleen, lung and sternal bone marrow. Nodules were recorded in the lung and pancreas in females at 125 mg/kg/day. Reduced haemoglobin concentration and packed cell volume, with increases in fibrinogen were attributed to inflammatory processes.

Males at 250 mg/kg/day had increases in spleen weights with minimal myeloid hyperplasia, which was considered to be related to the presence of abscesses. In animals with no abscesses, thrombus at the injection site, with or without chronic inflammation was observed. The applicant deemed the NOAEL to be 250 mg/kg/day. It is unclear as to the link between the development of malignant lymphomatous infiltration in the liver, spleen, lung and sternal bone marrow and the presence of abscesses in the male dosed at 65 mg/kg/day. Since this finding was only recorded in one animal with no dose response and was not seen in any other non-clinical species and the proposed clinical exposure is of short duration (<28 days), it is unlikely to translate into a clinical risk.

In the 13-week IV dog study with avibactam (65, 125 or 250 mg/kg/day) no major test article-related effects were noted at any dose. Histological changes observed were mainly at the injection sites and showed a similar incidence and/or severity in controls and treated groups. A relationship to treatment, therefore, could not be established. The NOAEL was considered to be 250 mg/kg/day, which was agreed upon by CHMP.

In the 4-week rat IV combination study poor tolerance at the injection sites at 2000 mg/kg/day CAZ and 2000/500 mg/kg/day CAZ-AVI led to early termination of these groups on day 15. Further mortality, as a result of poor local tolerance, also occurred in males at 500 mg/kg avibactam. Piloerection (2000/500 mg/kg/day CAZ-AVI), tail lesions (all treated groups), decreased body weight gain and food consumption (males treated with CAZ alone or 2000/500 mg/kg/day CAZ-AVI) and increased urine colour (CAZ alone or high-dose combination) were noted. Changes in haematological parameters and histopathological findings in all treated groups were associated with the poor local tolerance at the injection site. There was no evidence that avibactam was adding to the toxicity of ceftazidime, although the severity of the tolerability findings appeared to increase with the combination of ceftazidime and avibactam.

The derivation of the NOEL was not agreed since the animals dosed at 2000/500 mg/kg/day CAZ-AVI did not complete the full 28 day study duration, which is needed to support this MAA. However, since there were no major findings in the clinical safety studies the data obtained over 14 days in the rat is accepted by CHMP.

In 4-week IV combination study in the dog, emesis and excessive salivation (mainly in the females) were noted at 1000 mg/kg/day (CAZ only), 500/125 mg/kg/day (CAZ-AVI) and 1000/250 mg/kg/day (CAZ-AVI. Lower systolic and diastolic blood pressures (up to -35%) were seen in males at 1000 mg/kg/day ceftazidime (alone or in combination), but at 500 mg/kg/day ceftazidime (in combination with avibactam at 125 mg/kg/day) there were no effects on systolic or diastolic blood pressure. There are currently no reports of blood pressure effects in the clinical studies with ceftazidime. Based on the combined ceftazidime AUC and C_{max} for ceftazidime in both sexes at 500/125 mg/kg/day on day 28 (1186 µg.h/mL and 1192 µg/mL, respectively) the margins of safety would be approximately 1.3 for AUC and 12 for C_{max} based on exposure data from healthy subjects receiving 2/0.5 g CAZ-AVI.

High cholesterol (all treated groups) and triglycerides was seen in all treated females and males at 1000 mg/kg/day ceftazidime (alone or in combination). Urine volumes were higher in females given ceftazidime alone. Liver weights were higher at 1000 mg/kg/day ceftazidime (alone or in combination), which correlated with centrilobular hepatocellular hypertrophy. The applicant suggests that all these indicated an effect of ceftazidime. Low thymus weights in male dogs, mainly at 1000 mg/kg/day ceftazidime, were associated lymphoid depletion. Although a test article relationship cannot be excluded, this was most probably due to stress (as a result of the high incidence of emesis). Histopathological findings were recorded at the injection site only, which were related to the injection procedure and of no toxicological importance.

Compared to the individual agents, no new effects or unexpected toxicities were observed when avibactam was administered in combination with ceftazidime via the IV route in a 1:4 ratio. The main finding in both species concerned tolerability at the injection sites, the severity of which appeared to increase with the combination of ceftazidime and avibactam in the rat, but not in the dog.

In the combined (avibactam or ceftazidime) 4 week rat study using a combined AUC and C_{max} for avibactam in both sexes at 666/167 mg/kg/day on day 13 (92.5 µg.h/mL and 146 µg/mL, respectively) the margins of safety would be approximately 10 for C_{max}.

Genotoxicity

Three screening genotoxicity studies and four pivotal GLP genotoxicity studies were conducted with avibactam alone. Avibactam was negative for genotoxicity in a bacterial mutagenicity assay, in in vitro and in vivo micronucleus assays and in two in vitro rat liver UDS assays. In one mammalian chromosomal aberration assay in human lymphocytes, avibactam induced a small, non-reproducible, significant increase in chromosome aberrations at cytotoxic concentrations. These initial findings were not evident in a second assay at concentrations up to 5000 µg/mL avibactam. Overall, based on these results, it can be considered that avibactam was negative in the Ames assay, unscheduled DNA synthesis, chromosomal aberration assay and rat micronucleus test.

No genotoxicity studies have been conducted with ceftazidime or with ceftazidime/avibactam. This is considered acceptable by CHMP, based on the known safety profile ceftazidime (Capel-Edwards et al., 1981), and the absence of any nonclinical safety concerns for avibactam.

Carcinogenicity

No carcinogenicity studies were conducted with avibactam alone or in combination with ceftazidime due to the intended duration of therapy (<28 days), which is in line ICH guideline S1A. CHMP considered therefore that the lack of carcinogenicity studies is acceptable.

Reproduction Toxicity

No additional reproduction toxicity studies have been conducted with ceftazidime. The established safety profile of ceftazidime does not indicate any toxic potential to reproduction (Capel-Edwards et al., 1981).

Avibactam did not affect female fertility/reproductive performance or embryofoetal development following repeat IV administration to rats at doses up to 250 mg/kg/day. Small decreases in epididymal and prostate weights at 1000 mg/kg/day in the male fertility study were considered to be a secondary effect to a decrease in bodyweight gain at all doses.

In the rat embryofoetal development study, there were two malformed foetuses at 500 mg/kg/day (one with domed head, protruding tongue, malrotated right hind limb and hyperextension of the right forepaw and a second with scoliosis) and at 1000 mg/kg/day (anophthalmia). Given that not all external, visceral, and skeletal malformations were noted in the background data and that exposure to avibactam at 500 mg/kg/day was higher than that at 1000 mg/kg/day, the applicant's conclusion that the findings did not suggest an involvement of avibactam was questioned. Since there were no malformations and no overall effects on embryo-foetal development at 250 mg/kg/day, the exposures at this dose were considered as an appropriate reference for a no observed effect level (NOEL) for embryofoetal changes in the rat.

In the rabbit embryofoetal development study, there was an increased post-implantation loss at 1000 mg/kg/day and lower mean foetal weights with slightly retarded ossification of the metacarpal of the first digit, tarsal bone and sixth sternebra was observed at 300 mg/kg/day and above. There were no

other overt findings at 100 mg/kg/day and this dose is therefore deemed to be the NOEL for embryofoetal changes in the rabbit and the no observed adverse effect level (NOAEL) for maternal toxicity. The margins of safety at these exposures would be approximately 2.4 for AUC0-t and 22 for Cmax based on exposure data from healthy subjects receiving 2 g/0.5 g CAZ-AVI.

Avibactam administered alone during pregnancy and lactation to F0 rats was associated with a dose-related increase in the incidence of renal pelvic dilatation and ureter dilatation, with no associated pathological changes to the renal parenchyma. There was no evidence of recovery in the renal pelvic dilatation but the ureteric dilations were not seen in the young adult offspring. These findings were considered to be associated with administration of avibactam. The dose of 120 mg/kg/day is considered to be the NOEL for the unilateral or bilateral renal pelvic dilatation and/or luminal dilatation of the ureters.

The margins of safety at these exposures would be approximately 1.3 for AUC0-t and 11 for Cmax, based on exposure data from healthy subjects receiving 2 g/0.5 g CAZ-AVI. However, the possibility that these findings may be relevant for humans cannot be excluded, so the applicant has adequately addressed the findings in the kidneys and ureters from a reproductive toxicology perspective in sections 4.6 and 5.3 of the SmPC, which is acceptable.

The SmPC adequately addresses use in pregnancy. This combination is intended to be used in the controlled environment of a hospital for not more than 14 days (i.e. short duration of dosing) so that the reproductive data are sufficient to support this application.

No reproductive studies were conducted with ceftazidime in combination with avibactam based on the results observed with the individual compounds. This is considered acceptable by CHMP.

Local Tolerance

The applicant has assessed the local tolerance of avibactam, using data from the repeat dose toxicology studies and via a local tolerance study in the rabbit. Avibactam tolerance was assessed both alone and in combination with ceftazidime. Following repeated dosing in rats, substantial local reactions to ceftazidime and/or avibactam via peripheral vein were dose related. The severity of these findings appeared to increase with the combination, but this was not observed in the dog.

Other toxicity studies

An immune cell phenotyping test of avibactam at 0, 250, 500 and 1000 mg/kg/day in Sprague Dawley rats showed no depletions in CD3, CD4, CD8, NK cells (CD3-/CD161+) or NK T cell (CD3+/CD161+) populations. Cytotoxicity and plaque forming cell (PFC) assays indicated that there was no depletion of immune function. For the specific CD45RA B-cell subpopulation, lower values were observed in males at 500 and 1000 mg/kg/day, but without a dose-relationship. This result is considered equivocal with respect to biological relevance, since there were no associated depressions in B-cell function in the PFC assay. There were no histological changes in the lymphoid organs at any dose of avibactam.

Avibactam was detected in 11 of 12 control animals in this study, with plasma concentrations in three animals at day 21 (4078, 2232 and 1046 ng/ml in animal 8, 18 and 20, respectively) in line with the avibactam-levels in the dosed groups at 4 hours post-dosing. Historical control data on T-cell subsets, demonstrated that CD3, CD4 and CD8 T-cells in control animals are within the historical control range, thereby suggesting that any potential contamination did not significantly affect the T cell subset levels. Results from a keyhole limpet hemocyanin (KLH) assay, without contamination, indicated that T- and B-cell function is not impaired, which supports the lack of findings in the direct Plaque Forming Cell (PFC) assay in the immunotoxicity study. As a result, the immunotoxicity study is considered

acceptable even though the source of contamination is not known. Avibactam therefore has no adverse effects on the immune function in rats at intravenous doses up to 1000 mg/kg/day for 4 weeks.

All impurities which require qualification according to ICH guidelines (ICH Q3B (R2)) have been adequately qualified in the toxicology studies. The applicant has conducted a mutagenic assay for the potential impurity AZ1359137. Since AZ13591372 was negative in this assay, it is considered a non-mutagenic impurity and should be treated as such by the applicant.

Avibactam did not absorb in the UV wavelength (290 to 700 nm) and was negative in the in vitro Balb/c3T3 fibroblasts assay and is therefore considered not to have a photosafety concern.

Avibactam showed no potential to haemolyse human red blood cells in vitro at concentrations up to and including 20 mg/mL (alone) or at 5 mg/mL when in combination with 20 mg/mL ceftazidime.

Juvenile Toxicology

Two investigative studies were conducted to assess the renal cysts in neonatal/juvenile rats. The evidence from these two studies, combined with the lack of renal cysts in the repeat dose toxicity studies in the same species/strain of rat, suggests that the findings in the juvenile toxicity study are background lesions from one specific breeding facility. CHMP considered that it was therefore unlikely that the renal cysts have any clinical significance since they appear to arise spontaneously in untreated rats.

Ceftazidime/avibactam was dosed via an IV bolus injection into the tail vein of suckling rats once daily for 14 days from post-natal Day 7 to post-natal Day 20, using the intended clinical ratio of 4:1 ceftazidime: avibactam. Renal cortical cysts in all groups, including controls, were observed at necropsy and by histology and were still present at the end of the 5 week recovery phase. The cysts covered a small proportion of the cortex and did not appear to have any significant implications for the animals (no adverse clinical signs, no effects on body weight gain and no significant changes in clinical pathology or organ weights). Evidence from two additional supportive studies and the lack of renal cysts in the repeat dose toxicity studies in the same species/strain of rat, suggests that the findings are background lesions from one specific breeding facility. A reversible increase in extramedullary haematopoiesis was observed in the spleen and liver of both sexes at 455/115 mg/kg/day CAZ-AVI. Although not discussed by the applicant, one female at 50/13 mg/kg/day on PND 21 and one female at 455/115 mg/kg/day on PND 56 had unilateral pelvic dilatation in the kidney. These observations are consistent with findings from the pre- and postnatal development study, which were associated with administration of avibactam. The NOAEL is considered to be 455 /115 mg/kg/day CAZ-AVI.

The applicant has provided an additional discussion on the clinical relevance of the renal cortical cysts findings in the rat juvenile study. CHMP concluded that the cysts observed are substantially distinct from human polycystic renal disease where the numerous cysts disrupt the architecture of the kidney and affect renal function. In addition, nephrogenesis is still on-going in juvenile rats of the age used in the toxicology studies, whereas it is complete by 34 weeks gestation in humans, implying that the renal findings observed in the juvenile rats are unlikely to be relevant for humans. Furthermore, based on the nature and very low number of the renal cortical cysts, reflecting an effect on a minimal number of individual nephrons (i.e. each cyst indicating one single nephron), CHMP considered that should the finding occur in humans it would not have any clinical impact in paediatric patients, including pre-term neonates.

The cysts in the rat juvenile toxicity study covered a small proportion of the cortex and did not appear to have any significant implications for the animals. The observed cysts are known to be a common background finding in the developing kidney of Sprague-Dawley rats, are not seen in young adult

animals and appeared to produce only a little or no morphological change. CHMP agreed therefore that the cortical cysts have little relevance for humans, and would have no clinical impact should they arise.

2.3.5. Ecotoxicity/environmental risk assessment

Table 10 Summary of main study results ceftazidime

Substance (INN/Invented Name): Ceftazidime			
CAS-number (if available): 78439-06-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- logD_{ow}[a]	OECD107	LogD_{ow} < -2.20 (pH5) LogD_{ow} < -2.21 (pH7) LogD_{ow} < -2.17 (pH9)	Potential PBT **No**
PBT-statement :	**The log D values for ceftazidime are < 4.5 at all environmentally relevant pHs, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	30	µg/L	**>0.01 threshold Y**
$PEC_{surfacewater}$, refined	0.060	µg/L	**>0.01 threshold Y Used for Tier A assessment.**
Other concerns (e.g. chemical class)	None		
Outcome of Phase I :	**Both the default and refined PECsw values are > 0.01 µg/L action limit and therefore a Phase II environmental fate and effect analysis is required. The refined $PEC_{surfacewater}$ value to be used for Tier A assessment as a probable worst-case.**		

Phase II Tier A Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	≥1000 mg/L (pH5 and 7) No result (pH9)	Rapid hydrolysis of ceftazidime occurred at pH9 and therefore water solubility at this pH was not determined.
Definitive Hydrolysis	OECD 111	pH 5 half-life: 495 h at 25ºC; 31.4 h at 50ºC; 11.6 h at 60ºC. pH 7 half-life: 433 h at 25ºC; 21.9 h at 50ºC; 7.11 h at 60ºC. 35.4 h at pH 9 half-life: 25ºC; 9.09 h at 50ºC; 3.21 h at 60ºC.	Ceftazidime is hydrolytically unstable at pH 5, 7 and 9. The calculated hydrolysis half lives were 495, 433 and 35.4 hours at pH 5, 7 and 9, respectively.
Ready Biodegradation	OECD 301	<2.1% mineralisation after 28 days	Not readily biodegradable
Inherent Biodegradation	OECD 302B	65% biotic degradation after 14 days 31% abiotic degradation after 14 days	Degradation of Ceftazidime dihydrochloride is, in part, an abiotic process.

Adsorption-Desorption	OECD 106		Ceftazidime is not predicted to adsorb to solids during wastewater treatment. **>3700 L/Kg threshold N**.
Aerobic Transformation in Aquatic Sediment systems	OECD 308	Total system half-life (DT_{50}): 2.31 days high organic matter sediment (HOM); 9.99 days low organic matter sediment (LOM) Mineralisation (Day 93): 9.3% HOM 31.2% LOM One significant degradation product, M3, >10% of radioactivity in both the HOC and LOC systems. DT_{50} values = 20.8 and 101 days in the HOC and LOC, respectively. In the LOC a second metabolite M1, had a calculated half-life of 118 days. Mass Balance (day 14) : 88.6% to 112.2% (LOC); 87.2% to 98.4% (HOC).	Ceftazidime predicted to rapidly degrade into a number of degradation products. Ceftazidime anticipated not persisting in the aquatic environment.
Outcome of Phase IIA Physical-chemical properties and fate:	**The adsorption coefficient ($Kd_{(ads)}$) is < 3700 L/Kg and therefore a Tier B assessment of the terrestrial compartment is not required. As greater than 10% of the radioactivity was associated with the sediment phase, the effect of ceftazidime on sediment-dwelling organisms is required.**		

	% Organic Carbon	Mean Kd_{ads}	Mean Koc^{ads}
HOC soil A	3.8	1.36	34.0
LOC soil B	0.59	0.204	32.8
HOC sediment A	6.9	39.6	785
LOC sediment B	0.33	0.079	29.2
Activated sludge	35.7	0.961	2.64

HOC: High organic carbon
LOC: Low organic carbon

Phase II Tier A Effect studies

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} (3h) NOEC (3h)	> 1 1[b]	mg/L mg/L	[b]Used to calculate $PNEC_{microorganism}$
Algae, Growth Inhibition Test (green algae)	OECD 201	LOEC (72h) NOEC (72h)	>120 120	mg/L mg/L	*Selenastrum capricornutum (aka Pseudokirchneriella subcapitata)*
Algae, Growth Inhibition Test (blue green algae)	OECD 201	LOEC (72h) NOEC (72h)	0.025 0.013[c]	mg/L mg/L	*Anabaena flos-aquae* [c]Used to calculate $PNEC_{surfacewater}$
Daphnia sp. Reproduction Test	OECD 211	LOEC (21d) NOEC (21d)	>9.2 9.2[d]	mg/L mg/L	*Daphnia magna* [d]Used to calculate $PNEC_{groundwater}$
Fish Early-Life Stage Toxicity	OECD 210	LOEC (32d) NOEC (32d)	>8.0 8.0	mg/L mg/L	*Pimephales promelas*
$PNEC_{surfacewater}$ **$PEC/PNEC_{surfacewater}$**			1.3 **4.6×10^{-2}**	µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{groundwater}$			0.0015	µg/L	Unlikely to

$PNEC_{groundwater}$ **$PEC / PNEC_{groundwater}$**			920 **1.6×10^{-5}**	µg/L	represent a risk to the aquatic environment
$PNEC_{microorganisms}$ **$PEC / PNEC_{microorganisms}$**			100 **6.0×10^{-4}**	µg/L	Unlikely to represent a risk to wastewater micro-organisms
Phase II Tier B Studies					
Sediment-Water Chironomid Toxicity test	OECD 218	Total No. adults emerged Time to emergence. LOEC (28d) NOEC (28d)	No effects No effects >100 100	 mg/kg mg/kg	*Chironomus riparius*. PEC/PNEC ratio <1. Ceftazidime unlikely to represent a risk to terrestrial or sediment dwelling organisms.
$PEC_{sediment}$ $PNEC_{sediment}$ **$PEC / PNEC_{sediment}$**			0.56 1000 **5.6×10^{-4}**	µg/kg µg/kg	

Table 11 Summary of main results avibactam

Substance (INN/Invented Name): Avibactam			
CAS-number (if available): 1192491-61-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- $\log D_{ow}$[a]	OECD107	$LogD_{ow}$ < -1.39 (pH5) $LogD_{ow}$ < -1.36 (pH7) $LogD_{ow}$ < -1.30 (pH9)	Potential PBT **No**
PBT-statement :	**The log D values for avibactam are < 4.5 at all environmentally relevant pHs, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	7.5	µg/L	**>0.01 threshold Y**
$PEC_{surfacewater}$, refined	0.015	µg/L	**>0.01 threshold Y Used for Tier A assessment.**
Other concerns (e.g. chemical class)	None		
Outcome of Phase I :	**Both the default and refined PECsw values are > 0.01 µg/L action limit and therefore a Phase II environmental fate and effect analysis is required. The refined $PEC_{surfacewater}$ value to be used for Tier A assessment as a probable worst-case.**		
Phase II Tier A Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	>1020 mg/L (pH5) >1040 mg/L (pH7) No result (pH9)	Significant degradation of avibactam occurred at pH9 and therefore water solubility at this pH was not determined.
Definitive Hydrolysis	OECD 111	pH 5 half-life: 42 days at 25ºC; 16 days at 40ºC; 8.1 days at 50ºC. pH 7 half-life: 36 days at 25ºC; 8.6 days at 40ºC; 3.7 days at 50ºC.	Avibactam is hydrolytically unstable at pH 5, 7 and 9. The calculated hydrolysis half lives were 42, 36 and 4

		pH 9 half-life:	4.0 days at 25ºC; 0.82 days at 40ºC; 0.31 days at 50ºC.	days at pH 5, 7 and 9, respectively.
Aerobic Biodegradation	OECD 301B	<11% degradation after 28 days		Not readily biodegradable
Adsorption-Desorption	OPPTS 835.1110	Kd_{ads} = 5.1 L/Kg		Avibactam is not predicted to adsorb to solids during wastewater treatment. **>3700 L/Kg threshold N**.
Aerobic Transformation in Aquatic Sediment systems	OECD 308	Total system half-life: Mineralisation (Day 100): No degradation products representing >10% of the applied radioactivity were observed. Mass Balance = 100 ± 10%	7 days high organic matter sediment (HOM); 16 days low organic matter sediment (LOM) 72% HOM 73% LOM	Avibactam predicted to undergo significant mineralisation and primary degradation and will not persist in the environment.
Outcome of Phase IIA Physical-chemical properties and fate:	**The adsorption coefficient ($Kd_{(ads)}$) is < 3700 L/Kg and therefore a Tier B assessment of the terrestrial compartment is not required. As greater than 10% of the radioactivity was associated with the sediment phase, the effect of avibactam on sediment-dwelling organisms is required.**			

Phase II Tier A Effect studies

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} (3h) NOEC (3h)	> 1 1[b]	mg/L mg/L	[b]Used to calculate $PNEC_{microorganism}$
Algae, Growth Inhibition Test	OECD 201	EC_{50} (48h) NOEC (48h)	>120 120	mg/L mg/L	*Selenastrum capricornutum (aka Pseudokirchneriella subcapitata)*
Daphnia sp. Reproduction Test	OECD 211	LOEC (21d) NOEC (21d)	>100 100[c]	mg/L mg/L	*Daphnia magna* [c]Used to calculate $PNEC_{groundwater}$
Fish Early-Life Stage Toxicity	OECD 210	LOEC (32d) NOEC (32d)	>2.0 2.0[d]	mg/L mg/L	*Pimephales promelas* [d]Used to calculate $PNEC_{surfacewater}$
$PNEC_{surfacewater}$ **$PEC / PNEC_{surfacewater}$**			200 **7.5×10^{-5}**	µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{groundwater}$ $PNEC_{groundwater}$ **$PEC / PNEC_{groundwater}$**			0.0038 10000 **3.8×10^{-7}**	µg/L µg/L	Unlikely to represent a risk to the aquatic environment
$PNEC_{microorganisms}$ **$PEC / PNEC_{microorganisms}$**			100 **1.5×10^{-4}**	µg/L	Unlikely to represent a risk to wastewater micro-

					organisms
Phase II Tier B Studies					
Sediment-Water Chironomid Toxicity test	OECD 218	Total No. adults emerged Time to emergence. LOEC (28d) NOEC (28d)	No effects No effects >300 300	 mg/kg mg/kg	*Chironomus riparius*. PEC/PNEC ratio <1. Avibactam unlikely to represent a risk to terrestrial or sediment dwelling organisms.
$PEC_{sediment}$ $PNEC_{sediment}$ **$PEC/PNEC_{sediment}$**			0.016 3000 **5.3×10^{-6}**	µg/kg µg/kg	

CHMP agreed that the environmental toxicity profiles were established for avibactam and ceftazidime, in accordance with the ERA guideline. It was noted that the study on ceftazidime transformation in water/sediment systems (OECD 308) showed that both main transformation products M1 and M3 are very persistent as the DT_{50} values in the low organic content (LOC) system are higher than 60 days. As a result, Zavicefta should be considered as very persistent. The revised PEC/PNEC ratios indicate that avibactam and ceftazidime are unlikely to present a risk to sediment dwelling organisms.

2.3.6. Discussion on non-clinical aspects

Ceftazidime is a known active substance and CHMP agreed that no new non-clinical data need to be generated for ceftazidime. A comprehensive nonclinical testing program for the new active substance avibactam has been conducted by the Applicant. Animal models and PK/PD demonstrate that avibactam does not adversely affect the antibacterial activity of ceftazidime and restores the activity of ceftazidime against beta-lactamase-producing bacteria within its spectrum of activity and within the range of inhibition of avibactam. In a non-GLP study, avibactam was found to weakly block the hERG channel at up to 300 µM, with no IC_{50} value defined. There were no signals observed in a subsequent GLP study at up to 1000 µM and no safety concerns were identified in clinical studies, so the effect seen in the non-GLP safety pharmacology study is unlikely to transfer into patients. Intravenous administration of avibactam had no clinically relevant effects on the cardiovascular, respiratory, gastrointestinal or renal systems. Slightly decreased exposures to avibactam were observed in the 13 week intravenous dosing dog study when compared to 4 weeks of dosing, but since avibactam showed no inhibition of cytochrome P450 enzymes or UGT1A1 and no CYP induction potential within the clinically relevant exposure range, no further investigations are required. Avibactam had no effect on plasma protein binding and has low penetration into blood cells. Evidence showed that avibactam crosses the placenta and is also excreted in rat milk. The lack of data on avibactam excretion in human milk is addressed in the Zavicefta SmPC.

Avibactam is readily excreted in urine and is also eliminated by OAT1 and OAT3 transport across the renal epithelium (but not ceftazidime). Blood concentrations of avibactam may therefore be affected by other drugs which induce or inhibit OAT1 and/or OAT3 transportation. No PK drug-drug interactions were observed between avibactam and ceftazidime following single or repeat IV administration to rats and dogs for up to 28 days and ceftazidime does not interact with the active uptake of avibactam into the proximal tubular cells in the kidney.

The minimum lethal single IV dose of avibactam is >2000 mg/kg in both the mouse and rat. Following daily intravenous administration of avibactam for 4-weeks, the No Observed Effect Level (NOEL) was deemed to be 167 and 500 mg/kg/day in the rat and dog, respectively. In both species, the main findings at higher doses were associated with local tolerance issues at the injection site. In the 13-

week rat study, malignant lymphomatous infiltration in the liver, spleen, lung and sternal bone marrow was seen in one male dosed at 65 mg/kg/day (low dose), but it is unclear as to the link between the development of this finding and the presence of abscesses. Since this was only recorded in one animal with no dose response and was not seen in any other non-clinical species and the proposed clinical duration is of a short duration (<28 days), it is unlikely to translate into a clinical risk. In the dog, no major test article-related effects were noted at any dose. In both species the No Observed Adverse Effect Level (NOAEL) was deemed to be 250 mg/kg/day. In the 4-week rat IV combination study, the derivation of the NOEL was not agreed since the animals dosed at 2000/500 mg/kg/day CAZ-AVI did not complete the full 28 day study duration, which is needed to support this MAA. However, since there were no major findings in the clinical safety studies the data obtained over 14 days in the rat is accepted. In the 4-week IV combination study in the dog, emesis, excessive salivation (mainly in the females), together with increases in cholesterol, triglycerides and liver weights (with associated centrilobular hypertrophy) indicated an effect of ceftazidime. Lower systolic and diastolic blood pressures in males at 1000 mg/kg/day ceftazidime (alone or in combination) were also attributed to ceftazidime. At 500 mg/kg/day ceftazidime (in combination with avibactam at 125 mg/kg/day) there were no effects on systolic or diastolic blood pressure. There are currently no reports of blood pressure effects in the clinical studies with ceftazidime.

No major systemic toxicity was observed with avibactam or ceftazidime either alone or in combination; the main issue identified was local tolerance at the injection site in all non-clinical species used. The clinical relevance of this has been taken into account since the applicant has stated that adverse drug reactions were seen in the clinical trials with avibactam but there were no reports of severe reactions or patient discontinuations due to injection site tolerability. No new effects or unexpected toxicities were observed when avibactam was administered in combination with ceftazidime in a 1:4 ratio to rats and dogs compared to the individual agents.

Avibactam tested negative in the Ames assay, unscheduled DNA synthesis, chromosomal aberration assay and rat micronucleus test. No carcinogenicity studies were conducted with avibactam alone or in combination with ceftazidime.

Avibactam did not affect female fertility/reproductive performance or embryofoetal development following repeat IV administration to rats at doses up to 250 mg/kg/day. Small decreases in epididymal and prostate weights at 1000 mg/kg/day in the male fertility study were considered to be a secondary effect to a decrease in bodyweight gain at all doses. Two malformed foetuses at 500 mg/kg/day (one with domed head, protruding tongue, malrotated right hindlimb and hyperextension of the right forepaw and a second with scoliosis) and at 1000 mg/kg/day (anophthalmia) were reported in the rat embryofoetal development study. Given that not all external, visceral, and skeletal malformations were noted in the background data and that exposure to avibactam at 500 mg/kg/day was higher than that at 1000 mg/kg/day, the applicant's conclusion that the findings did not suggest an involvement of avibactam was questioned. However, since there were no malformations and no overall effects on embryo-foetal development at 250 mg/kg/day, the exposures at this dose were considered as an appropriate reference for a no observed effect level (NOEL) for embryofoetal changes in the rat. In the rabbit embryo/foetal development study, there was an increased post-implantation loss at 1000 mg/kg/day and lower mean foetal weights with slightly retarded ossification of the metacarpal of the first digit, tarsal bone and sixth sternebra was observed at 300 mg/kg/day and above. These findings have been adequately addressed in the Zavicefta SmPC. There were no other overt findings at 100 mg/kg/day and this dose is therefore deemed to be the NOEL for embryofoetal changes in the rabbit and the no observed adverse effect level (NOAEL) for maternal toxicity.

Avibactam administered alone during pregnancy and lactation to F0 rats was associated with a dose-related increase in the incidence of renal pelvic dilatation (without recovery) and ureter dilatation, with no associated pathological changes to the renal parenchyma. Ureter dilatation was not seen in the young adult offspring. The dose of 120 mg/kg/day is considered to be the NOEL. The possibility that these findings may be relevant for humans cannot be excluded, and this aspect has been adequately addressed in the Zavicefta SmPC. In the juvenile rat study, renal cortical cysts were observed in all groups, including controls and were still present at the end of the 5 week recovery phase. Evidence from two additional supportive studies and the lack of renal cysts in the repeat dose toxicity studies in the same species/strain of rat, suggests that the findings are background lesions from one specific breeding facility and therefore unlikely to have any clinical significance. Additional information also suggests that the cysts are substantially distinct from human polycystic renal disease and that since nephrogenesis is still ongoing in juvenile rats, whereas it is complete by 34 weeks gestation in humans, the renal findings observed in the juvenile rats are unlikely to be relevant for humans. Furthermore, the cysts in the rat juvenile toxicity study covered a small proportion of the cortex, did not appear to have any significant implications for the animals, are known to be a common background finding in the developing kidney of Sprague-Dawley rats, which are not seen in young adult animals and appeared to produce only a little or no morphological change. Overall, it can be considered that the cortical cysts have little relevance for humans, and would have no clinical impact should they arise. No reproductive studies were conducted with ceftazidime in combination with avibactam based on the results observed with the individual compounds. This is considered acceptable by CHMP.

All impurities which require qualification according to ICH guidelines (ICH Q3B (R2)) have been adequately qualified in the toxicology studies. The potential impurity AZ1359137 was negative in a mutagenic assay and is therefore considered a non-mutagenic impurity and should be treated as such by the applicant.

The study on ceftazidime transformation in water/sediment systems (OECD 308) shows that both main transformation products M1 and M3 are very persistent as the DT_{50} values in the low organic content (LOC) system are higher than 60 days. As a result, Zavicefta should be considered as very persistent. The revised PEC/PNEC ratios indicate that avibactam and ceftazidime are unlikely to present a risk to sediment dwelling organisms.

2.3.7. Conclusion on the non-clinical aspects

CHMP agreed that the non-clinical data do not point to any major concerns and that the clinically relevant findings have been adequately addressed in the Zavicefta SmPC.

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

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Phase 1 healthy subject studies									

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Safety; PK	NXL104/1001	Module 5.3.3.1	To assess the safety and tolerability of escalating doses of avibactam alone and in combination with ceftazidime; to investigate the PK of avibactam alone and in combination with ceftazidime	Single-center, single-ascending dose, randomized, double-blind, placebo-controlled study	Groups 1-7: 7 avibactam dose groups (10 subjects per group, 8 active and 2 placebo) avibactam (50, 100, 250, 500, 1000, 1500, and 2000 mg), single dose, IV placebo, single dose, IV Groups 3 and 4: (after a 7-day washout period) 2 CAZ-AVI dose groups (8 active and 2 placebo per group) ceftazidime 1000 mg + avibactam 250 mg, single dose, IV; ceftazidime 2000 mg avibactam 500 mg, single dose, IV; placebo, single dose, IV	70 randomized: avibactam (N=56) CAZ-AVI (N=16) placebo (N=14)	Healthy subjects	Groups 1, 2, 5, 6, and 7: 1 day (single dose) Groups 3 and 4: 2 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Safety; PK; BA	NXL104/1002	Module 5.3.3.1	To assess the safety, tolerability, and PK of avibactam administered alone or in combination with ceftazidime; to assess the absolute BA of a single oral dose as compared to IV administration	Single-center, 2-part study Part A was a multiple-ascending dose, randomized, double-blind, placebo-controlled study. Part B was a BA (IV vs oral), open-label, randomized, single-dose, crossover study.	4 dose groups (10 subjects per group, 8 active and 2 placebo) Part A: avibactam (500, 750, and 1000 mg), q8h for 5 days, IV; ceftazidime 2000 mg + avibactam 500 mg, q8h for 10 days, IV; placebo, q8h for 5 or 10 days, IV Part B: avibactam 500 mg, single dose, IV and avibactam 500 mg, single dose, oral	49 randomized: Part A: (N=41) avibactam alone (N=25) CAZ-AVI (N=8) placebo (N=8) Part B: avibactam alone (N=8)	Healthy subjects	Part A: 5 days (avibactam alone groups); 10 days (CAZ-AVI group) Part B: 2 days (single oral and single IV dose separated by a 7-day washout)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
QT; safety; PK	D4280C00007	Module 5.3.4.1	To investigate the effect of supratherapeutic doses of CAZ-AVI or CXL on the QT interval and additional ECG variables; to assess the PK of avibactam, ceftaroline, ceftazidime, and moxifloxacin	Single-center, double-blind, randomized, placebo-controlled, 4-period crossover study	Treatment A: avibactam 2000 mg + ceftaroline fosamil 1500 mg, single dose, IV Treatment B: ceftazidime 3000 mg + avibactam 2000 mg, single dose, IV Treatment C: moxifloxacin 400 mg, single dose, oral Treatment D: placebo, single dose, IV	51 randomized: ceftaroline (N=50) CAZ-AVI (N=46) moxifloxacin (N=46) placebo (N=47)	Healthy subjects	4 days (4 treatments with a 3-day washout period after each treatment)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
DME; PK; safety	D4280C00008	Module 5.3.2.2	To assess the mass balance recovery, metabolite profile, and metabolite identification of IV [^{14}C]avibactam ; to assess the IV PK of [^{14}C]avibactam ; to assess safety and tolerability	Single-center, single-dose, open-label study	[^{14}C]avibactam 500 mg (≤300 µCi [11.1 MBq]), single dose, IV	6 enrolled: avibactam (N=6)	Healthy subjects	1 day (single dose)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	D4280C00009	Module 5.3.3.1	To measure and compare the concentration of ceftazidime and avibactam in epithelial lining fluid and plasma; to assess the safety and tolerability	Single-center, multiple-dose, open-label, 2-part, 3-cohort study	Part 1: Procedural pilot; no administration of study drug Part 2: Cohort A: IV CAZ 2000 mg + avibactam 500 mg, q8h for 3 days, IV Cohort B: IV CAZ 3000 mg + avibactam 1000 mg, q8h for 3 days, IV	45 enrolled: Part 1: no study drug (N=2) Part 2: CAZ-AVI (N=43) Cohort A (N=22) Cohort B (N=21)	Healthy subjects	Part 2: 3 days; bronchoscopy with bronchial-veolar lavage performed once on each subject 2, 4, 6, or 8 hours after the last dose	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	D4280C00011	Module 5.3.3.4	To investigate single- and multiple-dose PK of ceftazidime and avibactam; to investigate DDI when coadministering CAZ-AVI; to assess safety and tolerability; to investigate drug metabolites of avibactam	2-center, 2-part, open-label study Part A was a multiple-dose study. Part B was a randomized, 3-way crossover study.	Part A: ceftazidime 2000 mg + avibactam 500 mg, Days 1 and 11: single dose, IV; Days 2-10: q8h, IV Part B: for each treatment, Days 1 and 4: single dose, IV; Days 2 and 3: q8h, IV Treatment A: avibactam 500 mg Treatment B: ceftazidime 2000 mg Treatment C: ceftazidime 2000 mg + avibactam 500 mg	43 randomized: Part A: CAZ-AVI (N=16) Part B: ceftazidime alone (N=27) CAZ-AVI (N=27) avibactam alone (N=27)	Healthy subjects	Part A: 11 days Part B: 4 days (with at least a 2-day washout period between treatments)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	D4280C00012	Module 5.3.3.4	To investigate the PK and DDI of CAZ-AVI and metronidazole when administered alone and in combination; to assess safety and tolerability	Single-center, multiple-dose, randomized, open-label, 3-way crossover study	Treatment A: ceftazidime 2000 mg + avibactam 500 mg, Days 1 and 4: single dose, IV; Days 2 and 3: q8h, IV Treatment B: metronidazole 500 mg, Days 1 and 4: single dose, IV; Days 2 and 3: q8h, IV Treatment C: metronidazole 500 mg followed by ceftazidime 2000 mg + avibactam 500 mg, Days 1 and 4: single dose, IV; Days 2 and 3: q8h, IV	28 randomized: CAZ-AVI (N=28) metronidazole alone (N=27) CAZ-AVI + metronidazole (N=28)	Healthy subjects	12 days (Treatment A, 4 days; Treatment B, 4 days; and Treatment C, 4 days; there was a washout period of at least 48 hours between treatments)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Safety; PK	CXL-PK-01	Module 5.3.3.1	To evaluate the safety, tolerability, and PK of single and multiple IV doses of ceftaroline fosamil and avibactam	Single-center, 2-part, randomized study Part A was a single-dose, open-label, 3-way crossover study Part B was a multiple dose, randomized, double-blind, placebo-controlled study	Part A: Treatment A: ceftaroline 600 mg, single dose, IV Treatment B: avibactam 600 mg, single dose, IV Treatment C: 1200 mg CXL (ceftaroline 600 mg + avibactam 600 mg), single dose, IV Part B: CXL/placebo Cohort 1: 1200 mg Cohort 2: 800 mg Cohort 3: 1800 mg Cohort 4: 1200 mg Cohorts 1 and 3: Days 1 and 10: single dose, IV; Days 2-9: q12h, IV Cohorts 2 and 4: Days 1 and 10: single dose, IV; Days 2-9: q8h, IV	60 enrolled: Part A: avibactam (N=12) ceftaroline (N=12) CXL (N=12) Part B: CXL (N=48)	Healthy subjects	Part A: 3 days (with a 5-day washout between treatments) Part B: 10 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Safety; PK	D4280C00023	Module 5.3.4.1	To investigate the effect of administration of CAZ-AVI and CXL on the intestinal flora; to investigate safety, tolerability, and PK	Single-center, multiple-dose open-label, study	Cohort 1: ceftazidime 2000 mg + avibactam 500 mg, Days 1-6: q8h, IV; Day 7: single dose, IV Cohort 2: ceftaroline 600 mg + avibactam 600 mg, Days 1-6: q8h, IV; Day 7: single dose, IV	28 planned: 14 CAZ-AVI planned 14 CXL planned	Healthy subjects	Cohort 1: 7 days Cohort 2 7 days	Ongoing

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Phase 1 patient studies									
PK; safety	NXL104/1003	Module 5.3.3.3	To assess the PK and tolerability of avibactam 100 mg in normal subjects and patients with varying degrees of renal impairment	Single-center, single-dose, open-label, parallel-group study	avibactam 100 mg, single dose, IV	31 randomized: avibactam (N=31) renal impairment (N=25) normal renal function (N=6)	Healthy subjects; subjects with mild, moderate, severe, or end-stage renal impairment	1 day (single dose)	Complete; full
PK; safety	CXL-PK-03	Module 5.3.3.3	To evaluate the PK of multiple doses of ceftaroline fosamil and avibactam in subjects with severe renal impairment and normal renal function; to evaluate safety and tolerability	Multicenter, multiple-dose, open-label, parallel-group study	Group I (subjects with severe renal impairment): ceftaroline 300 mg + avibactam 125 mg, q8h for 4 days, IV Group II (subjects with normal renal function): ceftaroline 600 mg + avibactam 600 mg, q8h for 4 days, IV	16 enrolled: CXL (N=16) Group I (N=8) Group II (N=8)	Healthy subjects; subjects with severe renal impairment	4 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	CXL-PK-04	Module 5.3.3.3	To assess the PK of ceftaroline fosamil and avibactam in adults with augmented renal clearance and sepsis to evaluate safety and tolerability	Multicenter, single-dose, open-label study	ceftaroline 600 mg + avibactam 600 mg, single dose, IV	12 enrolled: CXL (N=12)	Adult subjects with augmented renal clearance and sepsis	1 day (single dose)	Complete; full
PK; safety	CXL-PK-05	Module 5.3.3.1	To evaluate the PK of ceftaroline fosamil and avibactam in plasma and subcutaneous tissue in subjects with diabetic foot infections; to evaluate safety and tolerability	Single-center, multiple-dose, open-label study	ceftaroline 600 mg + avibactam 600 mg, q8h for 3 days (5-7 doses), IV	10 enrolled: CXL (N=10)	Adult subjects with diabetic foot infections	3 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	NXL104/1004	Module 5.3.3.3	To assess the effect of age and gender on the PK of avibactam; to assess safety and tolerability	Multicenter, single-dose, open-label, parallel-group study	avibactam 500 mg, single dose, IV	33 enrolled: avibactam (N=33)	Healthy subjects stratified by age and gender	1 day (single dose)	Complete; full
Safety; PK	D4280C00010	Module 5.3.3.3	To investigate the safety and tolerability of avibactam alone or in combination with ceftazidime; to investigate the PK and influence of avibactam alone or in combination with ceftazidime on intestinal bacterial flora	Single-center, multiple-dose, double-blind, randomized, placebo-controlled, parallel-group study	avibactam 500 mg, ceftazidime 2000 mg + avibactam 500 mg, or placebo Day 1: single dose, IV Days 3-6: q8h, IV Day 7: single dose, IV	16 randomized: avibactam (N=6) CAZ-AVI (N=7) placebo (N=3)	Healthy Japanese subjects	7 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	CXL-PK-06	Module 5.3.3.3	To evaluate the PK of ceftaroline fosamil and avibactam in subjects who were normal to overweight and in obese Classes I, II, and III; to assess safety and tolerability	Multicenter, single-dose, open-label, parallel-group study	ceftaroline 600 mg + avibactam 600 mg, single dose, IV	40 enrolled: 40 CXL (N=40) Cohort 1: 10 normal to overweight Cohort 2: 10 obese Class I Cohort 3: 10 obese Class II Cohort 4: 10 obese Class III	Healthy subjects who were normal to over-weight and in obese Classes I, II, and III	1 day (single dose)	Complete; full
Safety; PK	D4280C00020	Module 5.3.3.3	To assess the safety, tolerability, and PK of CAZ-AVI administered as single and repeated IV doses	Single-center, randomized, double-blind, placebo-controlled, multiple-dose study	ceftazidime 2000 mg + avibactam 500 mg or placebo Day 1: single dose, IV Days 2-8: q8h for 7 days, IV Day 9: single dose, IV	16 randomized: CAZ-AVI (N=12) placebo (N=4)	Healthy Chinese subjects	9 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
PK; safety	D4280C00014	Module 5.3.3.2	To assess the PK, safety and tolerability of a single dose of CAZ-AVI in a pediatric population	Open-label, single-dose study	Cohort 1 and Cohort 2 patients weighing ≥40 kg: 2000 mg ceftazidime + 500 mg avibactam, single dose, IV Cohort 2 patients weighing <40 kg, Cohort 3 and Cohort 4: 50 mg/kg ceftazidime + 12.5 mg/kg avibactam, single dose, IV	35 enrolled Cohort 1, aged ≥12 to <18 years (N=11) Cohort 2, aged ≥6 to <12years (N=8) Cohort 3, aged ≥2 to <6 years (N=8) Cohort 4, aged ≥3 months to <2 years (N=8)	Hospitalized pediatric patients, receiving systemic antibiotic therapy for suspected or confirmed infection	1 day (single dose)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Phase 2 controlled studies									
Efficacy; safety; PK	NXL104/2001	Module 5.3.5.1	To evaluate the efficacy, safety, and, tolerability of CAZ-AVI vs imipenem in the treatment of cUTI	Multicenter, investigator-blinded, randomized study	ceftazidime 500 mg + avibactam 125 mg, q8h for 7-14 days, IV imipenem cilastatin 500 mg, q6h for 7-14 days, IV Possible oral switch in either group to ciprofloxacin after 4 days	137 randomized: CAZ-AVI (N=69) imipenem (N=68)	Adult subjects with cUTI, including acute pyelon-ephritis	7-14 days	Complete; full
Efficacy; safety; PK	NXL104/2002	Module 5.3.5.1	To evaluate the efficacy, safety, and tolerability of CAZ-AVI plus metronidazole vs meropenem in the treatment of cIAI	Multicenter, double-blind, randomized study	ceftazidime 2000 mg + avibactam 500 mg + metronidazole 500 mg, q8h for 5-14 days, IV meropenem, 1000 mg, q8h for 5-14 days, IV	204 randomized: CAZ-AVI + metronidazole (N=102) meropenem (N=102)	Adult subjects with cIAI	5-14 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy; safety; PK	CXL-MD-02	Module 5.3.5.4	To evaluate the efficacy, safety, and tolerability of CXL vs doripenem in the treatment of cUTI	Multicenter, double-blind, randomized study	ceftaroline 600 mg + avibactam 600 mg, q8h for 7-10 days, IV ceftaroline 600 mg + avibactam 600 mg, q12h for 7-10 days, IV doripenem 500 mg, q8h for 7-10 days, IV	218 randomized: CXL, q8h (N=72) CXL, q12h (N=73) doripenem (N=73)	Adult subjects with cUTI	7-10 days	Complete; full
Phase 3 studies									
Efficacy; safety	D4280C00001/5 (RECLAIM)	Module 5.3.5.1	To assess the noninferiority, PK, safety, and tolerability of CAZ-AVI plus metronidazole vs meropenem in the treatment of cIAI	Multicenter, randomized, double-blind, double-dummy, parallel-group, comparative study	ceftazidime 2000 mg + avibactam 500 mg, q8h, IV, followed by metronidazole 500 mg, q8h for 5-14 days, IV meropenem, 1000 mg, q8h for 5-14 days, IV	1066 randomized (combined study databases): CAZ-AVI + metronidazole (N=532) 533 meropenem (N=534)	Adult subjects with cIAI	5-14 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy; safety	D4280C00002/4 (RECAPTURE)	5.3.5.1	To assess the noninferiority of CAZ-AVI vs doripenem; evaluate the PK of CAZ-AVI; and determine the efficacy, safety, and tolerability of CAZ-AVI compared with doripenem	Multicenter, randomized, double-blind, double-dummy, parallel-group, comparative study	ceftazidime 2000 mg + avibactam 500 mg, and doripenem placebo, q8h, for 5-14 days, IV doripenem 500 mg, and CAZ-AVI placebo, q8h for 5-14 days, IV Switch to 500 mg oral open-label ciprofloxacin twice daily was allowed after receiving a minimum of 5 full days of IV study therapy if all protocol-specified criteria for clinical improvement were met.	1033 randomized(combined study databases): CAZ-AVI (N=516) doripenem (N=517)	Hospitalized adults with cUTI including acute pyelo-nephritis, with a Gram-negative pathogen	5–10 days (and up to 14 days for patients who were bacteremic)	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy; safety	D4280C00006 (REPRISE) First DCO	Module 5.3.5.1	To determine the clinical and microbiological responses, PK, safety, and tolerability of CAZ-AVI and BAT for the treatment of infections caused by ceftazidime-resistant gram-negative pathogens	Multicenter, randomized, open-label study	ceftazidime 2000 mg and avibactam 500 mg, q8h for 5-21 days, IV cIAI patients also received metronidazole 500 mg, q8h for 5-21 days, IV BAT: investigator's standard of care and local label recommendation	126 randomized at first DCO: CAZ-AVI (N=6 cIAI) (N=58 cUTI) BAT (N=6 cIAI) (N=56 cUTI)	Hospitalized patients with cIAI or cUTI caused by a CAZ-resistant, Gram-negative pathogen	5-21 days	Ongoing (at first DCO); full
Efficacy; safety	D4280C00006 (REPRISE) Final	Module 5.3.5.1				333 randomized CAZ-AVI (N=153 cUTI) (N=12 cIAI) BAT (N=153 cUTI) (N=15 cIAI)			Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy; safety	D4280C00018 (RECLAIM3)	5.3.5.1	To assess the noninferiority of CAZ-AVI plus metronidazole vs meropenem; evaluate the PK of CAZ-AVI; and determine the efficacy, safety, and tolerability of CAZ-AVI plus metronidazole vs meropenem	Multicenter, randomized, double-blind, double-dummy, parallel-group, comparative study	meropenem placebo, ceftazidime 2000 mg + avibactam 500 mg, and metronidazole 500 mg, q8h for 5-14 days, IV meropenem, 1000 mg, CAZ-AVI placebo, and metronidazole placebo, q8h for 5-14 days, IV	441 randomized CAZ-AVI+ metronidazole (N=219) meropenem (N=222)	Hospitalized adults with cIAI from Asia-Pacific region	5-14 days	Complete; full

Type of study	Study identifier (acronym)	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, route of administration	No. of subjects enrolled or randomized	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy; safety	D4281C00001 (REPROVE)	NA	To assess the non-inferiority of CAZ-AVI vs meropenem; determine the PK of CAZ-AVI, and determine the clinical and microbiological responses, all-cause mortality, proportion of patients discharged from hospital up to the TOC visit; safety, and tolerability of CAZ-AVI vs meropenem	Multicenter, double-blind, double-dummy, randomized, parallel-group study	ceftazidime 2000 mg + avibactam 500 mg and meropenem placebo, q8h for 7-14 days, IV meropenem 1000 mg and CAZ-AVI placebo, q8h for 7-14 days, IV	1494 to 1600 will be recruited and randomized 1:1 to CAZ-AVI and meropenem	Adult subjects with NP, including VAP	7-14 days	Ongoing

2.4.2. Pharmacokinetics

The Applicant has presented in this file 12 clinical pharmacology studies conducted with AVI and/or CAZ-AVI as well as 5 studies that provided PK data on AVI when given alone or co-administered with ceftaroline. PK data (sparse sampling only) were also obtained from infected patients in the phase 2 and 3 studies and were incorporated into the POPPK and PK/PD (simulations of PTA) analyses.

For phase 1 and phase 2 clinical studies (except for three which used the final formulation) CAZ and AVI were supplied in separate vials for co-administration as a single infusion solution. The formulation used in Phase 3 studies, which contains sodium carbonate, is the same as the commercial product. Infusion concentrations in the clinical studies ranged from 4 to 24 mg/mL CAZ and from 0.2 to 16 mg/mL AVI. The infusion durations varied from 30 to 120 minutes. The Applicant proposed the inclusion of the 120 minutes duration in the Product Information and CHMP agreed.

CAZ and AVI (NXL-104) were the active moieties measured. There is no evidence that any CAZ and AVI metabolites are pharmacologically active. Due to low and concentration-independent plasma protein binding, total drug concentrations (bound plus free) were measured in human plasma and urine using validated HPLC/MS-MS methods.

Absorption

In a single dose study with AVI ± CAZ (**NXL104-1001**) AVI Cmax was generally observed at the end of the infusion and then concentrations declined rapidly in a poly-exponential manner (2 or 3 phases). CAZ Cmax also occurred at the end of the infusion and then concentrations declined quite rapidly in a poly-exponential manner (2 phases).

In a multiple dose study of AVI, CAZ and CAZ-AVI (**D4280C00011**) **Part A** explored the PK of AVI and CAZ after single and multiple doses of 2g/500 mg q8h for 11 days using 2 h infusions. The AVI plasma concentration-time profiles showed no obvious accumulation after 10 days ($RAUC_{0-T}$ 0.998 on day 4 and 0.957 on day 11). There was no accumulation of CAZ. There was no evidence of time-dependent kinetics for CAZ or AVI after multiple dosing.

Table 12: Summary of key PK parameters of avibactam in Part A

Parameter (unit)	Statistic	Day 1	Day 4	Day 11
AUC (µg*h/mL)	n	13[a]	NA	NA
	Geometric mean	42.1	NA	NA
	CV%	16.0	NA	NA
$AUC_{(0-\tau)}$ (µg*h/mL)	n	16	16	16
	Geometric mean	40.0	39.9	38.2
	CV%	16.1	17.5	18.9
C_{max} (µg/mL)	n	16	16	16
	Geometric mean	15.2	14.8	14.6
	CV%	14.1	15.5	17.0
t_{max} (h)	n	16	16	16
	Median	2.00	2.00	2.00
	(Minimum, Maximum)	(2.00, 2.02)	(2.00, 2.02)	(2.00, 2.02)
$t_{1/2}$ (h)	n	13[a]	16	16
	Arithmetic mean	2.33	1.55	2.78
	SD	0.782	0.131	0.594
CL (L/h)	n	13[a]	16	16
	Arithmetic mean	12.0	12.7	13.3
	SD	1.84	2.18	2.35
CL_R (L/h)	n	16	NA	16
	Arithmetic mean	14.4	NA	14.1
	SD	9.36	NA	3.35

Part B was a definitive study of interaction between CAZ and AVI. There was no interaction detected between the two components of CAZ-AVI.

Table 13: Summary of key PK parameters of avibactam in Part B

Analyte	Day	Parameter (unit)	Trt	n	Geo LS Mean	Pairwise Comparisons		
						Pair	Ratio (%)	90% CI
Avibactam	1	AUC (µg*h/mL)	A	25[a]	38.88			
			C	27	39.77	C/A	102.27	(100.63, 103.93)
		C_{max} (µg/mL)	A	27	13.94			
			C	27	14.21	C/A	101.97	(99.51, 104.50)
	4	$AUC_{(0-\tau)}$ (µg*h/mL)	A	27	38.51			
			C	27	37.81	C/A	98.18	(96.19, 100.22)
		C_{max} (µg/mL)	A	27	14.01			
			C	27	13.90	C/A	99.27	(96.70, 101.92)
Ceftazidime	1	AUC (µg*h/mL)	B	27	308.1			
			C	27	306.6	C/B	99.53	(96.47, 102.69)
		C_{max} (µg/mL)	B	27	94.40			
			C	27	93.60	C/B	99.16	(94.45, 104.09)
	4	$AUC_{(0-\tau)}$ (µg*h/mL)	B	27	306.8			
			C	26[b]	311.8	C/B	101.64	(98.77, 104.59)
		C_{max} (µg/mL)	B	27	99.43			
			C	26[b]	99.02	C/B	99.59	(94.58, 104.86)

Trt treatment; Geo geometric; LS least-squares; CI confidence intervals.
Part B/Treatment A: 2-hour infusion of 500 mg avibactam;
Part B/Treatment B: 2-hour infusion of 2000 mg ceftazidime;
Part B/Treatment C: 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime.
[a] AUC values for 2 volunteers in Treatment A were not reported as Rsq (coefficient of determination for calculation of λ_z) was less than 0.8 for λ_z estimation.
[b] Pharmacokinetic parameters for Volunteer E0002025 in Treatment C of Part B were excluded due to an abnormal pharmacokinetic profile of ceftazidime on Day 4.

Distribution

Protein binding

- In in-vitro studies AVI binding to human plasma proteins was 5.7% to 8.2% and was not concentration-dependent (up to 50 µg/mL). In PTA simulations the 8.2% value was applied.
- CAZ human plasma protein binding is stated to be from 5% to 22.8% in the literature and a value of 15% was applied in PK/PD modelling and simulations of PTA.

ELF penetration

D4280C00009 assessed concentrations of CAZ-AVI in bronchial ELF and plasma in healthy subjects who received either CAZ-AVI 2 g/0.5 g or 3 g/1 g infused in 100 mL over 2 h q8h for 3 days (9 doses). Each subject underwent a single bronchoscopy with BAL at defined post-dose intervals. The AVI median Tmax was at the end of infusion in plasma and ELF. The t1/2 in ELF (1.94 h) appeared slightly shorter vs. plasma but this may reflect the limited sampling schedule in ELF. The Cmax and AUCτ values in ELF were approximately 28%-35% and 32%-35% of the plasma Cmax and AUCτ, respectively. The elimination patterns were similar from ELF and plasma. Similar findings applied to CAZ concentrations with Cmax and AUCτ in ELF that were approximately 23%-26% and 31%-32% of the plasma values, respectively.

Compartmental POPPK modelling of CAZ and AVI in ELF was performed. For CAZ and AVI the ELF data were best described by an instantaneous equilibrium model between plasma and ELF compartment. ELF concentrations are assumed to be free concentrations.

- For CAZ some non-linearity was evident such that at high concentrations penetration is saturable, giving higher estimated ELF penetration at lower plasma concentrations than previously estimated. As the plasma:ELF ratios for CAZ are higher at lower concentrations, which are achieved at later time points, this results in ELF concentrations being maintained at levels around the plasma PK/PD targets for at least 50% of the dosing interval.
- For AVI saturation was less evident but at lower plasma concentrations the penetration into ELF was also greater than previously estimated. At the later time points, the ELF concentrations are maintained around the plasma PK/PD targets of 1 mg/L, although ELF PK/PD targets are expected to be lower.

Elimination

In **D4280C00008** 6 healthy male volunteers received a single IV infusion administration containing ~ 500 mg [14C]AVI in ~ 100 mL of saline over ~ 60 min after an overnight fast. An average of 97.22% of administered radioactivity was recovered during the study, with 97.02% from the urine and 0.20% from the faeces. Over 95% of the administered radioactivity was recovered from urine within 12 h and 62.43% was recovered in the first 2 h post-infusion. An average of 84.89% of administered AVI was recovered from the urine during the study, with over 50% being recovered within 2 h of the start of the infusion. Renal clearance of AVI was 9479 mL/h (i.e. 158 mL/min) on average, which is greater than GFR, suggesting active tubular secretion. Individual values ranged from 7810 to 12600 mL/h. The t½ for AVI ranged from 2.14 to 3.56 h (arithmetic mean t½=2.778 h). The gmean total clearance was 11200 mL/h (range 9070 to 14000 mL/h). Renal clearance represented approximately 85% of total clearance. There was little penetration of AVI into red blood cells.

Metabolite profiling indicated that AVI was the major drug-related component in human plasma. A [14C] related uncharacterised product (M13) was observed but it was also observed to a similar extent in control plasma fortified with [14C]AVI and processed similar to the pooled plasma from the study, indicating that M13 may arise from the sample processing. Avibactam accounted for 93% of the excreted radioactivity in urine over 24 h and decarbonylated avibactam (M1) accounted for approximately 7%. Approximately 97% of the dose was excreted in the urine in the period 0 to 24 h, of which 90% was avibactam and 7% was M1. M1 was not identified in human plasma but it was found in the dosing solution, suggesting that it may result from non-enzymatic processes. The amount of M1 was not quantified in the dosing solution.

Table 14: Relative quantities (%) of avibactam and metabolites observed in 0 to 4 hour plasma and 0 to 24 hour urine of humans administered an IV infusion dose of [^{14}C] avibactam

Metabolite number	β-RAM RT (min)	Human plasma	Human urine
M1[a]	4.3	ND	7.0
M13[b]	5.4	27.5	ND
avibactam	29.1	72.5	93.0
Total radioactivity[c]		100.0	100.0

[a] Present in the radiolabel stock solution
[b] Present in control plasma fortified with [^{14}C] avibactam following extraction
[c] Sum of radioactivity of all integrated peaks

Dose proportionality and time dependencies

In **NXL104-1001** after single doses of AVI given alone the Cmax and AUC generally showed dose proportionality over 50-2000 mg. Assuming the power model, when the dose increased by 2-fold within this range, Cmax increased by 2.07 (CI 90% [2.00-2.14]) and AUC0-∞ by 2.08 (CI 90% [2.04-2.12]). For both Cmax and AUC, a trend toward a slightly over-proportional increase was suspected but no formal statistical conclusion could be drawn. In **NXL104-1002** after multiple dosing q8h the day 5 data showed that when the dose increased by 2-fold within the 500-1000 mg dose range, AVI Cmax increased by 1.40 (CI 90%=[0.95-2.07]) and AUC_{0-8} increased by 1.62 (CI 90%=[1.34-1.97]) respectively. For both Cmax and AUC, the lower bound of the 90% CI of β was below the lower limit of the reference CI for β [0.68-1.32]. There was no evidence of time-dependent kinetics for avibactam or ceftazidime after multiple dosing.

Pharmacokinetics in target population

- The first POPPK analyses (CAZ-MS-01 and CAZ-MS-05) demonstrated that the primary covariates that impact the PK of ceftazidime and avibactam are CrCL and patient population (i.e. patients with cIAI or cUTI vs. healthy subjects).
- A further analysis (CAZ-MS-06) included data from 78 NP patients enrolled into REPROVE.
- During the procedure the applicant updated the CAZ and AVI POPPK models (CAZ-MS-07) with additional patient data compared to the prior model (CAZ-MS-06) as shown below.

Table 15: Breakdown of phase 3 ceftazidime and avibactam subjects by study, population and inclusion in the previous MS-06 analysis

Study	Population	New patients in analysis dataset	Number of CAZ patients	Number of AVI patients
31 = D4280C00001 (Reclaim)	cIAI	No	228	228
32 = D4280C00002(Recapture)	cUTI	Yes	248	250
34 = D4280C00004(Recapture)	cUTI	Yes	242	248
35 = D4280C00005 (Reclaim)	cIAI	No	262	267
36 = D4280C00006 (Reprise)	cUTI	No	56	57
36 = D4280C00006 (Reprise)	cUTI	Yes	92	92
36 = D4280C00006 (Reprise)	cIAI	No	6	6
36 = D4280C00006 (Reprise)	cIAI	Yes	6	6
38 = D4280C00018 (Reclaim3)	cIAI	Yes	195	195
Total number of subjects			1335	1349

Plasma concentration data were available from 308 patients (109 with VAP and 199 with HAP) in REPROVE. The updated model predicted similar plasma exposures in patients with HAP or VAP compared with patients with cIAI.

Table 16: Predicted $C_{max, ss}$ and $AUC_{ss, 0-24}$ in simulated patients with cIAI, cUTI, NP or VAP and normal renal function

PK parameter	cIAI		cUTI		NP		VAP	
	Geo mean	CV (%)	Geo mean	CV (%)	Geo mean	CV (%)	Geo mean	CV (%)
Ceftazidime								
$C_{max,ss}$ (µ/mL)	54.5	46.7	67.6	50.1	58.1	48.6	52.9	47.1
$AUC_{ss,0-24}$ (µg.h/mL)	708	43.0	913	45.5	742	43.1	683	40.3
Avibactam								
$C_{max,ss}$ (µ/mL)	11.6	80.0	11.3	83.9	13.1	79.5	12.4	79.8
$AUC_{ss,0-24}$ (µg.h/mL)	125	72.3	127	79.9	147	72.2	141	71.8

From this updated analysis, patients with NP were predicted to achieve exposures that exceed the PK/PD targets in at least 95% of patients up to an MIC of 8 mg/L (see table below). Based on the blinded demography dataset from REPROVE, 9% of patients have CrCL >180 mL/min. Thus, the applicant considered that the adequacy of the dose in patients with augmented renal clearance (ARC) was supported by both the comparable exposure in NP vs. patients with cIAI and the updated PTA analysis. Using the updated POPPK model, the table puts the predicted exposures in HAP/VAP patients and PTA into context.

Table 17: Comparison of geometric mean (CV5) of $C_{max,ss}$ and $AUC_{ss,\ 0\text{-}24}$ and rates of attainment for the joint T4 target (50%fT>MIC for CAZ and 50% fT>1 mg/L for AVI) for various subgroups of the phase 3 cIAI and cUTI patients

Covariate Category	N	Ceftazidime		Avibactam		T4 %Target Attainment (95% CI)
		$C_{max,ss}$ (mg/L)	$AUC_{ss,0\text{-}24}$ (mg.h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0\text{-}24}$ (mg.h/L)	
Population						
cUTI	648	81.9 (108.3)	1013 (112.7)	12.5 (154.5)	139 (160.5)	99.1 (98.3, 99.8)
cIAI	703	72 (95.7)	784 (105.5)	13.2 (149.6)	133 (150.1)	99.0 (98.3, 99.7)
Baseline Bacteremia						
No	1284	76.5 (103.4)	885 (113.3)	12.8 (151.5)	135 (154.7)	99.0 (98.4, 99.5)
Yes	67	78.5 (97.9)	911 (109.3)	14.1 (161.6)	152 (163.2)	100.0 (NA)
Baseline APACHE II Score						
Missing	649	81.9 (108.3)	1013 (112.6)	12.5 (154.5)	140 (160.4)	99.1 (98.3, 99.8)
≤10	626	71.5 (95.5)	768 (103.7)	12.9 (148.4)	128 (147.4)	98.9 (98.1, 99.7)
>10	76	76.1 (96.6)	930 (111.8)	15.6 (154.9)	178 (155.6)	100.0 (NA)
SIRS at Baseline						
Missing	221	79.8 (92.9)	858 (102.1)	14.3 (174.8)	141 (164.6)	99.1 (97.8, 100.0)
No	594	76.6 (99.9)	910 (111.8)	12.7 (146.8)	137 (153.9)	99.0 (98.2, 99.8)
Yes	536	75.3 (110.1)	873 (118.4)	12.4 (147.0)	133 (152.8)	99.1 (98.3, 99.9)
Baseline WBC (cells/uL)						
≤12000	670	78.8 (101.7)	941 (110.9)	12.6 (144.8)	137 (151.5)	99.1 (98.4, 99.8)
>12000	361	72.2 (107.9)	803 (115.6)	12.5 (155.1)	130 (157.8)	98.9 (97.8, 100.0)
Missing	320	77.2 (99.3)	875 (110.4)	13.6 (162.9)	141 (159.6)	99.1 (98.0, 100.0)
Fever at Baseline						
Missing	255	79.3 (94.4)	869 (103.4)	14 (175.4)	140 (164.8)	98.8 (97.5, 100.0)
No	805	75.3 (101.8)	885 (113.5)	12.6 (141.2)	135 (149.4)	99.1 (98.5, 99.8)
Yes	291	78.1 (113.0)	906 (119.9)	12.6 (158.5)	134 (162.7)	99.0 (97.8, 100.0)
Age (y)						
18 to 65	989	75 (100.5)	827 (109.1)	12.6 (154.7)	128 (156.4)	99.0 (98.4, 99.6)
>65 to 75	195	81.4 (103.8)	1028 (107.2)	13.2 (122.9)	151 (123.3)	99.5 (98.5, 100.0)
>75 to 89	167	80.9 (114.5)	1126 (116.0)	13.7 (166.4)	172 (166.3)	98.8 (97.2, 100.0)
Concomitant Use of OAT1/OAT3 Inhibitor(s)						
No	1225	76.2 (103.6)	881 (114.0)	12.7 (152.2)	135 (155.9)	99.0 (98.5, 99.6)
Yes	126	81.2 (97.6)	947 (102.6)	13.8 (149.9)	147 (148.2)	99.2 (97.7, 100.0)
Obesity						
normal	1084	77.4 (104.0)	876 (110.3)	12.9 (154.1)	134 (154.4)	99.1 (98.5, 99.6)
obesity I	182	76.6 (100.2)	961 (123.8)	13.1 (148.0)	150 (163.9)	98.9 (97.4, 100.0)

Covariate Category	N	Ceftazidime		Avibactam		T4 %Target Attainment (95% CI)
		$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.h/L)	
obesity II	62	68.7 (97.2)	899 (126.7)	11.4 (137.9)	137 (153.4)	98.4 (95.3, 100.0)
obesity III	23	63.4 (77.0)	795 (101.5)	9.73 (97.1)	115 (113.6)	100.0 (NA)
Race						
Caucasian/Other	1027	74.6 (104.6)	888 (117.3)	12.5 (156.2)	136 (161.6)	99.0 (98.4, 99.6)
Asian (non-Chinese; non-Japanese)	166	81.6 (94.5)	908 (95.9)	14.2 (131.5)	144 (129.6)	99.4 (98.2, 100.0)
Chinese & Taiwanese	126	81.2 (98.6)	807 (101.0)	13.1 (140.5)	120 (134.8)	98.4 (96.2, 100.0)
Japanese	32	102 (72.3)	1083 (71.5)	17.2 (137.1)	167 (128.9)	100.0 (NA)
Closest Creatinine Clearance to Day 3 (PK Day) (mL/min); Simulated CAZ/AVI treatment regimen						
8 to 15 (Severe 2); 750/187.5 mg q24h	4	34.8 (159.3)	573 (106.1)	6.91 (282.9)	96 (202.5)	100.0 (NA)
>15 to 30 (Severe 1); 750/187.5 mg q12h	8	53.4 (102.4)	864 (118.7)	11.6 (122.3)	187 (133.2)	100.0 (NA)
>30 to 50 (Moderate); 1000/250 mg q8h	83	63.1 (119.3)	979 (123.8)	10.4 (149.9)	146 (156.1)	98.8 (96.4, 100.0)
>50 to 80 (Mild); 2000/500 mg q8h	296	94.5 (99.8)	1213 (103.0)	15 (133.9)	175 (138.8)	99.3 (98.4, 100.0)
>80 to 150; 2000/500 mg q8h	783	77.2 (93.6)	850 (99.9)	13.1 (156.0)	132 (155.2)	99.1 (98.4, 99.8)
>150 to 180; 2000/500 mg q8h	101	61.7 (84.4)	662 (99.7)	9.99 (114.9)	100 (128.7)	99.0 (97.1, 100.0)
>180 to 395; 2000/500 mg q8h	76	56 (93.3)	550 (92.9)	10.1 (167.8)	92.2 (153.8)	97.4 (93.8, 100.0)

Special populations

Effects of renal function

NXL104-1003 assessed the effects of impaired renal function on AVI using a 100 mg dose. Renal clearance was almost directly proportional to CrCL and accounted for up to 95% of total clearance in subjects with normal function with an average of 75% to 80% in those with mild or moderate impairment and 55% in severe impairment. Plasma concentrations increased as renal function decreased. The mean haemodialysis clearance was ~80% of the mean CLr at normal renal function (11.93 L/h). Between 38 and 67 mg of a 100 mg dose was removed by a 4 h dialysis session.

In **CXL-PK-04** hospitalised adults with augmented renal clearance (ARC) and SIRS with suspected or documented infection (i.e. sepsis) received 600 mg q8h AVI (with ceftaroline). The mean CrCL was 190.38. The gmean clearance of AVI increased by 39.5% in ARC compared with healthy subjects, giving 28.4% lower AUC_{0-t} for AVI. The updated POPPK models for CAZ and AVI included data from 101 patients with $CrCL_{CG}$ 150 to 180 mL/min and a further 76 with $CrCL_{CG}$ 180 to 395 mL/min. For MICs ≤8 mg/L the average target attainment was 99% and 97.4%, respectively.

Table 18: Comparison of ceftazidime and avibactam exposure and target attainment in phase 3 patients stratified across different renal function groups

Covariate category: CrCl closest to Day 3 (mL/min)	n	CAZ $C_{max,ss}$ (mg/L)	CAZ $AUC_{ss,0-24}$ (mg.h/L)	AVI $C_{max,ss}$ (mg/L)	AVI $AUC_{ss,0-24}$ (mg.h/L)	Target attainment at MIC of 8 mg/L (%)
>50 to 80	296	94.5 (99.8)	1213 (103.0)	15 (133.9)	175 (138.8)	99.3 (98.4, 100.0)
>80 to 150	783	77.2 (93.6)	850 (99.9)	13.1 (156.0)	132 (155.2)	99.1 (98.4, 99.8)
>150 to 180	101	61.7 (84.4)	662 (99.7)	9.99 (114.9)	100 (128.7)	99.0 (97.1, 100.0)
>180 to 395	76	56 (93.3)	550 (92.9)	10.1 (167.8)	92.2 (153.8)	97.4 (93.8, 100.0)

Note: Geometric mean (%CV) are reported for $C_{max, ss}$ and $AUC_{ss,0-24}$. Target attainment rates are reported as the observed percent (95% CI) of patients who achieved 50% fT > CAZ-AVI MIC for ceftazidime and 50% fT >1.0 mg/L for avibactam. $AUC_{ss,0-24}$: steady-state total daily area under the plasma concentration-time curve; CI: confidence interval; $C_{max,ss}$: maximum steady-state drug concentration in plasma during a dosing interval; CrCl: creatinine clearance; CV: coefficient of variation; MIC: minimum inhibitory concentration.

For AVI the impact of CrCL was greatest at <80 mL/min. CrCL >80 mL/min leads to modest further increases in CL (25.4% per 100 mL/min increase in CrCL above 80 mL/min), implying an increase of 43.2% in AVI clearance as CrCL increases from 80 to 250 mL/min.

For CAZ the impact of CrCL is greatest at <100 mL/min. Higher estimated CrCL results in modest further increases in CL (12.5% per 100 mL/min increase at >100 mL/min).

Other intrinsic factors

NXL104-1004 compared AVI PK after a 500 mg dose in four cohorts defined by gender and age 18-45 years or ≥ 65 years. Mean Cmax was lowest for the elderly males while CV% was highest for the elderly females. Mean AUC_{0-t} was higher for the elderly females, who also had the lowest mean CL. Inter-subject variability was low for AUC_{0-t} and AUC_{0-inf} in all cohorts (12.6 to 23.3%). The t1/2 was slightly longer for the elderly and mean Vss was highest for elderly males. The ANOVA analysis suggested that:

- Age affects AUC but not Cmax
- Gender affects Cmax but not AUC

The updated POPPK models for CAZ and AVI (see above) took into account PK data from 167 patients aged 75-89 years. There is a modest increase in the predicted CAZ and AVI AUCs in patients aged 65-75 and 75-89 years vs. <65 years.

Table 19: Comparison of ceftazidime and avibactam exposure and target attainment in phase 3 patients stratified across different age groups

Covariate Category: Age (y)	n	CAZ $C_{max,ss}$ (mg/L)	CAZ $AUC_{ss,0-24}$ (mg.h/L)	AVI $C_{max,ss}$ (mg/L)	AVI $AUC_{ss,0-24}$ (mg.h/L)	Target attainment at MIC of 8 mg/L (%)
18 to 65	989	75 (100.5)	827 (109.1)	12.6 (154.7)	128 (156.4)	99.0 (98.4, 99.6)
>65 to 75	195	81.4 (103.8)	1028 (107.2)	13.2 (122.9)	151 (123.3)	99.5 (98.5, 100.0)
>75 to 89	167	80.9 (114.5)	1126 (116.0)	13.7 (166.4)	172 (166.3)	98.8 (97.2, 100.0)

Note: Geometric mean (%CV) are reported for $C_{max,ss}$ and $AUC_{ss,0-24}$. Target attainment rates are reported as the observed percent (95% CI) of patients who achieved 50% fT > CAZ-AVI MIC for ceftazidime and 50% fT >1.0 mg/L for avibactam. $AUC_{ss,0-24}$: steady-state total daily area under the plasma concentration-time curve; CI: confidence interval; $C_{max,ss}$: maximum steady-state drug concentration in plasma during a dosing interval; CV: coefficient of variation; MIC: minimum inhibitory concentration.

Overall in the Phase 3 studies, there were 369 patients with mild renal impairment. In this group the average $AUC_{ss,0-24}$ is 1213 mg.h/L for CAZ and 175 mg.h/L for AVI. These values closely resemble those in the older age groups, reflecting the fact that 61% with mild renal impairment were aged >65 years. The potential effect of age was tested in the CAZ and AVI POPPK models and found not to improve the fit to the data. Therefore, age does not appear as a covariate in the final model for either CAZ or AVI.

The updated POPPK models were used to derive exposure and target attainment in Phase 3 patients by obesity class. The final PK models for CAZ and AVI include an effect of weight on the central volume of distribution. An increase in the volume of distribution with increasing weight results in an increase in the t1/2 and a decrease in Cmax. The increase in the terminal half-life maintains the concentrations above the appropriate thresholds for longer periods, resulting in an average joint target attainment of 100% in obesity class III and greater than 98% in all other obesity categories.

Table 20: Comparison of ceftazidime and avibactam exposure and target attainment in phase 3 patients stratified across different obesity classes

Covariate Category: Obesity	n	CAZ $C_{max,ss}$ (mg/L)	CAZ $AUC_{ss,0-24}$ (mg.h/L)	AVI $C_{max,ss}$ (mg/L)	AVI $AUC_{ss,0-24}$ (mg.h/L)	Target attainment at MIC of 8 mg/L (%)
Normal	1084	77.4 (104.0)	876 (110.3)	12.9 (154.1)	134 (154.4)	99.1 (98.5, 99.6)
Obesity I	182	76.6 (100.2)	961 (123.8)	13.1 (148.0)	150 (163.9)	98.9 (97.4, 100.0)
Obesity II	62	68.7 (97.2)	899 (126.7)	11.4 (137.9)	137 (153.4)	98.4 (95.3, 100.0)
Obesity III	23	63.4 (77.0)	795 (101.5)	9.73 (97.1)	115 (113.6)	100.0 (NA)

The interaction between obesity and CrCL in terms of AUCs of CAZ and AVI showed that the lowest exposures occur in patients with CrCL >150 mL/min but the average target attainment is still >90%.

Pharmacokinetic interaction studies

No metabolism of AVI was observed in human hepatocytes. AVI showed no significant inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 or UGT1A1. It also displayed no induction potential of CYP1A2, CYP2B6, CYP2C9, CYP2E1 and CYP3A4 within the clinically relevant exposure range. CAZ showed no induction of CYP1A1/2, CYP2B6 and CYP3A4/5. AVI and CAZ do not inhibit MDR1, BCRP, MRP4, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 or BSEP in the clinically relevant exposure range. AVI is not a substrate of MDR1, BCRP, MRP4, or OCT2, but it is a substrate of human OAT1 and OAT3 *in vitro*.

D4280C00012 investigated the effects of co-administration of CAZ-AVI (2 g/500 mg) and metronidazole (500 mg) in healthy volunteers and found no evidence of interaction.

Discussion on pharmacokinetics

In healthy subjects who received the proposed clinical regimen there was a <10% difference in AVI PK parameters from days 1-11 of dosing with CAZ-AVI. There was no effect of co-administration on CAZ or AVI PK after dosing from days 1-4 with each agent alone and together. In general, the two agents are well matched for use together using q8h administrations. Both have short plasma half-lives and rapid, mainly renal, excretion of intact drug. In addition, they show approximate dose linearity, have similar volumes of distribution, similar penetration ratios into ELF and low plasma protein binding.

In the AVI mass balance study there was almost complete recovery of radioactivity in urine within 12 h. Renal clearance of AVI accounted for 85% of total clearance and suggested some contribution from active tubular secretion. Most of the radioactivity in plasma and urine was associated with intact AVI. AVI accounted for 90% of the excreted radioactivity in urine over 24 h and decarbonylated avibactam (M1) accounted for approximately 7%.

The data and the POPPK-predicted exposures in subjects and patients with renal impairment, normal function or ARC indicated the need for an appropriate schema of dose adjustments for infected patients with reduced renal function. This is discussed in the next section since it relied on estimates of PTA and not just PK data. The data, including the PTA, indicated that dose adjustment is not necessary in ARC.

The data, POPPK-predicted exposures and PTA indicate that dose adjustment is not necessary on the basis of age, gender, race or body weight/BMI.

The final POPPK analysis, which included PK data from patients with HAP and VAP, supported a conclusion that that the recommended dose and dose adjustments should suffice for treatment of NP, including VAP, although efficacy data will come only post-approval from REPROVE. CHMP considered that, taking into account use of the approved dose of CAZ, lack of interaction with AVI and the PTA, supported by the ELF data, there was sufficient evidence to allow a standalone indication for treatment of HAP, including VAP. The Zavicefta SmPC further clarifies the basis for the indication.

The risk of clinically significant drug-drug-interactions to occur with CAZ-AVI appears to be low. AVI was found to be a substrate of OAT1 and OAT3, which may contribute to its active uptake from blood and influence excretion. Since probenecid inhibited AVI uptake by 56% to 70% it may decrease AVI elimination and, in the absence of a clinical DDI study, co-administration is not recommended.

In summary, CHMP concluded that the PK of CAZ and AVI, alone and together, are straightforward. For the most part they are handled in a similar fashion after clinical dosing and inter-subject variability is low or at most moderate. The data do not point to any major concerns and have been adequately represented in the Zavicefta SmPC.

2.4.3. Pharmacodynamics

Mechanism of action

Ceftazidime is a cephalosporin antibacterial agent with a mechanism of action that is the same as for all other beta-lactam agents, i.e. inhibition of peptidoglycan formation.

Avibactam is a first-in-class non-β-lactam β-lactamase inhibitor that is able to inhibit class A ESBLs and carbapenemases, class C β-lactamases and some class D oxacillinases and carbapenemases. It has no inhibitory activity against the class B metallo-enzymes. Structurally, it is a diazabicyclo-octanone (DABCO) derivative that employs a reactive urea group to inhibit serine β-lactamases. Inhibition of β-lactamases is covalent but reversible, such that active AVI is generated by reverse deacylation rather than undergoing hydrolysis to an inactive, ring opened form. In-vitro studies using purified enzymes gave IC_{50} values <200 nM except for some class D and all class B enzymes tested.

Primary and Secondary pharmacology

Avibactam has weak antibacterial activity (MICs typically >16 mg/L) but MICs of 8 mg/L were observed for some *E. coli*, possibly via weak binding to PBP2. It does not induce *ampC* enzymes at < 32 mg/L.

The most relevant data for this application pertain to the activity of CAZ-AVI against CAZ-R pathogens. Studies included strains engineered to express single specific enzymes. For enzymes within range of inhibition by AVI, testing AVI at a fixed concentration of 4 mg/L (shown from panels of organisms to be optimal for separating predicted susceptible vs. resistant organisms) in combination with CAZ resulted in MICs for the combination that were mostly ≤ 1 mg/L for *E. coli*, ≤ 2 mg/L for *K. pneumoniae* and ≤ 4 mg/L for *P. aeruginosa.*

In addition, the in-vitro activity of CAZ-AVI was evaluated in a global surveillance program and a specific surveillance study of bacterial isolates from patients with HAP/VAP. In summary:

- For *Enterobacteriaceae* the CAZ-AVI MIC_{90} values ranged from 0.12 to 2 mg/L vs. 1 to 128 mg/L for CAZ alone.
- The CAZ-AVI MIC was ≤8 mg/L against 82% of 251 *Enterobacteriaceae* that were resistant to all available carbapenems.
- For *P. aeruginosa* the MIC_{90} values ranged from 4 to 8 mg/L vs. 8 to 64 mg/L for CAZ alone. In 2012 89% of 384 meropenem-non-susceptible isolates had CAZ-AVI MICs ≤8 mg/L.
- In the study of HAP/VAP isolates the CAZ-AVI MIC_{90} against all *P. aeruginosa* was 8 mg/L, including 86% of 207 isolates from VAP patients.

Beta-lactamase characterisation studies using clinical isolates

The molecular in-vitro characterisation of β-lactamase resistance mechanisms was carried out for the Gram-negative pathogens collected during the Phase 3 studies (see next section for details) that met pre-specified MIC criteria and focused on isolates with CAZ MIC ≥8 mg/L. They were investigated for the presence of β-lactamase mechanisms, including genes encoding ESBLs or carbapenemases and upregulation of transcription of chromosomal *bla*AmpC. Further analyses were conducted to relate the mechanism of resistance to efficacy in the mMITT populations.

Genes were grouped as follows for the purpose of these β-lactamase analyses:

- Category I genes encode β-lactamases expected to be inhibited by AVI

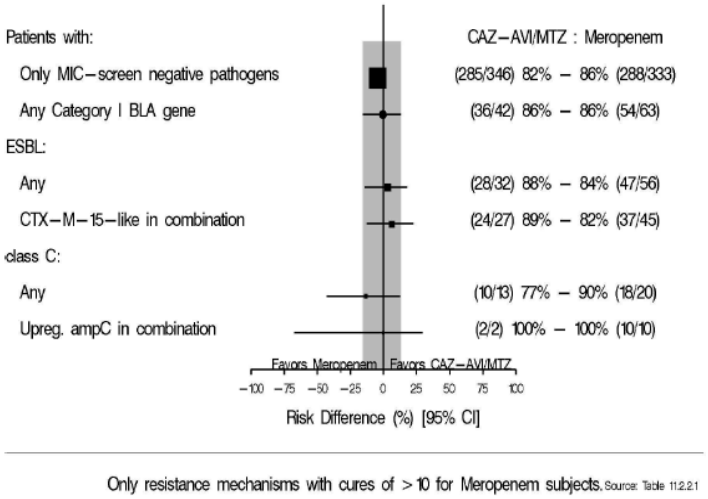
- Category II genes encode β-lactamases not expected to be inhibited by AVI
- Category III genes encode β-lactamases inhibited by AVI but not able to hydrolyse CAZ

An exception was OXA-48, which does not confer resistance to CAZ but does confer resistance to carbapenems. OXA-48 producers frequently produce other ESBLs that confer resistance to CAZ and these organisms were included in Category I.

Conclusions from RECLAIM:

Across treatment groups 105/823 (12.8%) mMITT patients had baseline isolates with Category I β-lactamases. CAZ-AVI was associated with a cure rate for patients with ESBL-producers of 28/32 and for class C producers of 10/13 in the mMITT population. Two patients infected with *P. aeruginosa* with CAZ-AVI MICs of 8 mg/L were clinical cures.

Figure 4 Forest plot of difference in clinical response at TOC by beta-lactamase status and resistance mechanism (mMITT population)



Only resistance mechanisms with cures of > 10 for Meropenem subjects. Source: Table 11.2.2.1

Conclusions from REPRISE:

Across treatment groups 292/302 (96.7%) mMITT patients had baseline isolates with Category I β-lactamases and most (289, 96%) did not have Category II β-lactamases. The clinical cure rates at TOC were >90% for cUTI and cIAI combined for CAZ-AVI and best available therapy [BAT] groups. Favourable microbiologic response rates at TOC were higher in the CAZ-AVI group 116/139 (83.5%) vs. 86/134 (64.2%) in the BAT group. Similar patterns were seen for the commonest species (*Escherichia coli* and *Klebsiella pneumoniae*) and those with the commonest β-lactamases (CTX-M-15-like and class C). There were six patients for whom pathogens had CAZ-AVI MICs of 8 mg/L and all were clinical and microbiological responders.

Table 21 Per-patient microbiological response at TOC by beta-lactamase status-cUTI (mMITT analysis set)

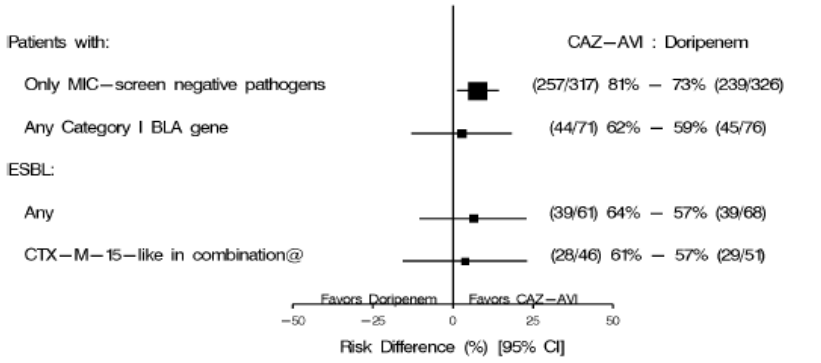
	Favorable microbiological response rate					
	CAZ-AVI (N=144)			BAT (N=137)		
Patient subgroup	n	m (%)[a]	95% CI[b]	n	m (%)[a]	95% CI[b]
All patients	144	118 (81.9)	75.1, 87.6	137	88 (64.2)	56.0, 71.9
Patients with any MIC-screened pathogen	143	118 (82.5)	75.7, 88.1	135	86 (63.7)	55.4, 71.5
Patients with only MIC-screen negative pathogens	1	1 (100)	14.7, 100	0	0	NA
Patients with any MIC-screen positive pathogens	142	117 (82.4)	75.5, 88.0	135	86 (63.7)	55.4, 71.5
Patients without any Category I β-lactamase gene identified	1	0 (0)	0.0, 85.3	1	0 (0)	0.0, 85.3
Patients with any Category I β-lactamase gene identified	139	116 (83.5)	76.6, 88.9	134	86 (64.2)	55.8, 71.9
Patients with only Category I β-lactamase gene identified	16	13 (81.3)	57.9, 94.4	13	9 (69.2)	42.3, 88.6

Conclusions from RECAPTURE:

Across treatment groups in the mMITT analysis set ~20% per group with screened isolates were infected with pathogens selected for study. Overall, 147/810 (18.1%) had isolates possessing Category I without Category II β-lactamase genes (71/393 CAZ-AVI and 76/417 doripenem). Of these 147, 12 CAZ-AVI and 13 doripenem patients had isolates with only Category I genes.

The microbiological response rates at TOC in these 147 patients were 62.0% for CAZ-AVI and 59.2% for doripenem with a similar pattern for the commonest species (*E. coli* and *K. pneumoniae*). For ESBL producers the corresponding rates were 63.9% and 57.4% and for those with class C enzyme genes the rates were 47.1% vs. 81.8%.

Figure 5 **Forest plot of difference in per-patient microbiological response at TOC by beta-lactamase status and resistance mechanism (mMITT analysis set)**



Only resistance mechanisms with cures of > 10 for Doripenem subjects.
@ In combination but not with Category II BLA gene.

RECLAIM3:

The listing provides the organisms and β-lactamases encountered from 23 *Enterobacteriaceae* (21 *E. coli* and 2 *K. pneumoniae*) with clinical outcomes for patients from Vietnam and South Korea. The listing shows that all of the patients with the 23 pathogens mentioned were clinical cures at TOC.

PK/PD indices and PD targets from nonclinical data

PK-PD index for CAZ:

Andes and Craig (2002) showed that ~30% *f*T>MIC CAZ was related to bacteriostasis over 24 h for *Enterobacteriaceae* in the neutropenic mouse lung infection model while 2 to 3 $\log_{10}$ kill was achieved by ~50% *f*T>MIC. For *P. aeruginosa*, stasis was achieved in the neutropenic thigh infection model at ~40% *f*T>MIC CAZ of ceftazidime (Craig 2003). Based on clinical data for CAZ 2 g q8h and 2-h infusions Muller *et al* (2013) reported that in patients with NP, including VAP, due to Gram-negative bacilli a %*f*T>MIC CAZ of ≥ 45% was associated with a favourable outcome. In another retrospective exposure-response analysis in patients with VAP due to Gram-negative bacilli MacVane *et al* (2014) reported that ≥ 53% *f*T>MIC CAZ was associated with microbiological success. A value of 50% *f*T>MIC CAZ was used as the target for PTA analyses. A protected CAZ MIC ≤ 8 mg/L (i.e. measured in the presence of 4 mg/L AVI) included ≥ 90% of clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* so this was selected as the CAZ MIC target for dose setting.

PK-PD index for avibactam

This was derived from hollow-fibre models and animal models of infection and concluded to be related to the percentage of the dosing interval in which free avibactam exceeded the required threshold (i.e. %*f*T>C_T). In the hollow-fibre model using CAZ-R *Enterobacteriaceae*, a minimum C_T of 0.5 mg/L avibactam was shown to be the appropriate PK/PD index for avibactam. Using the neutropenic mouse thigh infection model with *P. aeruginosa*, a mean %*f*T>C_T of 40% for a C_T of 1 mg/L avibactam was associated with bacterial stasis and a mean %*f*T>C_T of 50% for a C_T of 1 mg/L was associated with 1-log kill. Using the neutropenic mouse lung infection model with *P. aeruginosa*, the mean %*f*T>C_T values for a C_T of 1 mg/L associated with stasis, 1-log kill and 2-log kill were 20%, 24% and 30%, respectively. From these results the C_T was set at 1 mg/L.

The overall target exposure for CAZ-AVI was simultaneously achieving 50% *f*T>MIC for CAZ MIC of 8 mg/L while maintaining 50% *f*T>C_T of 1 mg/L for avibactam.

Phase 3 dose selection based on PTA

Because PK/PD targets could not be identified from the E-R analyses the nonclinical targets described above were used in Monte Carlo simulations (MCS) to estimate the PTA. Dose selection was based on the achievement of a high (>90%) joint PTA (see above) for patients with cIAI, cUTI or NP.

The CAZ-AVI dose regimen used for the Phase 2 study in patients with cIAI (NXL104-2002) was 2 g/0.5 g q8h using 30-min infusions for patients with CrCL >80 mL/min. The PTA analysis predicted that this dose regimen had inadequate joint PTA (<90%) at the CAZ-AVI MIC of 8 mg/L but prolongation of the infusion time to 120 min would increase the joint PTA to >90%. Therefore the Phase 3 regimen differed from the Phase 2 regimen only in terms of infusion time.

CAZ-AVI was not studied in any patients with NP prior to the start of REPROVE. Based on the PK analyses discussed under *PK in the target population* (see Table 10 for a summary) the applicant considers that the same dose can be used for NP and cIAI. To understand the potential impact of ARC in patients with NP, covariate distributions of CrCL that were biased towards high CrCL were used in the simulations and > 90% PTA was demonstrated.

Simulation of exposure and PTA analysis following Phase 3

To summarise the PTA using the applicant's revised dose recommendations by indication (i.e. refined after completing RECLAIM; see further below), the table below shows that PTA adequate at 8 mg/L and the adjusted doses for renal impairment are predicted to give PTA adequate to cover MICs of 16 mg/L.

Table 22 **Predicted joint PTA for the T4 PK/PD endpoint (50% fT>MIC for CAZ and 50% fT>1,0 mg/L for AVI) in simulated patients with cIAI, cUTI, HAP(NP) and VAP by renal function groups with associated dose adjustments**

Renal function	Original dose regimen	MIC (mg/L)	Percentage simulated patients				
			cIAI	cUTI	NP	VAP	HAP
NORM	2000 mg ceftazidime + 500 mg avibactam q8h	4	99.0	98.9	99.0	99.0	99.6
		8	98.8	98.9	98.8	98.8	99.6
		16	75.9	90.0	80.0	73.9	86.7
		32	17.3	37.3	18.6	14.6	21.3
MILD	2000 mg ceftazidime + 500 mg avibactam q8h	4	99.7	99.8	99.7	99.8	99.7
		8	99.7	99.8	99.7	99.8	99.7
		16	98.2	98.8	98.7	98.4	98.8
		32	61.7	80.4	65.4	62.8	68.3
MODE	1000 mg ceftazidime + 250 mg avibactam q8h	4	99.6	99.4	99.6	99.8	99.7
		8	99.5	99.4	99.6	99.7	99.7
		16	95.3	97.4	96.4	95.7	96.8
		32	42.3	67.6	47.2	43.1	50.0
SEV1	750 mg ceftazidime + 187.5 mg avibactam q12h	4	99.5	99.5	99.5	99.6	99.5
		8	99.4	99.5	99.4	99.6	99.5
		16	91.5	95.1	92.9	92.1	94.3
		32	33.2	54.7	36.6	33.1	38.9
SEV2	750 mg ceftazidime + 187.5 mg avibactam q12h	4	99.6	99.7	99.7	99.8	99.7
		8	99.5	99.7	99.6	99.7	99.7
		16	93.4	96.5	94.6	93.9	95.8
		32	44.1	63.4	47.9	44.6	50.1
ESRD	750 mg ceftazidime + 187.5 mg avibactam q48h	4	99.4	99.4	99.4	99.8	99.6
		8	99.4	99.4	99.4	99.8	99.6
		16	98.8	99.1	99.0	99.3	99.4
		32	84.3	92.5	86.8	85.2	88.8

Using the updated POPPK model, additional PTA simulations were conducted that extended the exploration of performance of dose to include ≥60% *f*T>MIC and simultaneous C_T>1 mg/L, i.e. an even more conservative joint target. Based on these more stringent targets and for a CAZ-AVI MIC of 8 mg/L the PTA exceeds 98% for all recommended doses of CAZ-AVI. Also, PTA >95% is predicted to be achieved for 70% *f*T>ceftazidime and avibactam targets. Thus, even if higher durations of exposure to the drug are needed to inhibit growth of certain clinical genera of clinical pathogens that produce β-lactamases within the spectrum of inhibition of AVI the recommended dose of CAZ-AVI is still predicted to be effective.

Table 23 **PTA analysis of ≥60% fT ceftazidime and avibactam PK/PD targets at a CAZ-AVI MIC of 8 mg/L**

Renal function group (CrCl)	Treatment	CAZ MIC (mg/L)	PTA for 60% fT>CAZ-AVI MIC for ceftazidime and C_T of 1 mg/L for avibactam				
			60%	70%	80%	90%	100%
Normal (>80 mL/min)	2000 mg CAZ + 500 mg AVI q8h	8	98.8	95.8	72.2	50.2	36.1
Mild (51 to 80 mL/min)	2000 mg CAZ + 500 mg AVI q8h	8	99.6	99.5	99.4	98.6	93.8
Moderate (31 to 50 mL/min)	1000 mg CAZ + 250 mg AVI q8h	8	99.5	99.4	99.4	99.4	99.2
Severe 1 (16 to 30 mL/min)	750 mg CAZ + 187.5 mg AVI q12h	8	99.3	99.3	99.3	99.2	98.8
Severe 2 (6 to 15 mL/min)	750 mg CAZ + 187.5 mg AVI q24h	8	99.5	99.5	99.5	99.3	98.9
ESRD (<6 mL/min)	750 mg CAZ + 187.5 mg AVI q48h	8	99.4	99.4	99.4	99.2	98.8

Confirmation of the suitability of the Phase 3 dose for patients with limited treatment options

The applicant concludes that the above analyses support bridging the efficacy seen in RECLAIM to justify using the same dose regimen to treat other infections due to aerobic Gram-negative organisms. Clinical efficacy data are not available for all β-lactamases that hydrolyse CAZ and are inhibited by AVI. An extrapolation is proposed to be justified based on:

- In-vitro data and animal infection models using organisms producing representatives of the TEM, SHV, CTX-M, CMY, PER, AmpC and KPC-type enzymes and multiple enzymes
- Clinical efficacy
- The understanding that the PK-PD relationship is not affected by β-lactamase production

Dose adjustments for patients with renal impairment

In RECLAIM, RECLAIM3, RECAPTURE and REPRISE dose adjustments were implemented for patients with CrCL ≤ 50 mL/min. The dose adjustments were based on those approved for CAZ, taking into account that the impact of renal impairment is similar for each of CAZ and AVI.

Following completion of RECLAIM, a subgroup efficacy analysis indicated that patients with moderate renal impairment treated with CAZ-AVI had a lower clinical cure rate vs. meropenem. More than half of the CAZ-AVI patients (24/41; 58.5%) and meropenem patients (26/43; 60.5%) with estimated CrCL ≤ 50 mL/min at baseline had rapid increases in estimated CrCL (within 48 h) while on study. The majority of these patients had an appropriate increase in the frequency and dose of CAZ-AVI or meropenem. However, since serum creatinine was estimated intermittently there were periods in which the dose regimen lagged behind the improvements in estimated CrCL.

The PK sampling time point was at Day 3, at which time the plasma exposures for CAZ and AVI were broadly comparable between patients with normal renal function or mild or moderate renal impairment at baseline. These data do not capture the first 72 h, during which some patients may have been under-dosed for variable periods.

For example, the table below shows that in patients who shift from moderate renal impairment to normal renal function, the adjusted dose (1 g/0.25 g q12h) provides a very low joint PTA (13.5%).

The impact of under-dosing on PTA was predicted to be relatively greater for CAZ-AVI because the dose was reduced to one-third whereas for meropenem the dose was reduced to two-thirds and would give 41% PTA for MICs 2 mg/L (the susceptibility breakpoint).

Other plausible CAZ-AVI dose regimens for each renal impairment group were explored by PTA such that the total daily dose was increased by 50% compared with the initial renal dose adjustments. As shown in the second table, using 1 g/0.25 g q8h in moderate impairment increases the PTA to 55.9% for a CAZ-AVI MIC of 8 mg/L for a patient who shifts rapidly to normal renal function.

Table 24 **Joint PTA, $C_{ss,max}$, and $AUC_{ss,0-24}$ in simulated cIAI patients with normal renal function, mild and moderate renal impairment receiving the original CAZ-AVI dose regimen for moderate renal impairment (1000 mg CAZ + 500 mg AVI, q12h), given as 120 min infusion**

Renal function	Dose regimen	Joint PTA at CAZ-AVI MIC of 8 mg/L (%)	Ceftazidime				Avibactam			
			$C_{ss,max}$ (µg/mL)		$AUC_{ss,0-24}$ (µg.h/mL)		$C_{ss,max}$ (µg/mL)		$AUC_{ss,0-24}$ (µg.h/mL)	
			Geo mean	CV (%)	Geo mean	CV (%)	Geo mean	CV (%)	Geo mean	CV (%)
NORM	2000 mg CAZ + 500 mg AVI q8h	98.4	55.6	28	600	39	11.2	53	114	75
NORM	1000 mg CAZ + 250 mg AVI q12h	13.5	26.3	26	200	39	5.33	47	38	75
MILD	2000 mg CAZ + 500 mg AVI q8h	99.7	71.1	29	934	39	13.1	55	155	76
MILD	1000 mg CAZ + 250 mg AVI q12h	52.5	31.7	26	311	39	6.14	48	51.6	76
MODE	1000 mg CAZ + 250 mg AVI q12h	97	39.9	29	505	40	7.76	53	85.3	76

Table 25 **Joint PTA, $C_{ss,max}$, and $AUC_{ss,0-24}$ in simulated cIAI patients with different renal function, receiving the revised dose regimens (moderate, severe 1, severe 2 renal impairment and ESRD) and the original dose regimen (normal renal function and mild renal impairment) with CAZ-AVI given as 120 min infusion**

Renal function	Dose regimen	Joint PTA at CAZ-AVI MIC of 8 mg/L (%)	Ceftazidime				Avibactam			
			$C_{ss,max}$ (µg/mL)		$AUC_{ss,0-24}$ (µg.h/mL)		$C_{ss,max}$ (µg/mL)		$AUC_{ss,0-24}$ (µg.h/mL)	
			Geo mean	CV (%)	Geo mean	CV (%)	Geo mean	CV (%)	Geo mean	CV (%)
NORM	2000 mg CAZ + 500 mg AVI q8h	98.4	55.6	28	600	39	11.2	53	114	75
MILD	2000 mg CAZ + 500 mg AVI q8h	99.7	71.1	29	934	39	13.4	55	155	76
MODE	1000 mg CAZ + 250 mg AVI q8h	99.7	48	32	757	40	9	59	128	76
SEV1	750 mg CAZ + 187.5 mg AVI q12h	99.7	42	33	670	41	8.03	60	116	78
SEV2	750 mg CAZ + 187.5 mg AVI q24h	99.8	47.1	35	750	46	9.25	61	134	81
ESRD	750 mg CAZ + 187.5 mg AVI q48h	99.7	74.7	49	1380	61	8.69	56	116	74

Similar analyses for patients with cUTI and NP confirmed the suitability of these doses since each would have >95% PTA for the joint PK/PD target for those with stable renal function and maintain at least 70% PTA if there was a rapid improvement to the next category. Therefore the Zavicefta SmPC recommends the adjustments shown above rather than those applied during completed Phase 3 studies.

Other pharmacodynamic studies

D4280C00007 was a double blind and placebo controlled TQT study in which 51 male subjects were randomized to receive all of the following in 4 treatment sequences with at least 3-day washout periods:

B: 2 g AVI and 3 g CAZ over 30 min plus placebo infusion (saline) over 30 min, each in 125 mL

C: Moxifloxacin 400 mg oral tablet

D: Placebo infusion (saline) over 60 min in 2x125 mL volumes

Total exposure to AVI after a 2 g dose was ~3-fold higher vs. AVI 500 mg given alone. The CAZ dose (3 g) resulted in substantially greater systemic exposures than reported with the clinical dose at 2 g. Assay sensitivity was confirmed from the comparison between moxifloxacin and placebo. In the primary comparison of QTcF with AVI vs. placebo the upper bound of the 2-sided 90% CI did not exceed 10 ms at any time point post-dose. Maximum absolute values and changes in QTcF from baseline did not exceed the recommended boundaries at any time point. Changes in heart rate, RR, PR, QT and QRS intervals were consistent between placebo and CAZ-AVI.

Breakpoints

The applicant has presented a rationale for the proposed MIC interpretive breakpoints and has approached EUCAST to set interpretive breakpoints for ceftazidime-avibactam in the EU.

The final susceptibility testing breakpoints established by the EUCAST were:

Organisms	Susceptible	Resistant
Enterobacteriaceae	≤8 mg/L	>8 mg/L
Pseudomonas aeruginosa	≤8 mg/L	>8 mg/L

Discussion on pharmacodynamics

Microbiology

The inhibitory range of AVI clearly exceeds that of tazobactam, sulbactam and clavulanic acid. AVI is being developed for clinical use in combination with several beta-lactam drugs. The CAZ-AVI FDC is the first of these combinations to be submitted for regulatory review.

The selection of CAZ as the partner effectively restricts, with very few exceptions, the clinical utility of the FDC to those types of infections in which aerobic Gram-negative pathogens predominate among the causative agents. For this reason the indications sought are limited to cIAI, cUTI and NP, all of which are already approved for CAZ alone. Nevertheless, CAZ is not active against, or cannot be relied upon to treat, certain aerobic Gram-negative bacteria, including *Acinetobacter spp., B. cepacia* and *S. maltophilia*. There are also some species against which CAZ is commonly active with little or no enhancement expected when it is combined with AVI (in particular, P. aeruginosa).

CAZ-AVI will not overcome all resistance to CAZ. For example, when one of the beta-lactamases expressed is not inhibited by AVI (all class B and some class D), when there is extreme over-

expression of an enzyme normally inhibited by AVI and/or when there is a non-enzymic mechanism of resistance that limits activity of the combination, such as a porin deficiency.

The applicant conducted a range of appropriate studies to document the activity of CAZ-AVI against CAZ-R pathogens involving various mechanisms. The results supported the findings of the in-vitro studies of AVI inhibition of beta-lactamases as well as those using organisms engineered to express single beta-lactamases. The use of a fixed concentration of 4 mg/L AVI for in-vitro susceptibility testing was based on data from a panel of well-characterised organisms suggesting that this serves to best differentiate those organisms predicted to be susceptible (based on mechanisms of resistance) from those predicted to be resistant. The concentration has no direct relationship to the human plasma concentrations of AVI. This is acceptable since PTA at a pre-defined MIC is based on simulated human exposures.

MICs of CAZ-AVI were not affected by testing in 10% pulmonary surfactant. MICs of CAZ and CAZ-AVI increased when the pH decreased from 7 to 5, although for CAZ-AVI the MICs did not exceed 4 mg/L. It is unclear whether this finding has potential relevance to activity of CAZ-AVI within the airways in which acidic conditions could prevail in association with raised CO2 levels. While ELF penetration was shown to be comparable for CAZ and AVI and was taken into account in simulations to estimate PTA, there remains some concern regarding the lack of any efficacy data to support use of the combination in NP. CAZ alone is indicated for treatment of NP in the EU but the clinical trial evidence to support this use was limited. Nevertheless, the additional PK data and the PTA using the updated POPPK models (including the assessment of the effect of ARC) are considered to be sufficient to allow an indication for use in NP in this particular situation in which the beta-lactam partner is already licensed for this indication at the same dose.

Data on clinical isolates

During the procedure the applicant provided detailed characterisation of beta-lactamases in isolates from patients in Phase 3 studies. Appropriately the focus has been on those with CAZ MICs at least 8 mg/L expressing enzymes expected to be inhibited by AVI. Overall these data are supportive of the adequacy of the AVI dose but there have been very few serine carbapenemases treated with CAZ-AVI so far.

Dose selection

The steps leading to selection of the PK-PD indices have been clearly described. The individual and combined PD targets identified are acceptable. The final estimates of PTA at CAZ-AVI MIC 8 mg/L reflect the POPPK analysis that included the Phase 3 sparse sampling data from infected patients who received the final proposed dose regimen. Essentially, the applicant's conclusion regarding the sufficiency of the dose can be agreed when MICs are up to 8 mg/L.

The analyses underlying the revision of the dose adjustments for various degrees of renal impairment were considered appropriate by CHMP.

2.4.4. Conclusions on clinical pharmacology

The CHMP agreed that the provided data were sufficient and adequate.

2.5. Clinical efficacy

During the procedure data were reported from 5 Phase 3 studies and efficacy data were reported in full from 4 studies. REPROVE is ongoing and double-blind and only PK data were reported.

RECLAIM (D4280C00001/5): A phase 3, randomised, multicentre, double-blind, double-dummy, parallel group, comparative study to determine the efficacy, safety and tolerability of CAZ-AVI plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections (cIAI) in hospitalized adults

REPRISE (D4280C0006); An open-label, randomised, multicentre, phase 3 study of CAZ-AVI and best available therapy for the treatment of infections due to ceftazidime-resistant Gram-negative pathogens

RECAPTURE (D4280C00002 and 00004) compared CAZ-AVI vs. doripenem, each followed by oral therapy, for treatment of cUTI, including acute pyelonephritis, in 1031 hospitalised adults.

RECLAIM3 (D4280C00018) compared CAZ-AVI plus MTZ with meropenem for treatment of cIAI in 404 hospitalised adults recruited in the Asia-Pacific region. This study has been completed since filing the application dossier and a full CSR was submitted.

REPROVE (D4281C00001) (ongoing): A phase 3, randomised, multicentre, double-blind, double-dummy, parallel group comparative study to determine the efficacy, safety and tolerability of CAZ-AVI versus meropenem in the treatment of nosocomial pneumonia, including ventilator-associated pneumonia in hospitalised adults

2.5.1. Dose response studies

There were no dose responses conducted. The PD section of the response presents the analyses that led to selection of the proposed dose regimen, including the dose adjustments that were used during the studies and those included in the SmPC in patients with varying degrees of renal impairment.

2.5.2. Main studies

Study title:

A phase 3, randomised, multi-centre, double-blind, double-dummy, parallel group, comparative study to determine the efficacy, safety and tolerability of CAZ-AVI plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalised adults (D4280C00001/5, RECLAIM study)

Methods

Study Participants

Eligible patients were aged 18 to 90 years of age and were to have either intraoperative/postoperative enrolment with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis in accordance with the criteria recommended by CHMP.

The most important exclusion criteria other than those expected for beta-lactams and in line with inclusion criteria, were CG-CrCL≤ 30 mL/min or having any type of dialysis and other potentially important laboratory findings (e.g. Haematocrit < 25% or haemoglobin < 8 g/dL, Absolute neutrophil count < 1,000/mm^3, Platelet count < 75,000/mm^3, Bilirubin > 3 x ULN, ALP, ALT or AST > 3 x ULN or up to 5 x ULN if directly related to the infectious process etc.)

Treatments

The study was of double blind, double-dummy design. Patients were randomized to CAZ-AVI (2 g/0.5 g q8h) in 100 mL over 2 h followed by metronidazole (500 mgq8h) over 1 h or Meropenem (1 g q8h) in 100 mL over 30 min.

There were dose adjustments in patients with moderate renal impairment. If CrCL fell below 31 mL/min on study investigators determined whether to implement a dose change or discontinue therapy. If *Enterococcus* species or MRSA was known or suspected open-label vancomycin, linezolid or daptomycin could be added to either study regimen and discontinued based on culture results.

Objectives

Primary

To assess non-inferiority of CAZ-AVI vs. meropenem for cure at TOC in MITT and CE populations

Secondary

- To assess non-inferiority for cure at TOC in mMITT and ME populations
- To compare clinical outcomes at EOT and LFU in the various patient populations
- To compare per-patient and per-pathogen microbiologic responses at EOT, TOC and LFU
- To evaluate efficacy against CAZ-R pathogens
- To evaluate CAZ-AVI exposure and the antimicrobial response relationship

Outcomes/endpoints

Clinical response definitions at the EOT, TOC and LFU visits were cure, failure and indeterminate.

An independent expert surgical review panel reviewed all patients assessed as clinical failure by the investigator for the adequacy of surgical source control while blinded to IV study therapy. In addition, the panel reviewed all patients assessed as clinical cure at TOC and/or LFU by the investigator and who underwent an additional procedure to assess whether clinical cure criteria had indeed been met. If the SRP determined that the patient met the definition of failure, they went on to further assess whether source control was adequate. If it was determined that source control at the study qualifying procedure was adequate, the patient's final clinical response was failure. If it was determined that there was inadequate source control, the final clinical response was indeterminate. If a discrepancy existed in clinical outcome, the SRP's assessment prevailed.

Cultures from the intra-abdominal site of infection and blood were collected at the time of surgery. Baseline clinical isolates were shipped to the central laboratory for confirmation of identification and susceptibility. If discrepancies existed and could not be resolved the central laboratory results prevailed.

Baseline pathogens included bacteria identified from either intra-abdominal cultures or blood cultures which could be reasonably implicated as an aetiologic agent of cIAI. Bacteria for which at least one of the study agents would have been an inappropriate choice for empiric treatment (e.g. *Stenotrophomonas spp*. and *Acinetobacter spp*.), fungi and bacteria considered to be contaminants (e.g. *S. epidermidis)* were not considered baseline pathogens. Classification of baseline pathogens was performed by the Microbiology Review Committee. Per-pathogen and per-patient responses were determined.

Sample size

The sample size of the combined study database provided 90% power for a 10% non-inferiority margin and > 95% power for a 12.5% margin using 95% confidence intervals. Assuming that both treatments had an underlying clinical cure rate of 70% in the mMITT analysis set, 442 randomised patients per treatment group were needed. This sample size also provided at least 90% power for the MITT and CE analysis sets. Assuming that 80% of all randomised patients were included in the mMITT analysis set, 553 randomised patients per treatment group (1106 total) were needed across the two studies.

Randomisation

Eligible patients were randomised 1:1 to treatment groups using an IVRS/IWRS and a block size of 4.Patients were stratified by APACHE II score (≤10 or >10 to ≤30) and by region (North America and Western Europe, Eastern Europe or ROW). Additionally, the number of patients with a perforated appendix or an appendiceal abscess was limited to approximately 40% of the study population in the combined study database.

Blinding (masking)

The study was double-blind with double dummy infusions. The unblinded pharmacist/designee at each site was responsible for maintaining accountability and preparing the blinded IV study therapy.

Statistical methods

Analysis populations

MITT analysis set = all randomised and treated who met the disease definition of cIAI

mMITT analysis set = all randomised who met the disease definition of cIAI and had at least 1 aetiologic pathogen at study entry except for those not expected to respond to either treatment

CE analysis set = patients with an appropriate diagnosis of cIAI and (a) received therapy for ≥ 48 h with ≥80% of the scheduled drug administered or (b) received therapy for < 48 h before discontinuing due to an AE. In addition, these patients had a documented outcome at ≥ 1 of EOT, TOC or LFU visits and no important protocol deviations that would affect assessment of efficacy, including adequate source control.

ME analysis set = CE with **≥** 1 Gram-negative aerobic pathogen in the initial/pre-study culture susceptible to both treatments

Extended ME (eME) analysis set = CE patients with ≥ 1 Gram-negative aerobic pathogen in the initial/pre-study culture regardless of susceptibility.

Patients in the CE, ME and eME analysis sets were analysed according to the treatment they received while the MITT and mMITT analysis sets were analysed according to randomised treatment.

Statistical analyses of comparisons between CAZ-AVI vs. meropenem calculated 2-sided 95% CIs using the unstratified method of Miettinen and Nurminen (1985). Patients with a missing assessment at the EOT, TOC or LFU visit were assigned a clinical response of indeterminate, in which case they were counted as failures in the statistical analysis for the mMITT set at the relevant time point.

Non-inferiority was to be concluded if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) was greater than –12.5% for the primary outcome variable. Assuming that both treatments had an underlying clinical cure rate of 70% in the mMITT analysis set, 442 randomised patients per treatment were needed. This number provided at least 90% power for the MITT and CE analysis sets. Assuming that 80% of all randomised patients were included in the mMITT analysis set, 553 randomised patients per treatment group (1106 total) were needed across the two studies.

Results

There were 1058 patients randomised (529 per treatment group) who received at least one dose of assigned study therapy. The majority (89.1% CAZ-AVI and 92.5% meropenem) completed treatment and few patients discontinued due to AEs (14 [2.6%] CAZ-AVI and 7 [1.3%] meropenem). The majority of patients (~90%) also completed the study.

Baseline data

There were no important differences between treatment groups for demographic characteristics in any of the primary analysis sets. Mean and median baseline APACHE II scores were 6.5 and 6.0, respectively, and scores were ≤ 10 for 84.5% of patients. The majority (91.5%) had normal renal function or mild renal impairment while 8.1% had moderate renal impairment. In the MITT analysis set, the most common primary diagnoses were appendiceal perforation (41.3%), acute gastric and duodenal perforation (18.7%) and cholecystitis (15.7%). About half was enrolled preoperatively (48.5% CAZ-AVI and 49.7% meropenem) and 76.8% underwent laparotomy as the initial surgical intervention. Prior antibacterial therapy within 72 h before randomisation was reported for 62% per group (much of this was metronidazole) but < 6% had received > 24 h and ~6% had a previous treatment failure.

Regarding baseline pathogens:

- The mMITT population comprised 77.2% of randomised patients and ≥ 1 *Enterobacteriaceae* was reported for >80% of these patients. 21 [4.2%] CAZ-AVI vs. 14 [2.7%] meropenem patients were bacteraemic, with *E. coli* in 14/35.
- Twelve patients were included in the eME but not in the ME at TOC analysis sets due to 13 Gram-negative aerobic pathogens not susceptible (3) or missing result (10).
- For 794 *Enterobacteriaceae* in the mMITT set the **CAZ MIC** range was ≤ 0.03 to > 64 µg/mL with MIC_{90} 16 µg/mL. Of these, 108 were CAZ-R (MIC ≥ 8 µg/mL), including 59 *E. coli*, 26 *K. pneumoniae* and 10 *E. cloacae*. There were also 6 CAZ-R *P. aeruginosa* (MIC ≥ 16 µg/mL).
- For the CAZ-R *Enterobacteriaceae* the **CAZ-AVI MIC** range was ≤ 0.008 to > 32 µg/mL with an MIC_{90} of 2 µg/mL. CAZ-AVI MICs > 8 µg/mL occurred in 8 CAZ-R isolates.

Outcomes and estimation

In the MITT population 99% received 80-120% of the assigned medication. The median duration was 7 days for CAZ-AVI vs. 8 days for meropenem and 93.2% vs. 97% received 5-14 days.

Non-inferiority was demonstrated in the US FDA primary analysis (cure rates in mMITT at TOC) and in the CHMP primary analysis (cure rate in MITT and CE at TOC). Sensitivity analyses and analyses of the primary outcome adjusted for the pre-specified stratification factors gave results that were consistent with the primary analysis in each case.

Table 26 Clinical response at TOC (mMITT analysis set)

	Number (%) of patients		
Response	CAZ-AVI + Metronidazole (N=413)	Meropenem (N=410)	Difference[a] (95% CI)[b]
Clinical cure	337 (81.6)	349 (85.1)	-3.5 (-8.64, 1.58)
Clinical failure	37 (9.0)	30 (7.3)	
Indeterminate	39 (9.4)	31 (7.6)	

Table 27 Clinical response at TOC (MITT analysis set)

Response	Number (%) of patients: CAZ-AVI + Metronidazole (N=520)	Meropenem (N=523)	Difference[a] (95% CI)[b]
Clinical cure	429 (82.5)	444 (84.9)	-2.4 (-6.90, 2.10)
Clinical failure	47 (9.0)	39 (7.5)	
Indeterminate	44 (8.5)	40 (7.6)	

Table 28 Clinical response at TOC (CE at TOC analysis set)

Response	Number (%) of patients: CAZ-AVI + Metronidazole (N=410)	Meropenem (N=416)	Difference[a] (95% CI)[b]
Clinical cure	376 (91.7)	385 (92.5)	-0.8 (-4.61, 2.89)
Clinical failure	34 (8.3)	31 (7.5)	

Forest plots for the MITT analysis set reflected the almost consistent numerical inferiority of CAZ-AVI in all subgroups of any reasonable size and in many of the small subgroups. Lower cure rates at TOC were observed for CAZ-AVI in patients with APACHE II scores > 10 in each analysis set. In particular, in the mMITT set the rates were 59.3% vs. 75.8%. Nevertheless, CHMP agreed that, despite this limitation, the benefit-risk of Zavicefta in cIAI was positive (see also uncertainties of the benefit-risk at the end of this report)

Figure 6 Difference in clinical cure rate at TOC by baseline patient characteristic subgroup-forest plot (MITT analysis)

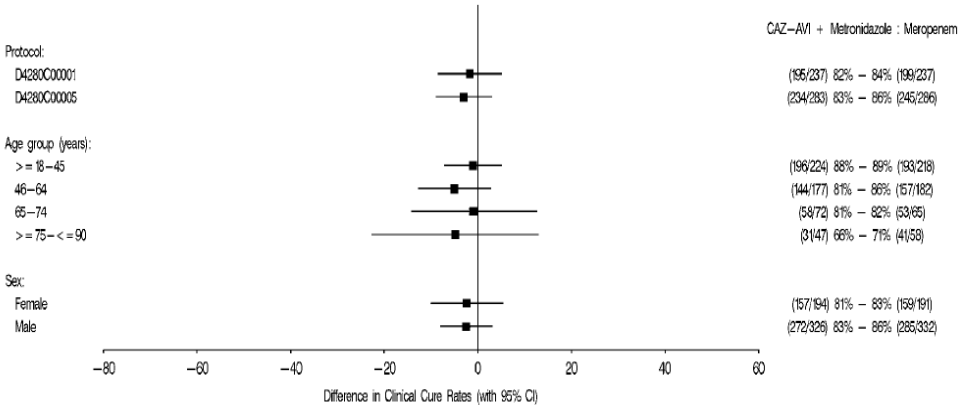
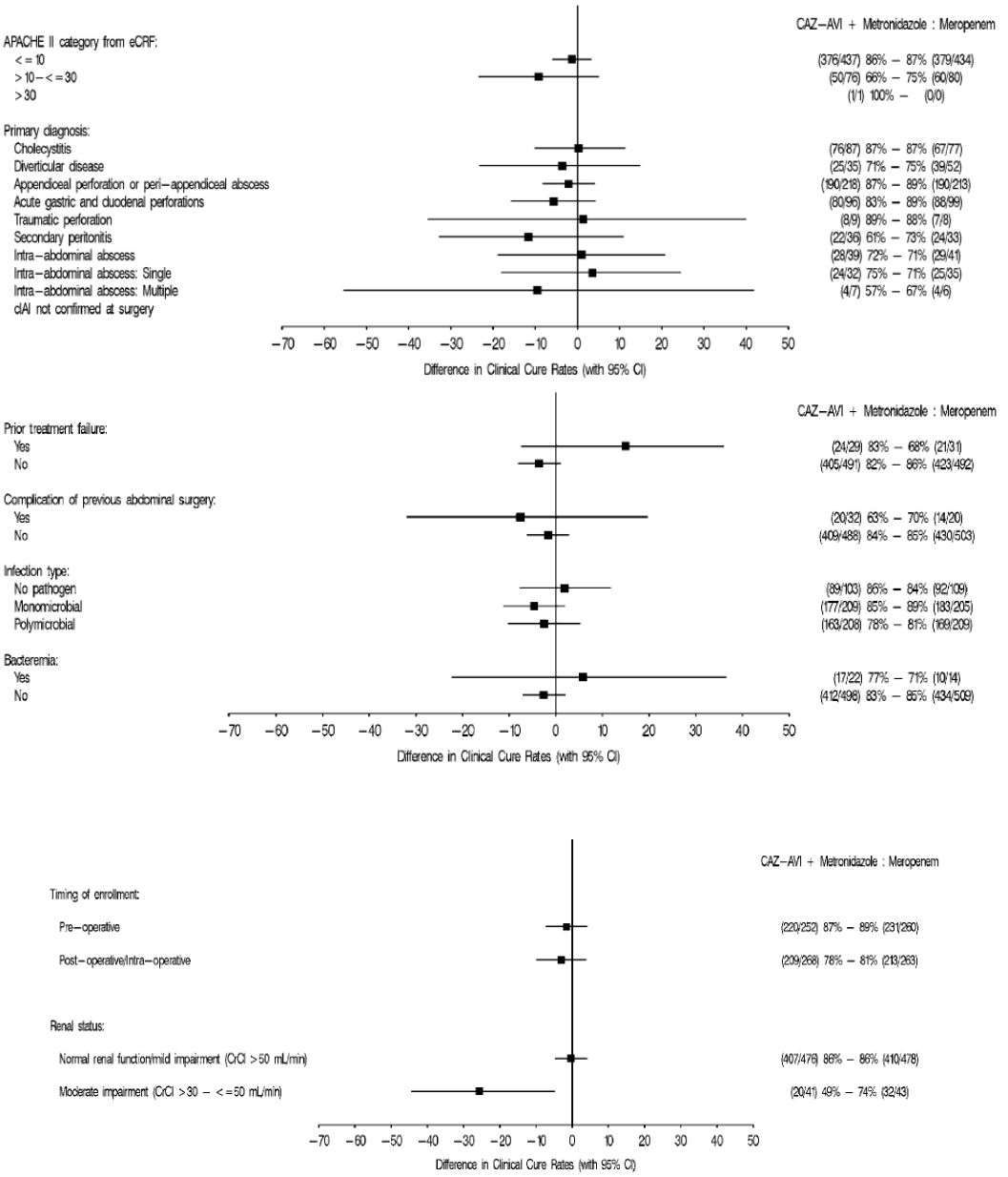


Figure 7 Difference in clinical cure rate at TOC by baseline disease characteristic subgroup-forest plot (MITT analysis)



Ancillary analyses

In the MITT and mMITT analysis sets the cure rates were 48.8% and 45.2% for CAZ-AVI in patients with moderate renal impairment at baseline (MRIB) vs. 74.4% and 74.3%, respectively, in the meropenem group. CAZ and AVI plasma exposures on Day 3 were similar for those with CrCL > 30 to ≤ 50 mL/min vs. > 50 mL/min at baseline. However, based on serum creatinine values there were 27/41 CAZ-AVI and 30/43 meropenem MITT patients with baseline moderate impairment who had an increase on treatment to > 50 mL/min within 72 h so were potentially under-dosed some period of time during early treatment.

To assess whether disease severity could explain the observed treatment difference in the MRIB subgroup, a multivariate logistic regression model was constructed using clinical failure as the response variable; key variables assessing patient disease severity (including APACHE II score) were tested in conjunction with MRIB status. The MRIB by treatment interaction remained even when severity of illness factors (including APACHE II, age, diagnosis, type, bacteraemia and serum albumin) were corrected for.

- When MRIB treatment interaction term was included in the model, it was found to be significant, indicating that the outcome in MRIB status groups was significantly different between treatment arms
- When APACHE II category was instead included in the model as the interaction term, this was not significant, indicating that outcome in APACHE II category groups was not significantly different between treatment arms.

The investigation was extended to include a range of variables thought to be indicative of severity. A series of univariate analyses were performed on potential severity factors (age group [≥75 vs <75 years old], diagnosis type [appendicitis vs non-appendicitis], bacteraemia, albumin, MRIB status and APACHE II category [≤10 vs >10]). All were found to have significant main effects at the 0.2 level, indicating they were prognostic of clinical outcome overall but only MRIB had a significant interaction with treatment.

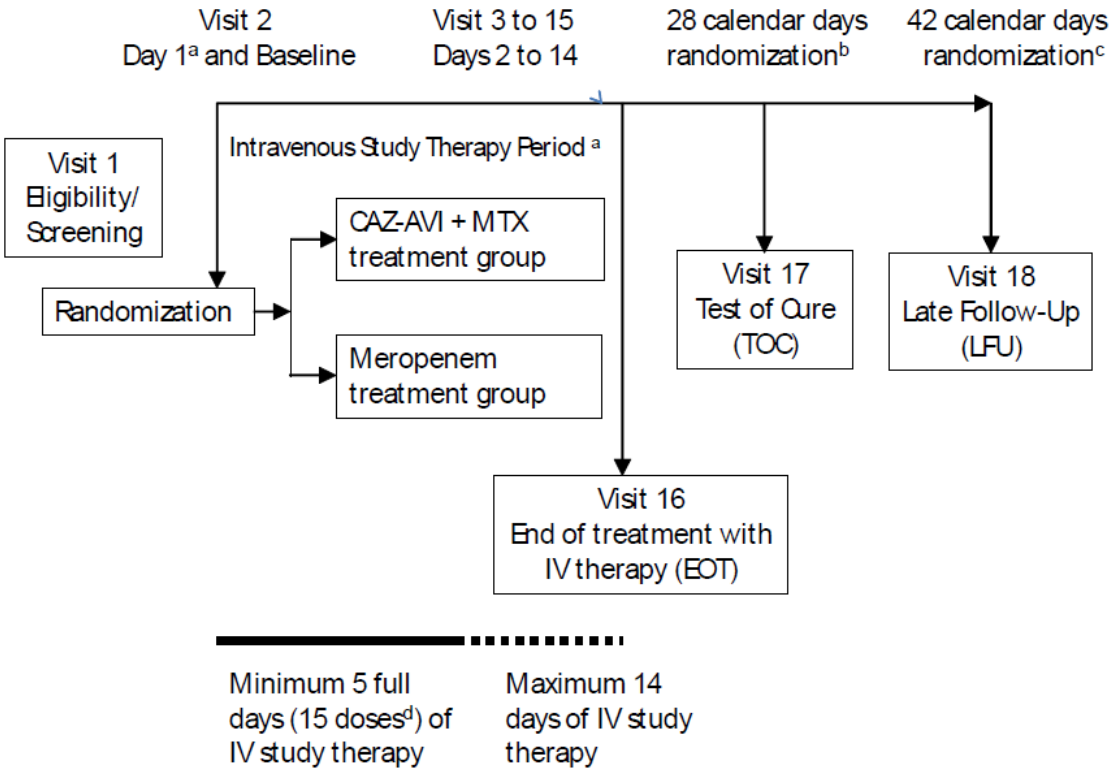
The multivariate analysis was repeated using the severity of illness terms above and including the MRIB by treatment interaction term. The result of this analysis showed that the MRIB by treatment interaction remained significant (p=0.0467) in a model that corrected for the severity terms. Thus, there was statistical evidence of a difference in the treatment effect in the MRIB subgroups when severity factors had been corrected for.

In MITT subgroups with ≥15 patients per treatment arm (21 subsets in total), numerical inferiority in the CAZ-AVI group was most prominent in patients recruited into D4280C0005, aged 46 to 64 or 65 to 74, females, Whites, located at Rest of World sites, with acute gastric and duodenal perforations, who had not failed prior therapy, without complication of previous abdominal surgery, with monomicrobial infections, enrolled post- or intra-operatively and with MRIB. In each case the 95% CIs spanned zero and if patients with MRIB were removed from the analysis the treatment difference was greatly reduced or disappeared in the majority of these patient subsets.

In the mMITT analysis set cure rates at TOC in patients with one or more *Enterobacteriaceae* were 81.4% for CAZ-AVI and 86.4% for meropenem. For *E. coli* (271 CAZ-AVI and 285 meropenem group) cure rates at TOC were 80.4% vs. 87.0%, respectively, and failures in the CAZ-AVI group were observed at low CAZ-AVI MIC values (commonly these were 0.06 µg/mL and 0.12 µg/mL). Against *K. pneumoniae* the cure rates at TOC were comparable (78.4% and 75.5%) while for *P. aeruginosa* the rates were 85.7% and 94.4%, respectively. Similar results were seen in the extended ME and ME analysis sets.

There were 111 mMITT patients (47 CAZ-AVI and 64 meropenem) with CAZ-R Gram-negative isolates, including *E. coli* in 24 vs. 37 and *K. pneumoniae* in 13 per treatment group. The cure rates at TOC for all *Enterobacteriaceae* were 81.8% and 85.5%, respectively. In the ME analysis set the clinical cure rates at TOC for CAZ-R *Enterobacteriaceae* were 90.9% and 98.0%, respectively, In the extended ME analysis set rates were 88.6% and 98.0%, respectively.

Participant flow



[a] Administration of the first dose of IV study therapy marked the beginning of study Day 1. Subsequent study days were based on 24-hour periods from the start time of the first infusion.

[b] If it was not possible to perform the TOC visit 28 calendar days from randomization (eg, the patient was on holiday), the allowed visit window was 28 to 35 calendar days from randomization.

[c] If it was not possible to perform the LFU visit 42 calendar days from randomization (eg, the patient was on holiday), the allowed visit window was 42 to 49 calendar days from randomization.

[d] For patients with normal renal function and patients with mild renal impairment.

Study title:

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults (D428-C00018, RECLAIM 3)

RECLAIM3 was a Phase 3 randomized, multicentre, double-blind, double-dummy, parallel group, comparative study designed to determine the efficacy, safety and tolerability of CAZ-AVI plus MTZ versus meropenem, in the treatment of cIAIs in hospitalized adults recruited from centres in the Asia-Pacific region.

Methods

Study participants

Inclusion criteria: Hospitalized patients (18 to 90 years of age, inclusive) with a presumed (preoperative) or definitive (intraoperative or postoperative) diagnosis of cIAI.

The exclusion criteria were similar to those used in the RECLAIM trial.

Patients were stratified by baseline APACHE II score (≤10 or >10 to ≤30) and by country (China and non-China). It was planned to enrol 404 patients, of which ~250 were to be enrolled in China to provide ~200 CE Chinese patients.

Treatments

Patients randomized to receive CAZ-AVI plus metronidazole, received IV meropenem placebo (0.9% saline) immediately followed by IV CAZ-AVI (2000 mg of ceftazidime and 500 mg of avibactam), immediately followed by IV metronidazole (500 mg). Patients randomized to receive meropenem, received IV meropenem (1000 mg) immediately followed by IV CAZ-AVI placebo (0.9% saline), immediately followed by IV metronidazole placebo (0.9% saline). Treatments were repeated every 8 hours (±30 minutes). Dose adjustments were made for CAZ-AVI or meropenem for patients whose creatinine clearance (CrCl) dropped to between 31 and 50 mL/min while on IV study therapy.

Objectives

The primary efficacy objective was to assess the non-inferiority of CAZ-AVI plus metronidazole compared to meropenem alone with respect to clinical cure at the TOC in patients that were clinically evaluable

Key secondary objectives included determination of the efficacy of CAZ-AVI plus MTZ compared to meropenem with respect to: clinical cure across visits and analysis sets, per-patient and per-pathogen microbiologic response, pathogens resistant to ceftazidime, and evaluation of the safety and tolerability profile of the 2 treatments.

Results

There were 432 randomised and treated of which 398 completed treatment and 295 (67%) had at least one acceptable baseline pathogen. Demographic, patient and disease characteristics were balanced across the treatment groups. The mean age was 48.5 years, with 58 aged 65-74 and 31 aged >74 years. The majority (93.3%) had normal renal function or mild renal impairment at baseline. In the MITT analysis set, the most common primary diagnoses were appendix perforation or peri-appendiceal abscess (37.6%), secondary peritonitis (17.2%) and cholecystitis (13.9%). Only 5 CAZ-AVI and 10 meropenem patients had bacteraemia and only 29 (7%) had APACHE II scores >10-30.

The primary analysis in the CE population (361 patients; 82% of total) met the pre-defined criterion for concluding non-inferiority. After adjustment for stratification factors, the difference in cure rates at TOC for CE patients was estimated as 0.4% (95% CI: -4.97 to 5.69).

Table 28 Clinical response at TOC (CE analysis set)

	Number (%) of patients		
Response	CAZ-AVI + MTZ (N=177)	Meropenem (N=184)	Difference[a] (95% CI)[b]
Clinical cure	166 (93.8)	173 (94.0)	-0.2 (-5.53, 4.97)
Clinical failure	11 (6.2)	11 (6.0)	

[a] Difference in clinical cure rates (CAZ-AVI + MTZ treatment group minus meropenem treatment group)
[b] The confidence interval (CI) for the difference is calculated using the unstratified Miettinen & Nurminen method

Results were consistent in the MITT (83.2% vs. 86.6%; -10.33, 3.35) and ME (92.9% vs. 94.7%; -9.25, 5.09) populations. Rates for the mMITT population were 83.2% vs. 88.8%; -13.8, 2.36). Rates for cure at LTFU in the CE population were 157/168 (93.5%) and 168/179 (93.9%).

The cure rates at TOC in the CE population by subgroups were generally consistent with the overall results. In patients with APACHE II score >10 to ≤30 the cure rates in the mMITT analysis set were 5/7 (71.4%) for CAZ-AVI and 12/12 (100%) for meropenem; rates for the CE analysis set were 7/8 vs. 11/12.

Clinical cure rates for MITT patients with MRIB were 92.3% for CAZ-AVI (n=13) and 81.3% for meropenem (n=16); rates in the mMITT analysis set were 91.7% (n=12) and 81.8% (n=11).

In the eME population the microbiological response rates at TOC were 93% for CAZ-AVI vs. 95% for meropenem (-9.33, 4.63). Corresponding rates in the mMITT population were the same as the clinical cure rates reported above.

Microbiological response rates by pathogen at TOC were 92.9% vs. 96.3% for *E. coli* and >90% for *Enterobacteriaceae* and ~90% for *P. aeruginosa* for both treatments. Clinical cure rates at TOC for ME patients with CAZ-S *Enterobacteriaceae* were 91.4% vs. 96.3%, reflecting the rates for *E. coli* (92.6% vs. 96.2%). Clinical responses for CAZ-R pathogens are shown below for the eME population. The corresponding rates for the mMITT population were 81.5% for CAZ-AVI and 92.9% for meropenem. For CAZ-S and CAZ-R pathogens the microbiological response rates followed the clinical cure rates.

Table 29 Clinical response at TOC for patients infected by ceftazidime resistant Gram-negative pathogens (extended ME analysis set)

	Number of patients							
	CAZ-AVI + Metronidazole (N=100)			Meropenem (N=119)			Comparison between groups	
Pathogen	Cure Rate (%)	Number of clinical cures	n	Cure Rate (%)	Number of clinical cures	n	Difference[a](%)	95% CI[b] for % difference
All	95.7	22	23	96.2	25	26	-0.5	(-17.93, 15.43)
Enterobacteriaceae	95.2	20	21	96.0	24	25	-0.8	(-19.51, 15.78)
Escherichia coli	92.9	13	14	95.7	22	23	-2.8	(-28.19, 15.54)
Klebsiella pneumoniae	100	3	3	100	1	1	0.0	(-63.06, 83.67)
Gram negative pathogens other than *Enterobacteriaceae*	100	2	2	100	1	1	0.0	(-74.23, 85.21)

Study title

An Open-Label, Randomized, Multicenter, Phase III Study of Ceftazidime-Avibactam (CAZ-AVI) and Best Available Therapy for the Treatment of Infections Due to Ceftazidime-Resistant Gram-Negative Pathogens (D4280C00006 [REPRISE])

Methods

Study Participants

Patients had to have cUTI or cIAI due to CAZ-R pathogens. Identification of pathogens and susceptibility results were recorded by local and central reference laboratories. The local laboratory result is used to determine study eligibility whilst the central laboratory result is used to determine inclusion in the mMITT population unless only the local result is available. The central laboratory uses CLSI methods while local laboratories may use other methods.

- Based on central laboratory results aerobic Gram-negative pathogens with CAZ MICs ≥ 8 µg/mL for *Enterobacteriaceae* and ≥ 16 µg/mL for *P. aeruginosa* are deemed to be CAZ-R. If only local laboratory disk testing is available then zone diameters ≤ 20 mm for *Enterobacteriaceae* and ≤ 17 mm for *P. aeruginosa* are applied.

- Susceptibility to CAZ-AVI is provisionally based on MICs ≤8 µg/mL for all aerobic Gram-negatives and on zone diameters ≥16 mm for *Enterobacteriaceae* and ≥15 mm for *P. aeruginosa*.

cIAI Patients

Inclusion criteria were generally similar to those applied in RECLAIM but patients needed to have at least two signs and symptoms suggesting systemic manifestations of infection and peritonitis.

cUTI Patients

- Patients needed to have a positive urine culture in the 5 days prior to screening, containing ≥ 10^5 CFU/mL of ≥ one Gram-negative CAZ-R uropathogen and accompanied by pyuria (≥ 10 WBCs/hpf or ≥ 10 WBCs/mm^3 in unspun urine).
- Patients had acute pyelonephritis or cUTI defined by the following criteria:

(a) Acute pyelonephritis indicated by flank pain (with onset or worsening within 7 days of enrolment) or costovertebral angle tenderness on examination and ≥ one of i) fever (> 38°C) ± rigor, chills or warmth or ii) nausea and/or vomiting

(b) Complicated lower UTI indicated by qualifying symptoms and ≥ one complicating factor as follows:

Symptoms - at least 2 of the following including at least one Group A symptom (dysuria, urgency, frequency, suprapubic pain) and any Group B symptom (fever defined as in pyelonephritis)

Complicating factors - any of history of urinary retention (male patients), obstructive uropathy scheduled to be medically or surgically relieved before EOT, functional or anatomical abnormality of the urogenital tract or post-void residual urine volume of at least 100 mL, use of intermittent bladder catheterisation or an indwelling bladder catheter for at least 48 h prior to qualifying culture, or any urogenital procedure (such as cystoscopy or urogenital surgery) within 7 days before qualifying culture.

Exclusion criteria

The exclusion criteria were similar to those used in the RECLAIM trial.

Treatments

CAZ-AVI was dosed as in RECLAIM with metronidazole added for cIAI patients. The dose of CAZ-AVI is adjusted in case of renal impairment. The preferred BAT options for cUTI were meropenem, imipenem, doripenem and colistin. The preferred BAT options for cIAI were meropenem, imipenem, doripenem, tigecycline and colistin (latter ± metronidazole for cIAI patients). If another BAT was chosen, or combination therapy was given, the investigator had to document the reason. Intravenous therapy (CAZ-AVI or BAT) was continued for 5-21 days as selected by the investigator.

Objectives

The primary objective was to estimate the per-patient clinical response to CAZ-AVI and BAT at TOC in patients with cIAI or cUTI due to CAZ-R pathogens. The study is not powered for inferential testing.

Outcomes/endpoints

Clinical and microbiological outcomes in cIAI are assessed as for RECLAIM. The primary efficacy variable for cUTI patients is the microbiological response defined as eradication < 10^4 cfu/mL and persistence ≥ 10^4 cfu/mL.

Sample size

Approximately 400 patients (200 CAZ-AVI) with cIAI or cUTI caused by CAZ-R Gram-negative pathogens were to be enrolled. The study was not powered for inferential testing.

Randomisation

Patients were randomly assigned in a 1:1 ratio to CAZ-AVI or their pre-determined BAT using IVRS/IWRS with stratification by diagnosis (cIAI or cUTI) and by region.

Blinding

This was an open label study.

Statistical methods

Two-sided 95% CI for the treatment group response rates are calculated using the Jeffreys method for the percentages in the efficacy summaries. No formal statistical comparisons between treatment groups will be performed.

Results

The majority of patients had cUTI (91.9%) and only 27/333 had cIAI. There were 332 treated of which 322 completed treatment and 302 completed the TOC visit. The mean age was 63 years and >80% came from E. Europe. Among cUTI patients 45.2% had acute pyelonephritis. There were 25 CAZ-AVI (17.4%) and 24 BAT (17.5%) patients without a proven CAZ-R pathogen at baseline.

Overall, 97% of BAT patients received a carbapenem, mostly imipenem or meropenem monotherapy. Six patients had baseline pathogens resistant to the BAT received (of which 4 or 5 were nevertheless cures).

In both the mMITT and extended microbiologically evaluable (eME) analysis sets, CAZ-AVI generally achieved similar clinical cure rates to BAT at each visit. Comparable cure rates were observed at TOC.

Table 30 Clinical response at TOC (mMITT analysis set)

	Number (%) of patients					
	cIAI		cUTI		cIAI+cUTI	
Response	CAZ-AVI+ MTZ (N=10)	BAT (N=11)	CAZ-AVI (N=144)	BAT (N=137)	CAZ-AVI[a] (N=154)	BAT (N=148)
Clinical cure	8 (80.0)	6 (54.5)	132 (91.7)	129 (94.2)	140 (90.9)	135 (91.2)
95% CI[b] for clinical cure	(49.7, 95.6)	(27.0, 80.0)	(86.3, 95.4)	(89.3, 97.2)	(85.6, 94.7)	(85.9, 95.0)
Clinical failure	0	0	2 (1.4)	2 (1.5)	2 (1.3)	2 (1.4)
Indeterminate	2 (20.0)	5 (45.5)	10 (6.9)	6 (4.4)	12 (7.8)	11 (7.4)

[a] CAZ-AVI includes metronidazole for cIAI patients.
[b] Confidence intervals for the individual treatment groups were calculated using the Jeffreys method.

Cure rates for pyelonephritis were 91.2% vs. 90% for BAT and for cUTI the rates were 92% vs. 98.5%. The two clinical failures treated with CAZ-AVI did not have documented CAZ-AVI-R isolates at baseline or at time of failure.

In the mMITT analysis set, the per-patient favourable microbiological response for cUTI patients at the TOC visit was higher in the CAZ-AVI group. A similar result was obtained in the eME population.

Table 31 Per-patient microbiological response at TOC (mMITT analysis set)

	Number (%) of patients					
	cIAI		cUTI		cIAI+cUTI	
Microbiological response	CAZ-AVI+MTZ (N=10)	BAT (N=11)	CAZ-AVI (N=144)	BAT (N=137)	CAZ-AVI[a] (N=154)	BAT (N=148)
Favorable	8 (80.0)	6 (54.5)	118 (81.9)	88 (64.2)	126 (81.8)	94 (63.5)
95% CI for Favorable response[b]	(49.7, 95.6)	(27.0, 80.0)	(75.1, 87.6)	(56.0, 71.9)	(75.2, 87.3)	(55.6, 70.9)
Unfavorable	0	0	17 (11.8)	42 (30.7)	17 (11.0)	42 (28.4)
Indeterminate	2 (20.0)	5 (45.5)	9 (6.3)	7 (5.1)	11 (7.1)	12 (8.1)

[a] CAZ-AVI included metronidazole for cIAI patients.
[b] Confidence intervals for individual treatment groups were calculated using the Jeffreys method.

The per-pathogen favourable microbiological response rate at the TOC visit for the most common Gram-negative pathogens isolated from urine of cUTI patients was also higher in the CAZ-AVI group.

The definition used for eradication of urinary pathogens was absence of causative pathogen or urine quantification $<10^4$ CFU/mL. Data using the EU definition of eradication ($<10^3$ CFU/mL) were not collected. However, the majority of patients with a favourable microbiological response at post-baseline visits had urine specimens that showed no growth.

Table 32 Per patient microbiological response by visit REPRISE cUTI (mMITT analysis set)

Visit	Response[b,c]	Number (%) of patients[a]	
		CAZ-AVI (N=144)	BAT (N=137)
Test of cure	Favorable	118 (81.9)	88 (64.2)
	95% CI for favorable response	(75.1, 87.6)	(56.0, 71.9)
	No growth	89 (61.8)	67 (48.9)
	Other	29 (20.1)	21 (15.3)
	Unfavorable	17 (11.8)	42 (30.7)
	Indeterminate	9 (6.3)	7 (5.1)

Four cUTI patients had *E. coli* that had CAZ-AVI MICs of 8 µg/mL and all were cures at TOC. One patient with *K pneumoniae* (MIC >256 µg/mL) and one with *E. cloacae* (MIC >256 µg/mL) were clinical cures as were two patients with *P. aeruginosa* for which MICs were 8 µg/mL. Nine other patients had *P. aeruginosa* isolates with CAZ-AVI MICs 16-256 µg/mL. Seven were clinical cures and the two had indeterminate responses.

In the mMITT analysis set at TOC 17 cUTI patients (11.8%) in the CAZ-AVI group and 42 (30.7%) in the BAT group had persistence of the baseline species. At the FU1 visit, there were 29 (20.1%) vs. 50 (36.5%) in respective groups with persistence, and 35 (24.3%) vs. 54 (39.4%) at the FU2 visit. A mixture of species accounted for these persisters. A *post hoc* manual review indicated that BAT patients with persistence appeared to be dosed appropriately and the duration of exposure to study treatment was similar between treatment groups. The majority of baseline MIC values for the relevant BAT were in the susceptible range with the exception of 7 cUTI patients, of which one had an unfavourable microbiological response from the EOT visit, 3 had an unfavourable microbiological response from the TOC visit onwards and one at the FU2 visit. In the mMITT analysis set, there were 19 cUTI patients in the CAZ-AVI group and 18 cUTI patients in the BAT group with MRIB, of which 17/19 and 16/18 were clinical cures at the TOC visit while 14 and 13, respectively, had a favourable microbiological response. All nine and four with baseline CrCL of 16 to 30 mL/min or 6 to 15 mL/min were clinical cures at TOC.

Study title:

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam Versus Doripenem Followed by Appropriate Oral Therapy in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, With a Gram-Negative Pathogen in Hospitalized Adults (D4280C0002/0004, RECAPTURE)

This was a Phase 3, randomised, double-blind, double-dummy study that compared CAZ-AVI vs. doripenem (500 mg q8h) for treatment of cUTI, with a switch to oral ciprofloxacin (500 mg BID; if Cip-R, SMX-TMP could be used) allowed after at least 5 days IV (total 10-14 days IV/PO).

Randomisation was stratified by type of infection (acute pyelonephritis or other cUTIs without pyelonephritis) and region (North America and Western Europe, Eastern Europe and ROW). The primary analysis was based on microbiological response (FDA definition) at TOC (21-25 days after randomisation). The pre-defined NI margin was -12.5% but analysis was repeated using -10% and also using the EU criterion for eradication ($<10^3$ CFU/mL). The sample size calculation gave 90% power to address the EU-recommended primary analysis.

There were 1020 randomised and treated (IV) patients of which 588 also received oral treatment and 944 completed the recommended treatment.

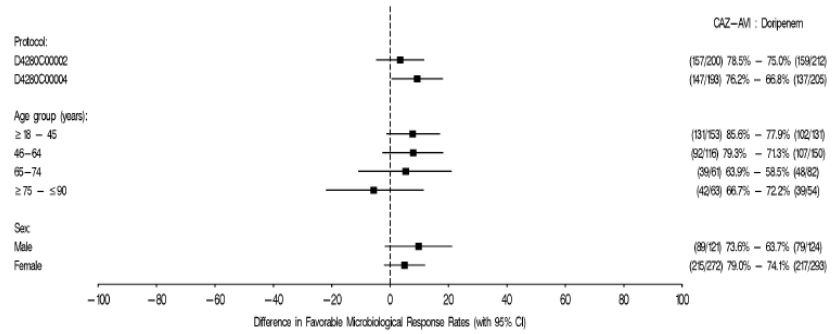
Patient and disease characteristics were well balanced between treatment arms. The mean age was 52.4 years, with 143 aged 65-74 and 117 aged ≥75 years. Most (90%) had normal renal function or mild impairment. Baseline microbiology showed the expected predominance of *E. coli* (in 73.8% of patients).

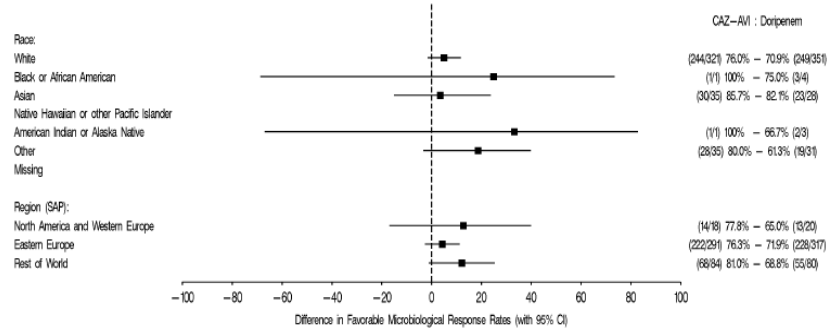
Overall 810 were included in the mMITT set (207 did not have a qualifying culture) and 603 were eligible for the eME set. Overall in the mMITT population 72% had pyelonephritis, of which 503 had no complicating factors, and 28% had cUTI.

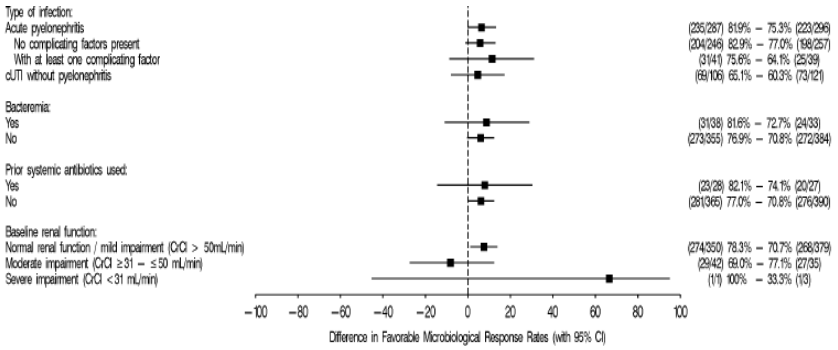
Non-inferiority (based on 10% NI margin) of CAZ-AVI vs. doripenem was demonstrated for rates of microbiological response (at $< 10^4$ cfu/mL) and symptomatic response at TOC. For microbiological responses the lower bound of the 95% CI was above zero. The same finding applied after adjusting the microbiological response rates for stratification factors. The per-patient microbiological responses at the end of intravenous therapy (EOT [IV]) visit were 95.2% for CAZ-AVI vs. 94.7% for doripenem. Microbiological responses at TOC also favoured CAZ-AVI in the ME and eME sets.

The subgroup analyses of microbiological responses at TOC in the mMITT population favoured CAZ-AVI except in the subset aged >74 years and in those with MRIB.

Figure 8 Difference in per-patient favourable microbiological response rate at TOC by baseline patient characteristics subgroup-forest plot (mMITT analysis set)







When the EU criterion ($<10^3$ CFU/mL) was applied there was still numerical superiority for CAZ-AVI and the lower bound of the 95% CI just exceeded zero.

Table 33 Summary of per-patient microbiological response and combined response at TOC (mMITT analysis set)

		Number (%) of patients		
		CAZ-AVI (N=393)	Doripenem (N=417)	Difference[a] (%) (95% CI[b])
Per-patient microbiological response				
$<10^3$ CFU/mL cut-off	Favorable	299 (76.1)	291(69.8)	6.3 (0.17, 12.38)
	Unfavorable	63 (16.0)	85 (20.4)	
	Indeterminate	31 (7.9)	41 (9.8)	
$<10^4$ CFU/mL cut-off	Favorable	304 (77.4)	296 (71.0)	6.4 (0.33, 12.36)
	Unfavorable	58 (14.8)	83 (19.9)	
	Indeterminate	31 (7.9)	38 (9.1)	
Combined response				
$<10^3$ CFU/mL cut-off	Favorable	275 (70.0)	264 (63.3)	6.7 (0.16, 13.10)
	Unfavorable	86 (21.9)	111 (26.6)	
	Indeterminate	32 (8.1)	42 (10.1)	
$<10^4$ CFU/mL cut-off	Favorable	280 (71.2)	269 (64.5)	6.7 (0.30, 13.12)
	Unfavorable	81 (20.6)	109 (26.1)	
	Indeterminate	32 (8.1)	39 (9.4)	

[a] Difference in favorable response rates (CAZ-AVI treatment group minus doripenem treatment group)
[b] The CI for the difference is calculated using the unstratified Miettinen and Nurminem method

The per-pathogen microbiological eradication rates were generally comparable between treatments for common pathogens, including *E cloacae, E. coli, K. pneumoniae, P. mirabilis and P. aeruginosa.*

CAZ-R Gram-negative pathogens were found in 75 CAZ-AVI and 84 doripenem mMITT patients. The favourable per-patient microbiological response rates at TOC for this subset were 47 [62.7%] and 51 [60.7%] in respective groups. At LFU the corresponding rates were 46 [61.3%] and 38 [45.2%].

The apparent numerically superior responses to CAZ-AVI vs. doripenem did not reflect baseline resistance to doripenem. In the mMITT analysis set, for all *Enterobacteriaceae* isolates (n=772) the doripenem MIC range was ≤0.008 µg/mL to >16 µg/mL with MIC_{90} 0.06 µg/mL. Four isolates (2 from each treatment) had MICs ≥2 µg/mL (1 *K. oxytoca;* 3 *K. pneumoniae*) but all other isolates had doripenem MICs ≤1 µg/mL. For 38 *P. aeruginosa* isolates the doripenem MIC range was 0.06 µg/mL to >16 µg/mL with an MIC_{90} of 16 µg/mL while 13 (8 CAZ-AVI group, 5 doripenem group) had MICs ≥4 µg/mL and all others were susceptible (MIC ≤2 µg/mL). Pathogens (27) resistant to one or both study drugs were excluded from the ME analysis but CAZ-AVI was still numerically superior to doripenem for per patient microbiological responses at TOC.

Supportive studies

Study NXL104 –2001 (cUTI) was a Phase 2, multi-center, investigator-blinded, randomized, two arm, parallel group (1:1) study to estimate the efficacy, safety, and tolerability of CAZ-AVI. A total of 137 patients received CAZ-AVI (500 mg CAZ /125 mg AVI 30 min IV infusion, q8h) vs. imipenem cilastatin (500 mg, 30 min IV infusion, q6h) in the treatment of adults with cUTI. After at least 4 days of IV therapy, patients with clinical improvement were permitted to switch to oral ciprofloxacin 500 mg every 12 hours to complete the treatment course. Patients were to receive 7-14 days of total antibiotic therapy (IV plus oral therapy). Approximately two-thirds of the patients enrolled in either treatment group had acute pyelonephritis. The study was not statistically powered to demonstrate non-inferiority to comparator.

Similar favourable microbiological response rates were seen in both treatment groups in the ME population at TOC (primary endpoint); 19/27 (70.4%) in the CAZ-AVI group and 25/35 (71.4%) in the

imipenem group. Similar favourable response rates were also seen across treatment arms at the end of IV therapy and at the late follow up.

Study NXL104 –2002 (cIAI) was a Phase 2, multi-center, double-blind, randomized study to evaluate the efficacy, safety, and tolerability of CAZ-AVI (500 mg/2 g IV over 30 min every 8 hours) plus metronidazole (500 mg IV over 1 hr every 8 hours) vs. meropenem (1 g IV over 30 min every 8 hours) for 5-14 days in adults with cIAI. A total of 102 patients were randomized into each treatment group. About half the patients in either treatment arm were enrolled with appendicitis. Race, gender, age, Apache II score (> 80% in each group had score ≤ 10), and BMI were generally similar across the treatment groups. *E. coli* was the most common pathogen isolated from the intra-abdominal site of infection in 73% of the patients across treatment groups. The study was not statistically powered to demonstrate non-inferiority to comparator.

Similar favourable clinical response rates in the ME population at TOC (primary endpoint) were seen in both treatment groups; 62/68 (91.2%) in the CAZ-AVI group and 71/76 (93.4%) in the meropenem group (observed difference [CAZ-AVI – meropenem] -2.2%, 95% confidence interval [-20.4%.12.2%]). The response rates were also similar at the discontinuation of IV therapy and Late Follow-up. In the APACHE II score category of 6-10 the cure rates were higher in the meropenem group (21/23, 91.3% vs. 17/21, 81% in the CAZ-AVI group). However, generally similar favourable response rates were seen in both treatment groups in each of these subgroup analyses.

In the ME population, 43 patients (26 in CAZ-AVI group and 17 in meropenem group, including 1 patient who had 2 baseline resistant pathogens) had baseline Gram negative pathogens that were resistant to CAZ alone. Favourable responses were seen for 25 of the 26 CAZ-R pathogens in the CAZ-AVI group, a response rate similar to that seen in the meropenem group (17/18 pathogens).

2.5.3. Discussion on clinical efficacy

For this FDC that combines a new beta-lactamase inhibitor with an approved beta-lactam, with which there is no PK interaction, the critical issue to support all the indications is to substantiate that the dose of AVI is sufficient to protect CAZ from hydrolysis by beta-lactamases proposed to be within the range of inhibition of AVI. The PTA analyses support 2 g/0.5 g q8h using 2 h infusions to treat each of cIAI, cUTI and NP. In addition, the applicant's revised dose adjustments for renal impairment are predicted to improve the PTA compared those applied during the reported Phase 3 studies, in which it seems that some moderate renal impairment at baseline (MRIB) patients may have been temporarily under-dosed.

Indication for use in patients with limited therapeutic options

This is supported by the microbiological data. Due to the ability of AVI to inhibit serine carbapenemases as well as a wide range of ESBLs and AmpC enzymes it is clear that the combination has potential utility for treatment of aerobic Gram-negative pathogens within the spectrum of CAZ. There are some clinical data already available to support clinical activity in two indications (cIAI and cUTI) against CAZ-R organisms that express a range of beta-lactamases although it should be noted there have been very few patients treated with CAZ-AVI who were infected with organisms expressing serine carbapenemases.

Standard indications claimed (cIAI, cUTI and NP)

As a result of an Article 30 harmonisation referral procedure, CAZ alone has (amongst others) the following indications for treatment:

• *Nosocomial pneumonia*

• *Complicated urinary tract infections*

• *Complicated intra-abdominal infections*

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

These indications are supported by the available data on CAZ, including the scientific literature include in this application.

The highest intermittent dose regimen for CAZ to treat all indications (except for CF) is 2 g q8h, which is the dose used in the CAZ-AVI FDC. The duration of infusion for CAZ alone is not specified, whereas 2 h is used for CAZ-AVI as a result of the PK-PD analyses. Since the adequacy of the dose of AVI is the critical issue for this application the following comments are made on each of the three standard indications currently sought:

Nosocomial pneumonia

There are no clinical efficacy data with CAZ-AVI in NP patients. The updated PTA analyses have included more extensive PK data from patients in REPROVE and have substantiated the adequacy of the plasma exposures, including for patients with ARC. The ELF data are supportive but it is not possible to place undue reliance of the analyses using these data. Although the available data on CAZ alone demonstrate efficacy in in the NP indication, it has some limitations, as previously highlighted in the Article 30 procedure. Therefore, although there seems to be sufficient evidence to allow an indication for NP it is essential that the SmPC adequately reflects the basis for this usage. Since the efficacy assessment in NP patients is primarily based on PK-PD analysis (complemented by clinical data on CAZ alone and on CAZ-AVI in other infections, as well as PK data from HAP patients), it is considered necessary to verify the impact on CAZ-AVI use on clinical outcomes, in order to confirm the efficacy assumptions. Therefore, provision of the full CSR from REPROVE, a post-authorisation efficacy study, is included as a condition in Annex II to the marketing authorisation.

cIAI

Although the initial Phase 2 study (NXL104/2002) suggested very high cure rates with CAZ-AVI 2 g/ 0.5 g q8h using 30 min infusions, analyses of the sparse sampling data suggested that 2 h infusions would provide more reliable cover for organisms with MICs at the upper end of desired range (8 mg/L). Therefore 2 h infusions were used in the Phase 3 studies RECLAIM and RECLAIM3.

RECLAIM was of adequate design and conduct and nearly 80% had at least one valid pathogen but the baseline APACHE scores were mostly low. The study met its pre-defined primary endpoint for demonstration of non-inferiority in compliance with CHMP and FDA requirements but CAZ-AVI (plus metronidazole for anaerobic cover) showed almost consistent numerical inferiority to meropenem in each pre-defined analysis population and patient subgroup.

Further analyses investigated the possible reasons for the lower cure rates especially in the MRIB population and those with APACHE II scores. It seems that the differences were mostly driven by the cure rates in the MRIB group since removal of these patients from the analyses removed or lessened the differences between treatments. In the MRIB group the cure rates in the MITT and mMITT analysis sets were 48.8% and 45.2% for CAZ-AVI vs. 74.4% and 74.3%, respectively, for meropenem. CAZ and AVI plasma exposures on Day 3 were similar for 35 CAZ-AVI patients with CrCL >30 to ≤50 mL/min vs. those with CrCL > 50 mL/min at baseline. Although day 3 plasma levels suggested appropriate dose adjustment, the patients on CAZ-AVI with rapid recovery in CrCL were more likely to have been temporarily under-dosed than similar patients on meropenem based on the greater %

reduction in recommended dose for the former vs. latter. This is a plausible explanation but there are no PK data to substantiate this claim.

It is of further concern that MITT patients with MRIB at baseline (n=84; 41 CAZ-AVI) predominated among the 21 total deaths such that 8/13 CAZ-AVI and 3/8 meropenem deaths involved such patients. Also, among the 9 deaths that were considered to be due to disease progression 5/6 in the CAZ-AVI group and 1/3 in the meropenem group were patients with MRIB.

While the observed differences between CAZ-AVI and meropenem in the MRIB sub-population are of concern the previous section has described the applicant's revisions of the dose adjustment schema in an attempt to reduce the risk of potential under-dosing. The dose for moderate renal impairment is increased from q12h to q8h and there are other adjustments to doses for lower CrCL. Nevertheless, the impact of the treatment responses in the MRIB group on the overall study cure rates should be stated in the SmPC.

The second cIAI study (RECLAIM3) had even fewer patients with high APACHE II scores and MRIB. This study generally showed very comparable cure rates between CAZ-AVI and meropenem and there was no numerical inferiority for CAZ-AVI in the small MRIB sub-group although there was in the sub-group with the highest APACHE II scores. This study supports the results of RECLAIM.

In general RECLAIM3 supports the findings of RECLAIM. However, the results in the mMITT population infected with enterobacterial species are somewhat anomalous and should be explored.

Overall, taking into account the revised dose adjustment schema, the data are considered sufficient to support an indication for cIAI but the MRIB results and the limitations of the patient population treated (including the low APACHE II scores, should be reported in section 4.4 of the SmPC).

cUTI

Since both CAZ and AVI are mainly excreted unchanged in urine it is expected that very high concentrations are reached in urine, which is important for cUTI. For acute pyelonephritis the tissue concentrations are also important but there are no specific concerns from available data regarding treatment of this subset with the same predicted dose as for cUTI.

In support of this indication there are clinical efficacy data from RECAPTURE, in which at least 5 days IV was required before oral switch, and from REPRISE in infections due to CAZ-R pathogens. Nearly half of patients in REPRISE and 72% in RECAPTURE had acute pyelonephritis but the response rates were generally similar to those for the cUTI population.

Although neither study pre-defined a primary endpoint as recommended by CHMP the data from RECAPTURE could be analysed accordingly and were reassuring regarding the comparative efficacy of CAZ-AVI vs. doripenem. The data from REPRISE were reported for $<10^4$ CFU/mL and for no growth and suggested that CAZ-AVI was at least as efficacious as BAT (noting that this study was not powered for formal inferential testing). REPRISE also provided a substantial body of evidence supporting the CAZ-AVI dose for treatment of CAZ-R pathogens although, due to high drug concentrations predicted in the urinary tract, it cannot necessarily be assumed that the same level of efficacy will be exerted at other sites. It should also be noted that very few pathogens expressing serine carbapenemases have been treated with CAZ-AVI.

2.5.4. Conclusions on the clinical efficacy

Taking into the information already available on the efficacy of CAZ, the clinical efficacy data for CAZ-AVI in cUTI and cIAI, including CAZ-R pathogens, and the PK-PD analyses that support the dose

adjustment schema and the application of the same posology to NP patients, the applicant's proposed indications are acceptable.

CHMP noted that the various limitations of the data are adequately reflected in the Zavicefta SmPC and agreed that the proposed indications were acceptable. The Applicant is requested to submit the final clinical study report for REPROVE as an annex II condition. The submission of the CSRs from the two ongoing paediatric studies was also requested by CHMP.

2.6. Clinical safety

The applicant's initial analysis of safety was based on the following datasets:

- **Phase 1 pool**: 11 Phase 1 CAZ-AVI or AVI-only studies that enrolled healthy volunteers or special populations and the AVI-only cohort from CXL PK-01
- **cIAI pool** (referred to as **DBC**): Phase 2 study (2002) and Phase 3 study (RECLAIM), which used the same CAZ-AVI standard dose regimen (2 g/0.5 g q8h) but different infusion times (30 min in Phase 2 and 2 h in Phase 3)
- **Phase 2 cUTI** study (2001), which used a lower dose of 0.5 g/0.125 g q8h

Patient exposure

The initial analyses focussed on the DBC cIAI pool, in which 630 patients received CAZ-AVI plus metronidazole and 631 received meropenem. The mean and median durations of exposure were ~ 8 days and 72% vs. 76% in respective treatment groups received 5-10 days.

During the procedure full CSRs were provided from RECLAIM3, RECAPTURE and REPRISE. The new/updated safety analysis sets added 890 CAZ-AVI patients to give a total of 1672 patients. The main safety features of these studies reported during the procedure are described separately below. However, integrated data are also described under some headings to provide a more complete picture (e.g. deaths).

Adverse events

In the DBC cIAI pool the incidences of AEs and other major features of the safety profile up to the last study visit were slightly higher for CAZ-AVI (with metronidazole) vs. meropenem.

Table 34 Adverse events up to last visit in any category –DBC cIAI pool (safety analysis set)

	Number (%) of patients[a]					
	Phase 2 cIAI (NXL104/2002)		Phase 3 cIAI (RECLAIM)		Total	
AE category	CAZ-AVI+MTZ (N=101)	Meropenem (N=102)	CAZ-AVI+MTZ (N=529)	Meropenem (N=529)	CAZ-AVI+MTZ (N=630)	Meropenem (N=631)
Any AE	65 (64.4)	59 (57.8)	243 (45.9)	227 (42.9)	308 (48.9)	286 (45.3)
Any AE with outcome of death[b]	3 (3.0)	2 (2.0)	8 (1.5)	5 (0.9)	11 (1.7)	7 (1.1)
Any SAE	9 (8.9)	11 (10.8)	42 (7.9)	40 (7.6)	51 (8.1)	51 (8.1)
DAE[c]	5 (5.0)	3 (2.9)	14 (2.6)	7 (1.3)	19 (3.0)	10 (1.6)
Any AE of severe intensity	4 (4.0)	8 (7.8)	30 (5.7)	36 (6.8)	34 (5.4)	44 (7.0)

[a] Patients with multiple AEs in the same category are counted only once in that category. Patients with AEs in more than 1 category are counted once in each of those categories.
[b] Deaths due to disease progression are not presented.
[c] Action taken with the IP was permanently stopped. Includes AEs and SAEs with an onset date and time on or after the date and time of the first dose and up to and including the last visit.

The differences in rates of the most common (≥ 2%) AEs were considered to reflect the known profiles of CAZ and metronidazole, including the higher rates of gastro-intestinal system AEs for CAZ-AVI. There were only 3 CAZ-AVI and 7 meropenem patients with infusion site reactions.

The majority of AEs were mild or moderate in intensity (severe AEs were reported by 5.4% CAZ-AVI and 7% meropenem patients). Four CAZ-AVI but no meropenem patients had severe acute renal failure, which were all SAEs (see further below). Also, 5 CAZ-AVI patients but no meropenem patients had 6 severe AEs relating to perforations (duodenal, ileal, gastric, intestinal, large intestine and small intestine), of which four were SAEs. The SRP determined there was inadequate source control for 3 patients with 4 perforations.

Treatment-related AEs were reported for 7.9% CAZ-AVI and 6.8% meropenem patients. The most common in respective groups were diarrhoea (1.7% and 0.5%), increased ALT (1.0% for both), increased AST (1.0% for both) and nausea (1.0% and 0.6%).

Table 35 AEs (≥2% in the CAZ-AVI plus MTZ or meropenem groups) up to the last visit by SOC and PT- DBC cIAI pool (safety analysis set)

	Total number (%) of patients[a]	
System organ class Preferred term	CAZ-AVI +MTZ (N=630)	Meropenem (N=631)
Patients with any AE	308 (48.9)	286 (45.3)
Infections and infestations	62 (9.8)	51 (8.1)
Wound infection	13 (2.1)	11 (1.7)
Blood and lymphatic system disorders	24 (3.8)	23 (3.6)
Anaemia	15 (2.4)	13 (2.1)
Nervous system disorders	35 (5.6)	28 (4.4)
Headache	18 (2.9)	12 (1.9)
Vascular disorders	57 (9.0)	57 (9.0)
Hypertension	17 (2.7)	27 (4.3)
Respiratory, thoracic and mediastinal disorders	57 (9.0)	57 (9.0)
Cough	17 (2.7)	17 (2.7)
Gastrointestinal disorders	135 (21.4)	102 (16.2)
Abdominal pain	15 (2.4)	9 (1.4)
Constipation	12 (1.9)	21 (3.3)
Diarrhoea	45 (7.1)	22 (3.5)
Nausea	46 (7.3)	30 (4.8)
Vomiting	38 (6.0)	15 (2.4)
General disorders and administration site conditions	61 (9.7)	62 (9.8)
Pyrexia	33 (5.2)	35 (5.5)
Investigations	49 (7.8)	44 (7.0)
Alanine aminotransferase increased	12 (1.9)	16 (2.5)
Aspartate aminotransferase increased	13 (2.1)	17 (2.7)

Liver disorders

In the DBC cIAI pool, liver disorder AEs occurred in 3.3% CAZ-AVI and 3.6% meropenem patients, mainly reflecting increased ALT (1.9% and 2.5%) and AST (2.1% and 2.7%). One CAZ-AVI patient had SAEs of increased hepatic enzymes and localized intra-abdominal fluid collection and discontinued. PCS

ALT results were reported for 3.7% vs. 4.9% and PCS AST in 4.4% vs. 3.3% while 10 CAZ-AVI vs. 9 meropenem patients had ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN but all had non-drug-related explanations for these results.

Diarrhoea

In the cIAI DBC pool one CAZ-AVI patient discontinued study drug due to non-serious diarrhoea. One patient in each treatment group had AEs of *C. difficile* colitis, which were both toxin-positive but were non-serious and moderate in intensity.

Hypersensitivity/anaphylaxis

No AEs of anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme have occurred thus far. In the DBC cIAI pool rates of hypersensitivity AEs were 4.1% for CAZ-AVI vs. 2.7% for meropenem, most of which concerned rash (2.9% vs. 2.1%). Two CAZ-AVI patients had rashes that resulted in study discontinuation. One had a pruritic rash on day 12 accompanied by abnormal LFTs and the rash resolved after discontinuation. The other had a macular rash starting on day 5, which resolved after discontinuation. One other CAZ-AVI patient had a SAE of hypersensitivity and study drug was discontinued. PCS elevated eosinophils occurred in 2 CAZ-AVI and 1 meropenem patient at any time before their last visit, one of whom also had erythema and pruritus. Also, two patients had AEs of eosinophil count increased.

Haematological disorders

In the DBO cIAI pool 3.8% CAZ-AVI vs. 4.4% meropenem patients had any haematological AE. One CAZ-AVI patient had a non-serious AE of low WBC but did not discontinue. Rates for individual abnormalities were generally balanced between treatments and there were no remarkable findings in CAZ-AVI patients in other studies. The Coombs seroconversion rates for those with data (local labs only) were 11.5% (37/322) for CAZ-AVI and 2.8% (9/319) for meropenem patients. Ten CAZ-AVI patients who had a positive Coombs test result at EOT reverted to a negative Coombs test result at some point up to the last visit. No patients had an AE of haemolytic anaemia during the study and hyperbilirubinaemia was observed at very low rates for both treatments.

Renal disorders

In the DBO cIAI pool renal disorder AEs were reported for 18 (2.9%) CAZ-AVI and 10 (1.6%) meropenem patients. Taking into account data from the studies reported during the procedure there were 57 subjects/patients (5 AVI, 29 CAZ-AVI +/- MTZ and 23 comparator) who had AEs identified as part of the search strategy used for the Renal disorder Safety Topics of Interest and/or met PCS elevations in creatinine (>2.0 × ULN and >100% increase from baseline). This group was stratified according to 3 categories of AKI likelihood, suggesting that 25/57 either had no clear laboratory evidence of AKI or had pre-existing renal impairment/were on HD, which confounded interpretation of the findings. Of the remaining 32 patients (19 CAZ-AVI):

- 9 (3 CAZ-AVI) had PCS elevations in creatinine without any reported AEs.
- 23 (16 CAZ-AVI) had AEs reported and creatinine clearance trends indicative of renal dysfunction.

There were 22/32 with normal renal function or mild renal impairment at baseline. Rates of PCS creatinine increases and renal disorder AEs were balanced (11 CAZ-AVI vs. 11 comparator patients). However, 9/11 CAZ-AVI and 8/11 comparator patients had an alternative aetiology explaining the renal dysfunction or had other factors that confounded assessment of AKI and/or the AEs were reported with a timeline that did not make it plausibly indicative of treatment-related AKI. The

remaining 10/32 had MRIB or SRIB and showed an imbalance in cases with 8 CAZ-AVI (4 from RECLAIM) vs. 2 comparator patients. Seven of the 8 CAZ-AVI patients had an alternative aetiology for renal dysfunction or other factors that confounded assessment of AKI and/or the AEs were reported with a timeline that did not make it plausibly indicative of AKI due to CAZ-AVI. Six received furosemide and/or aminoglycosides. The two comparator arm patients received concomitant medications that have the potential to cause AKI.

The BUN and creatinine shift and PCS tables for the entire Phase 2 and Phase 3 pool were analysed to assess whether CAZ-AVI may be associated with a higher risk of nephrotoxicity than the comparators. There were very few instances of major shifts/PCS results in either the pooled CAZ-AVI or comparator groups and no signal for an excess in the CAZ-AVI patients. These findings applied to patients with CrCL >50 mL/min or ≤50 mL/min at baseline, for which separate tabulations were provided.

Serious adverse event / deaths / other significant events

Serious adverse events

In the DBC cIAI pool 8.1% of patients in each treatment group had an SAE up to their last visit. The most common SAEs by PT in the CAZ-AVI group were acute renal failure, pulmonary embolism and respiratory failure. Two SAEs per treatment group were assessed as drug-related, including hypersensitivity (45 minutes into infusion on Day 3 with rash, dyspnoea and sweating) and hepatic enzymes increased (on Days 7-10 that recovered post-treatment) in CAZ-AVI patients and drug eruption and transaminases increased in meropenem patients. Three of the 6 CAZ-AVI patients with acute renal failure SAEs died (see below).

Table 36 SAEs occurring in ≥2 patients or were considered related to study drug up to last visit by SOC and PT-DBC cIAI pool (safety analysis set)

	Number (%) of patients[a]	
System organ class Preferred term	CAZ-AVI plus MTZ (N=630)	Meropenem (N=631)
Patients with any SAE	51 (8.1)	51 (8.1)
Infections and infestations	13 (2.1)	13 (2.1)
Abdominal abscess	0 (0.0)	2 (0.3)
Bronchopneumonia	2 (0.3)	2 (0.3)
Candida sepsis	2 (0.3)	0 (0.0)
Enterococcal bacteraemia	1 (0.2)	1 (0.2)
Pneumonia	2 (0.3)	2 (0.3)
Postoperative abscess	1 (0.2)	1 (0.2)
Sepsis	1 (0.2)	1 (0.2)
Septic shock	1 (0.2)	1 (0.2)
Immune system disorders	1 (0.2)	0 (0.0)
Hypersensitivity[b]	1 (0.2)	0 (0.0)
Metabolism and nutrition disorders	1 (0.2)	3 (0.5)
Hypoglycaemia	0 (0.0)	2 (0.3)
Cardiac disorders	8 (1.3)	8 (1.3)
Acute myocardial infarction	1 (0.2)	1 (0.2)
Atrial fibrillation	0 (0.0)	2 (0.3)
Cardiac failure	2 (0.3)	1 (0.2)
Cardiac failure congestive	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.2)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	9 (1.4)	11 (1.7)
Pleural effusion	1 (0.2)	1 (0.2)
Pulmonary embolism	3 (0.5)	1 (0.2)
Respiratory distress	2 (0.3)	1 (0.2)

Respiratory failure	3 (0.5)	3 (0.5)
Gastrointestinal disorders	15 (2.4)	9 (1.4)
Abdominal pain	2 (0.3)	0 (0.0)
Intestinal obstruction	1 (0.2)	3 (0.5)
Localized intraabdominal fluid collection	2 (0.3)	0 (0.0)
Small intestinal obstruction	1 (0.2)	1 (0.2)
Volvulus	1 (0.2)	(0.2)
Hepatobiliary disorders	1 (0.2)	1 (0.2)
Bile duct obstruction	1 (0.2)	1 (0.2)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.2)
Drug eruption[b]	0 (0.0)	1 (0.2)
Renal and urinary disorders	6 (1.0)	1 (0.2)
Renal failure acute	5 (0.8)	1 (0.2)
General disorders and administration site conditions	3 (0.5)	1 (0.2)
Multi-organ failure	2 (0.3)	0 (0.0)
Investigations	1 (0.2)	3 (0.5)
Hepatic enzyme increased[b]	1 (0.2)	0 (0.0)
Transaminases increased[b]	0 (0.0)	2 (0.3)
Injury, poisoning, and procedural complications	9 (1.4)	6 (1.0)
Abdominal wound dehiscence	1 (0.2)	1 (0.2)
Gastrointestinal stoma complication	1 (0.2)	1 (0.2)
Gastrointestinal stoma necrosis	2 (0.3)	0 (0.0)

Deaths

In the initial safety analysis there were 31 deaths across all clinical studies, including 18 in CAZ-AVI patients. Two of the 18 CAZ-AVI patients died after the last visit so were removed from the total. Most (26/31) deaths occurred in the DBO cIAI pool (i.e. 16 CAZ-AVI and 10 meropenem; 13 vs. 8 in RECLAIM) and occurred after Day 7 (10/16 CAZ-AVI and 7/10 meropenem). After pooling all the data with the studies reported during the procedure the total is 37 deaths (21 CAZ-AVI), giving rates of 1.3% for CAZ-AVI vs. 1.0% for pooled comparators.

	Number (%) of patients					
	Phase 2		Phase 3		Total	
Category	CAZ-AVI [a] (N=169)	Comparator [b] (N=169)	CAZ-AVI [a] (N=1419)	Comparator [b] (N=1423)	CAZ-AVI [a] (N=1588)	Comparator [b] (N=1592)
Total number of deaths	3 (1.8)	3 (1.8)	18 (1.3)	13 (0.9)	21 (1.3)	16 (1.0)
Death due to disease progression	0 (0.0)	0 (0.0)	8 (0.6)	3 (0.2)	8 (0.5)	3 (0.2)
Number of patients with any AE with outcome=death	3 (1.8)	3 (1.8)	10 (0.7)	10 (0.7)	13 (0.8)	13 (0.8)

When shown by indication there remained an imbalance in rates for cIAI patients (2.1% vs. 1.4%).

	Number (%) of patients					
	cIAI		cUTI		Total	
Category	CAZ-AVI+MTZ (N=857)	Comparator [b] (N=863)	CAZ-AVI (N=731)	Comparator [b] (N=729)	CAZ-AVI [a] (N=1588)	Comparator [b] (N=1592)
Total number of deaths	18 (2.1)	12 (1.4)	3 (0.4)	4 (0.5)	21 (1.3)	16 (1.0)
Death due to disease progression	8 (0.9)	3 (0.3)	0 (0.0)	0 (0.0)	8 (0.5)	3 (0.2)
Number of patients with any AE with outcome=death	10 (1.2)	9 (1.0)	3 (0.4)	4 (0.5)	13 (0.8)	13 (0.8)

Most deaths occurred before days 14-21 on study. There were slightly more deaths that occurred after day 21 with CAZ-AVI in Phase 3 studies.

Deaths in patients with normal renal function or mild impairment included 6 patients per treatment group with AEs with outcome of death and 2 CAZ-AVI vs. 4 comparator patients in whom death was considered to be due to disease progression. In the MRIB/SRIB group 6 CAZ-AVI and 5 comparator patients had AEs with outcome of death but deaths due to disease progression occurred in 7 vs. 1 in respective treatment groups. It was not possible to ascribe the numerical imbalance of deaths due to disease progression to under-dosing when using the prior dose adjustment schema except for one patient. Further assessment by an independent reviewer suggested that there were three patients (one CAZ-AVI) for whom it cannot be ruled out that lack of efficacy contributed to death.

Thirty patients who died had cIAI and had APACHE II scores from 5 to 27 with a median of 12. Baseline APACHE II scores for the patients who died were higher than median baseline APACHE II scores across cIAI CAZ-AVI studies. This finding applied in both treatment groups.

Laboratory findings

In the DBC cIAI pool the haematology findings were either expected based on experience with CAZ (e.g. thrombocytosis in 5.2% CAZ-AVI patients) or balanced between treatments (e.g. leucocytosis in 3.0% CAZ-AVI vs. 3.1% meropenem patients). The most common PCS findings included decreased haemoglobin (7.2% vs. 8.2%) and decreased erythrocyte volume fraction (7.2% vs. 9.8%) in respective groups. PCS INR and PT values were higher for the CAZ-AVI group, thought to be due to metronidazole which can potentiate warfarin-type oral anticoagulants. The mean chemistry values and shifts over time were similar between treatment groups and there were no trends or safety concerns for CAZ-AVI.

Safety in special populations

After pooling data with those from studies reported during the procedure for 369 (185 CAZ-AVI) patients aged ≥75 years there was no evidence of an overall increased risk of AEs vs. comparators.

Table 37 Adverse events up to the last visit for elderly patients ≥75 years of age (safety analysis set)

AE Category	Number (%) of patients[a]	
	CAZ-AVI[b] (N=185)	Comparator[c] (N=184)
Any AE	84 (45.4)	97 (52.7)
Any AE with an outcome of death[d]	7 (3.8)	6 (3.3)
Any SAE	19 (10.3)	22 (12.0)
Any AE leading to discontinuation of IP[e]	5 (2.7)	3 (1.6)
Any AE of severe intensity	15 (8.1)	21 (11.4)

[a] Patients with multiple AEs in the same category are counted only once in that category. Patients with AEs in >1 category are counted once in each of those categories.
[b] CAZ-AVI includes CAZ-AVI and CAZ-AVI plus MTZ patients.
[c] Comparator includes BAT, meropenem, imipenem cilastatin, and doripenem patients.
[d] Deaths due to disease progression are not presented here.
[e] Action taken was IP permanently stopped. Includes AEs and SAEs with an onset date and time on or after the date and time of first dose and up to and including the LFU visit.

The most frequently reported AEs (≥2%) in the CAZ-AVI group were nausea, (4.3%) and AF (3.2%). The rates were 2.7% for each of constipation, diarrhoea, headache, hypertension, oedema peripheral and wound infection and 2.2% for insomnia and anaemia (2.2% each). The number of patients with renal failure events (renal failure, renal failure acute and renal impairment) were balanced (5 CAZ-AVI and 4 comparators). The analysis for 145 cIAI patients aged ≥75 years (61 CAZ-AVI) also showed similar total AE rates (63.9% vs. 66.7%). In each of the abovementioned SOCs the rates were lower in the CAZ-AVI group except for renal and urinary disorders (5 [8.2%] CAZ-AVI and 5 [6.0%] for comparators).

The incidence of any AE was slightly higher in the CAZ-AVI group for female patients. This was largely driven by a cumulative effect of slightly higher rates for women than men in each SOC.
The highest BMI subgroup (≥ 30 kg/m^2) had slightly higher rates for AEs with an outcome of death, SAEs, AEs leading to discontinuation and severe AEs in the CAZ-AVI group, mainly reflecting rates of psychiatric disorders, nervous system disorders, skin and subcutaneous tissue disorders and Injury, poisoning and procedural complications. Most *Candida* infections were in the highest BMI subgroup. There was an increased incidence in all categories of AEs with declining renal status that was generally higher in the CAZ-AVI group. Using the updated safety database, the applicant provided the following table of SAEs in MRIB patients.

Table 38 SAEs up to last visit by SOC and PT for patients with baseline creatinine clearance 31-50 mL/min-pooled phase 2/3 studies (safety analysis set) (studies D4280C00001, D4280C00002, D4280C00006, D4280C00018, NXL104/2001 AND NXL104/2002)

System organ class/ Preferred term	Number (%) of patients [a]	
	CAZ-AVI [b] (N=132)	Comparator [c] (N=144)
Patients with any SAE	23 (17.4)	17 (11.8)
Infections and infestations	7 (5.3)	5 (3.5)
Abdominal abscess	0 (0.0)	1 (0.7)
Abdominal infection	1 (0.8)	0 (0.0)
Bronchopneumonia	1 (0.8)	1 (0.7)
Candida sepsis	1 (0.8)	0 (0.0)
Clostridium difficile colitis	1 (0.8)	0 (0.0)
Diverticulitis	1 (0.8)	0 (0.0)
Empyema	1 (0.8)	0 (0.0)
Lobar pneumonia	0 (0.0)	1 (0.7)
Pneumonia	0 (0.0)	1 (0.7)
Sepsis	1 (0.8)	0 (0.0)
Systemic candida	0 (0.0)	1 (0.7)
Metabolism and nutrition disorders	1 (0.8)	1 (0.7)
Dehydration	1 (0.8)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (0.7)
Nervous system disorders	0 (0.0)	1 (0.7)
Tension headache	0 (0.0)	1 (0.7)
Cardiac disorders	7 (5.3)	4 (2.8)
Acute myocardial infarction	1 (0.8)	0 (0.0)
Atrial fibrillation	1 (0.8)	2 (1.4)
Cardiac arrest	1 (0.8)	0 (0.0)
Cardiac failure	1 (0.8)	0 (0.0)
Cardiac failure congestive	1 (0.8)	0 (0.0)
Cardio-respiratory arrest	1 (0.8)	1 (0.7)
Myocardial infarction	0 (0.0)	1 (0.7)
Right ventricular failure	1 (0.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (1.5)	4 (2.8)
Pneumonia aspiration	0 (0.0)	1 (0.7)
Pulmonary congestion	0 (0.0)	1 (0.7)
Respiratory disorder	0 (0.0)	1 (0.7)
Respiratory distress	1 (0.8)	0 (0.0)
Respiratory failure	1 (0.8)	1 (0.7)
Gastrointestinal disorders	3 (2.3)	3 (2.1)
Abdominal pain lower	1 (0.8)	0 (0.0)
Gastrointestinal haemorrhage	1 (0.8)	0 (0.0)
Ileus	0 (0.0)	1 (0.7)
Intestinal obstruction	0 (0.0)	1 (0.7)

Localised intraabdominal fluid collection	1 (0.8)	0 (0.0)
Volvulus	0 (0.0)	1 (0.7)
Renal and urinary disorders	6 (4.5)	0 (0.0)
Calculus ureteric	1 (0.8)	0 (0.0)
Nephrolithiasis	1 (0.8)	0 (0.0)
Renal failure	1 (0.8)	0 (0.0)
Renal failure acute	3 (2.3)	0 (0.0)
Renal impairment	1 (0.8)	0 (0.0)
General disorders and administration site conditions	2 (1.5)	2 (1.4)
Impaired healing	0 (0.0)	1 (0.7)
Multi-organ failure	1 (0.8)	0 (0.0)
Sudden death	1 (0.8)	1 (0.7)
Injury, poisoning and procedural complications	3 (2.3)	1 (0.7)
Accidental overdose	1 (0.8)	0 (0.0)
Gastrointestinal stoma complication	1 (0.8)	0 (0.0)
Gastrointestinal stoma necrosis	1 (0.8)	0 (0.0)
Wound evisceration	0 (0.0)	1 (0.7)

As shown above, the updated rates of MRIB patients with at least one SAE were CAZ-AVI 17.4% vs. comparator 11.8%. Rates of SAEs were balanced across treatment groups except for renal and urinary disorders (see above).

Discontinuation due to adverse events

In the DBC cIAI pool 3.0% CAZ-AVI and 1.6% meropenem patients discontinued study drug due to AEs. For 6 CAZ-AVI and 4 meropenem patients the AEs were assessed by the investigator as causally related to study drug. In the CAZ-AVI group these AEs were diarrhoea, drug eruption, hepatic enzyme increased, headache, hypersensitivity, rash macular and rash pruritic**.**

Additional safety data from REPRISE

In patients with cUTI, the median total days on treatment was 10 days for CAZ-AVI and BAT with ~37% receiving > 10 days. All but 4 patients received the recommended treatment duration of 5 to 21 days. The incidence of AEs, including AEs with a fatal outcome, SAEs and AEs leading to discontinuation of study treatment was low and similar between treatment groups. There were 3 deaths in each treatment group for cUTI patients, and 1 cIAI patient died in the BAT group. All 7 patients had an AE with an outcome of death that was not considered related to study treatment by the investigator; no deaths were due to disease progression.

Table 39 Adverse events up to EOT visit in any category (safety analysis set)

	Number (%) of patients[a]					
	cIAI		cUTI		cIAI+cUTI	
AE category	CAZ-AVI+ MTZ (N=12)	BAT (N=15)	CAZ-AVI (N=152)	BAT (N=153)	CAZ-AVI[b] (N=164)	BAT (N=168)
Any AE	8 (66.7)	11 (73.3)	39 (25.7)	45 (29.4)	47 (28.7)	56 (33.3)
Any AE with outcome of death[c]	0	1 (6.7)	1 (0.7)	1 (0.7)	1 (0.6)	2 (1.2)
Any SAE	2 (16.7)	5 (33.3)	2 (1.3)	2 (1.3)	4 (2.4)	7 (4.2)
Any AE leading to discontinuation of IP[d]	0	1 (6.7)	1 (0.7)	1 (0.7)	1 (0.6)	2 (1.2)
Any AE of severe intensity	2 (16.7)	5 (33.3)	1 (0.7)	4 (2.6)	3 (1.8)	9 (5.4)

Up to the EOT visit, the incidence of AEs reported across treatment groups by SOC in cUTI patients was generally balanced, with the exception of Nervous system disorders and Gastrointestinal disorders

for which the incidence of AEs was higher in the BAT group (3.3% vs. 7.2% and 5.9% vs. 14.4%, respectively). Diarrhoea and headache also occurred more often with BAT. In the CAZ-AVI group, the number of AEs occurring in ≥2% of cUTI patients was low and included nausea and pyrexia. Overall, the majority of AEs were mild or moderate in intensity. The table below shows AEs up to LFU.

Table 40 Adverse events up to LFU visit by system organ class and by preferred term (≥2% of cUTI-cIAI patients for CAZ-AVI or ≥2% cUTI patients in any treatment group) (safety analysis set)

SOC/ PT[b]	Number (%) of patients[a]					
	cIAI		cUTI		cIAI+cUTI	
	CAZ-AVI+ MTZ (N=12)	BAT (N=15)	CAZ-AVI (N=152)	BAT (N=153)	CAZ-AVI[c] (N=164)	BAT (N=168)
Patients with any AE[d]	8 (66.7)	12 (80.0)	43 (28.3)	54 (35.3)	51 (31.1)	66 (39.3)
Infections and infestations	**3 (25.0)**	**3 (20.0)**	**10 (6.6)**	**15 (9.8)**	**13 (7.9)**	**18 (10.7)**
Vulvovaginal candidiasis	0	0	3 (2.0)	0	3 (1.8)	0
Psychiatric disorders	**3 (25.0)**	**4 (26.7)**	**3 (2.0)**	**2 (1.3)**	**6 (3.7)**	**6 (3.6)**
Insomnia	2 (16.7)	4 (26.7)	2 (1.3)	0	4 (2.4)	4 (2.4)
Nervous system disorders	**4 (33.3)**	**3 (20.0)**	**5 (3.3)**	**12 (7.8)**	**9 (5.5)**	**15 (8.9)**
Headache	2 (16.7)	1 (6.7)	1 (0.7)	11 (7.2)	3 (1.8)	12 (7.1)
Gastrointestinal disorders	**8 (66.7)**	**5 (33.3)**	**13 (8.6)**	**25 (16.3)**	**21 (12.8)**	**30 (17.9)**
Nausea	3 (25.0)	1 (6.7)	5 (3.3)	9 (5.9)	8 (4.9)	10 (6.0)
Vomiting	2 (16.7)	1 (6.7)	4 (2.6)	2 (1.3)	6 (3.7)	3 (1.8)
Diarrhea	2 (16.7)	0	3 (2.0)	8 (5.2)	5 (3.0)	8 (4.8)
Abdominal pain	0	1 (6.7)	3 (2.0)	4 (2.6)	3 (1.8)	5 (3.0)
Dyspepsia	0	0	2 (1.3)	5 (3.3)	2 (1.2)	5 (3.0)
General disorders and administration site conditions	**0**	**2 (13.3)**	**11 (7.2)**	**8 (5.2)**	**11 (6.7)**	**10 (6.0)**
Pyrexia	0	0	4 (2.6)	2 (1.3)	4 (2.4)	2 (1.2)
Edema peripheral	0	0	3 (2.0)	1 (0.7)	3 (1.8)	1 (0.6)

The incidence of AEs considered to be causally related to study treatment by the investigator in cUTI patients up to the EOT visit was low and balanced across treatment groups (3.9% vs. 5.9% BAT).

In the initial dossier the overall (cUTI and cIAI combined) Coombs seroconversion rate up to the LFU visit was 19.4% (14/72 tested) in the CAZ-AVI group vs. 2.7% (2/73) in the BAT group. However, the rate computed after submission of further study reports (see below) during the procedure was 82/762 (10.8%). This is still higher than reported in the ceftazidime SmPC, in which it is stated that *The development of a positive Coombs test associated with the use of ceftazidime in about 5% of patients may interfere with the cross-matching of blood*. There were no events or laboratory findings of haemolytic anaemia in the 82 patients who had seroconversion across the clinical studies. The rates obtained are subject to a large amount of missing data and an unknown bias effect.

No new safety concerns were identified from the Safety Topics of Interest. The frequency of PCS changes in clinical laboratory tests was low and balanced across treatment groups. There were no Hy's Law cases. No new safety concerns were identified for any of the clinical laboratory, ECG, physical examination and vital signs assessments.

Additional safety data from RECLAIM 3

The median duration of exposure was 6 days in both treatment groups and > 90% received 5 to 14 days. The overall frequency and pattern of AEs were comparable between the treatment groups and almost all were mild or moderate in severity.

The commonest AEs are shown below. AEs considered by the investigator to be drug-related and reported for >1 CAZ-AVI patient up to LFU were nausea (5 [2.3%]) and diarrhoea (3 [1.4%]). There was no excess of AESIs in the CAZ-AVI group.

Table 41 Adverse events up to the LFU visit in any category (safety analysis set)

	Number (%) of patients [a]	
AE category	CAZ-AVI + Metronidazole (N=215)	Meropenem (N=217)
Any AE	82 (38.1)	83 (38.2)
Any AE with outcome=death[b]	0	1 (0.5)
Any SAE	9 (4.2)	11 (5.1)
Any AE leading to discontinuation of IP[c]	7 (3.3)	3 (1.4)
Any AE of severe intensity	5 (2.3)	5 (2.3)

Table 42 Adverse events up to the LFU visit by SOC, PT and investigator's causality assessment for events that occurred in ≥2% of patients in either treatment group (safety analysis set)

	Number (%) of patients[a]			
	CAZ-AVI + Metronidazole (N=215)		Meropenem (N=217)	
	Causality		Causality	
System organ class/preferred term[b]	Not related	Related	Not related	Related
Patients with any AE[c]	67 (31.2)	15 (7.0)	73 (33.6)	10 (4.6)
Respiratory, thoracic, and mediastinal disorders				
Cough	3 (1.4)	0	7 (3.2)	1 (0.5)
Productive cough	5 (2.3)	0	6 (2.8)	0
Gastrointestinal disorders				
Constipation	5 (2.3)	0	2 (0.9)	1 (0.5)
Diarrhoea	10 (4.7)	3 (1.4)	15 (6.9)	1 (0.5)
Nausea	13 (6.0)	5 (2.3)	4 (1.8)	0
General disorders and administration site conditions				
Pyrexia	9 (4.2)	0	13 (6.0)	0

Table 43 Adverse events of special interest (safety analysis set)

	Number (%) of patients[a]	
Patients with at least 1 AE with a PT relevant to special interest category[b]	CAZ-AVI + Metronidazole (N=215)	Meropenem (N=217)
Liver disorder	6 (2.8)	10 (4.6)
Diarrhea	13 (6.0)	16 (7.4)
Hypersensitivity/anaphylaxis disorder	7 (3.3)	8 (3.7)
Hematological disorder	2 (0.9)	1 (0.5)
Renal disorder	1 (0.5)	1 (0.5)

Two deaths in the CAZ-AVI group were due to disease progression and one meropenem patient had an AE with an outcome of death. The incidences of SAEs and of discontinuations due to AEs were low.

Coombs test shifts from negative to positive up to the LFU visit occurred in 20.8% CAZ-AVI patients vs. 2.9% meropenem patients. There was a high proportion of missing data (~ 67.4%) and all data were from local laboratories. No AE or laboratory evidence of haemolysis was identified.

Additional safety data from RECAPTURE

The median duration of exposure to IV therapy was 7 days for CAZ-AVI and 8 days for doripenem. More than half of patients switched to oral therapy. During IV therapy the AE rates were low and comparable.

Table 44 Adverse events up to EOT (IV) visit in any category (safety analysis set)

	Number (%) of patients[a]	
AE category	CAZ-AVI (N=511)	Doripenem (N=509)
Any AE	143 (28.0)	136 (26.7)
Any AE with outcome=death	0	0
Any SAE	9 (1.8)	5 (1.0)
Any AE leading to discontinuation of IP[b]	7 (1.4)	6 (1.2)
Any AE of severe intensity	6 (1.2)	5 (1.0)

The AE rate was higher in the CAZ-AVI group up to the LFU visit (36.2% vs. 31%) but most AEs throughout the study were of mild or moderate intensity. During IV therapy the commonest AEs were as shown below.

Table 45 Adverse events up to EOT (IV) vist by SOC and PT that occurred in ≥2% of patients in either treatment group (safety analysis set)

	Number (%) of patients[a]	
System organ class/preferred term[b]	CAZ-AVI (N=511)	Doripenem (N=509)
Patients with any AE[c]	143 (28.0)	136 (26.7)
Nervous system disorders		
Headache	38 (7.4)	37 (7.3)
Gastrointestinal disorders		
Nausea	12 (2.3)	10 (2.0)
Constipation	10 (2.0)	6 (1.2)
Diarrhea	10 (2.0)	5 (1.0)

Rates for AEs considered drug-related by investigators were low (total 6.8% CAZ-AVI vs. 7.1% doripenem) and similar between treatment groups. AESIs that occurred up to LFU are shown below.

Table 46 Adverse events of special interest (safety analysis set)

	Number (%) of patients[a]	
Patients with at least 1 AE with a PT relevant to special interest category[b]	CAZ-AVI (N=511)	Doripenem (N=509)
Liver disorder	3 (0.6)	5 (1.0)
Diarrhea	16 (3.1)	6 (1.2)
Hypersensitivity/anaphylaxis disorder	8 (1.6)	10 (2.0)
Hematological disorder	2 (0.4)	3 (0.6)
Renal disorder	2 (0.4)	0

The rates of SAEs were low and there were no deaths in the study. There were 7 CAZ-AVI and 6 doripenem patients who discontinued assigned treatment due to AEs, including 2 in the CAZ-AVI group who had diarrhoea. Seroconversion rates for the Coombs test up to the LFU visit occurred in 3.2% in the CAZ-AVI group vs. 0.9% in the doripenem group. There was a high proportion of missing data (~58%) and all data were from local laboratories.

Post marketing experience

Avycaz (ceftazidime-avibactam) was approved in the US on 25 February 2015 and launched 23 April 2015. No AEs associated with Avycaz were reported from 25 February 2015 to 24 May 2015 and one patient with two AEs associated with Avycaz was reported from 25 May 2015 to 24 August 2015. These AEs were thrombocytopenia and Off-label use for treatment of carbapenem-resistant Enterobacteriaceae in the blood and sputum of a 59-year-old male. Treatment was discontinued due to the thrombocytopenia. No laboratory values were reported. Both AEs were non-serious.

2.6.1. Discussion on clinical safety

Thus far, the safety profile of CAZ-AVI has generally reflected that already known for CAZ alone. Nevertheless, although the safety database is considered to be adequate in size, it is not possible to draw any definitive conclusions regarding the possible effects of AVI on the ADR profile of CAZ. In addition, since the dose used in CAZ-AVI is the highest intermittent dose recommended for non-CF patients whereas the ADR frequencies reported for CAZ alone reflect broader usage, it is not appropriate to compare frequencies between CAZ-AVI and those of CAZ. Other constraints for interpretation of the data include the fact that reasonable comparisons of safety are possible only vs. carbapenems and only in patients with cIAI or cUTI. Hence it is not really so surprising that rates of some AEs more associated with cephalosporins than carbapenems are higher with CAZ-AVI. What is more, all CAZ-AVI patients with cIAI also received metronidazole, which confounds the comparisons made.

It is appropriate that the CAZ-AVI SmPC should include warnings pertaining to hypersensitivity, antibacterial agent-associated colitis and pseudo-membranous colitis due to Clostridium difficile, concurrent treatment with nephrotoxic medicinal products and development of a positive Coombs' test (although this is stated to occur in ~5% of patients, which under-estimates the observed rate in CAZ-AVI studies; see below). However, it is considered important that the list of ADRs in section 4.8 and their frequencies should be driven by the safety data from the CAZ-AVI Phase 2/3 studies. Additional data provided during the CHMP review were not available at the time the US FDA approved this FDC. Therefore it is not necessarily appropriate to propose the exact same table of ADRs as was approved in the US. After updating of the safety data during the procedure there was only a small imbalance in death rates for CAZ-AVI vs. pooled comparators across indications (37 deaths [21 CAZ-AVI], giving rates of 1.3% for CAZ-AVI vs. 1.0% for pooled comparators). When shown by indication there was a greater imbalance in rates for cIAI patients (18 [2.1%] vs. 12 [1.4%]). This number included 2 CAZ-AVI (both ascribed to disease progression) and 1 meropenem death in RECLAIM3. There were no deaths in RECAPTURE (all cUTI) and very few deaths in REPRISE (mostly UTI), with no imbalance.

In the cIAI patients most deaths occurred before days 14-21 on study. Further exploration of the deaths revealed that in the MRIB/SRIB group 6 CAZ-AVI and 5 comparator patients had AEs with outcome of death but deaths due to disease progression occurred in 7 vs. 1 in respective treatment groups. It is not possible to ascribe or to rule out a contribution to the imbalance in deaths due to disease progression to temporary under-dosing. It can be observed that baseline APACHE II scores for the patients who died were higher than median baseline APACHE II scores across cIAI CAZ-AVI studies but this finding applied in both treatment groups.

Overall, it remains possible that the remaining imbalance in deaths in cIAI patients occurred by chance

and/or reflected at least in part dosing of MRIB patients in the initial phase of treatment and/or an imbalance in adequate surgical management. The imbalance should be reflected in the SmPC.
Across all completed Phase 1 through Phase 3 studies of the CAZ-AVI programme there were 57 subjects/patients (5 AVI, 29 CAZ-AVI +/- MTZ and 23 comparator) who had AEs identified as part of the search strategy used for the Renal disorder Safety Topics of Interest and/or met PCS elevations in creatinine (>2.0 × ULN and >100% increase from baseline). A detailed analysis of these patients and of all PCS values relating to renal function was undertaken.
Of the 57 subjects/patients 37 could be verified as having laboratory evidence that supported the AEs reported. Another 5 had baseline renal dysfunction and findings that did not suggest a contribution from AVI. In the remaining 32 patients (19 CAZ-AVI) there were 22 (11 CAZ-AVI) with normal function or mild impairment and 10 with MRIB/SRIB (8 CAZ-AVI). However, the information available provided a more likely explanation than CAZ-AVI-related AKI for most cases. The shifts and PCS tables do not suggest an excess risk for CAZ-AVI over comparators.
The SmPC contains the statements and AEs that are based on information available on CAZ, i.e. that CAZ can be associated with nephrotoxicity especially if combined with other nephrotoxic agents. It is not possible from available data to definitively conclude whether adding AVI increases the risk of AKI and whether the resulting rates of AKI exceed those observed with other commonly used antibacterial agents. The matter has been reflected in the RMP.
There was an increased incidence in all categories of AEs with declining renal status. There were very few patients with SRIB. In the MRIB subgroup there were 6 CAZ-AVI patients with renal failure acute [3], renal failure [2] and renal impairment [1] but only one in the comparator group (renal impairment). These patients were investigated as described above. Other SOCs or PTs for which there was a higher reporting rate in the CAZ-AVI MRIB group were not indicative of AKI. In addition, in the MRIB population the only SOCs that showed higher rates for CAZ-AVI were cardiac disorders (12.9% vs. 8.3%), gastrointestinal disorders (22.7% vs. 14.6%; rates of diarrhoea were comparable between treatments), injury/poisoning/procedural complications (9.1% vs. 4.9%) and renal disorders (8.3% vs. 4.2%).
In Phase 3 studies (except for RECAPTURE), the Coombs seroconversion rate was very high and much higher than what is reported for CAZ. In each study the denominator is only a fraction of the total study population but it does seem to be consistent that rates are much higher than reported for CAZ alone. However, further exploration of the data did not suggest that the rates reflected an effect of AVI. Text was added to the SmPC but the actual rates per study vs. comparators must be stated because the mean rate reported by the applicant is much lowered by the unexplained and unusually low rate in RECAPTURE. It should also be remembered that the DAGT results all came from local labs.
The applicant also explored in detail all cases of raised transaminases, including PK-PD analyses to ascertain whether exposure to CAZ and/or AVI was related to the increases observed. It appeared that AVI exposure was not a factor but there was a weak association with CAZ exposure.
Overall the rates make these ADRs common, which is the same as in the CAZ SmPC. There have not been any cases that meet Hy's Law criteria.

2.6.2. Conclusions on the clinical safety

CHMP agreed that the additional safety data generated by the recently completed comparative studies conducted in cIAI and cUTI added considerably to the database and have been mainly reassuring.

2.7. Risk Management Plan

Safety concerns

Important identified risks	*Clostridium difficile*-associated diarrhoea Anaphylaxis and other severe hypersensitivity reactions
Important potential risks	Hepatotoxicity Superinfection (bacterial or fungal) Bacterial resistance development In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced
Missing information	Pregnancy exposure Lactation exposure Pre-existing significant hepatic impairment Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy Immunocompromised population exposure

Pharmacovigilance plan

On-going and planned additional PhV studies / activities in the Pharmacovigilance Plan

Study / activity type, title, and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Resistance Surveillance Programme Category 3	To track the longitudinal in vitro activity of CAZ-AVI and comparator agents against relevant clinical isolates (those pathogens identified in the SmPC against which CAZ-AVI demonstrated clinical efficacy) in cIAI, cUTI and NP.	Bacterial resistance development	Planned	Reports will be submitted annually for 5 years once CAZ-AVI is on the market; the final report will be Year 5.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Clostridium difficile-associated diarrhoea	Statements within SmPC Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects)	None
Anaphylaxis and other severe hypersensitivity reactions	Statements within SmPC Sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), and 4.8 (Undesirable effects)	None
Important potential risks		
Hepatotoxicity	Statements within SmPC Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties)	None
Superinfection (bacterial or fungal)	Statements within SmPC Section 4.4 (Special warnings and precautions for use)	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bacterial resistance development	Statement within SmPC Section 5.1 (Pharmacodynamic properties) Product labels will provide information concerning resistant organisms and instructions for proper use in an attempt to limit bacterial resistance development.	None
In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced	Statements within SmPC Sections 4.4 (Special warnings and precautions for use) and 4.9 (Overdose)	None
Missing information		
Pregnancy exposure	Statements within SmPC Sections 4.6 (Fertility, pregnancy, and lactation) and 5.3 (Nonclinical safety data)	None
Lactation exposure	Statements within SmPC Sections 4.6 (Fertility, pregnancy, and lactation) and 5.3 (Nonclinical safety data)	None
Pre-existing significant hepatic impairment	Statements within SmPC Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties)	None
Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy	Statements within SmPC Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 4.9 Overdose, and 5.2 (Pharmacokinetic properties)	None
Immunocompromised population exposure	None proposed	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1 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.

2.9. Product information

2.9.1. 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.*

2.9.2. 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:

Although above the limit of 10ml (20 ml vial), the space available on the vial does not allow displaying the full particulars in a readable manner, in particular for the multilingual label. For that reason and because it is to be administered by a healthcare professional, the QRD Group accepted the request to have only the minimum particulars on the vial label.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zavicefta (ceftazidime / avibactam) 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

Benefits

Beneficial effects
Zavicefta is a fixed-dose combination containing ceftazidime, an approved betalactam, and avibactam, a novel betalactamase inhibitor.

Ceftazidime is a third generation cephalosporin with an antibacterial activity against Gram-negative aerobes, including *P. aeruginosa*, is already licensed for the proposed indications cIAI, cUTI and NP/HAP, and CHMP agreed that the available data on its safety and efficacy are adequate and sufficient.

The inhibitory range of avibactam clearly exceeds that of tazobactam, clavulanic acid and sulbactam. *In vitro* data, including studies with CAZ-R organisms and enzyme inhibition studies, indicate a potential inhibition by avibactam of serine-based carbapenemases and of AmpC enzymes, as well as a wide range of ESBLs. The clinical efficacy data against CAZ-R pathogens support the *in vitro* findings although CHMP noted that numbers of pathogens treated expressing certain enzymes expected to be within the spectrum of inhibition of AVI was so far low.

The selection of the PK-PD indices and identification of the individual and combined PD targets was accepted by CHMP. The final estimates of PTA at CAZ-AVI MIC 8 mg/L reflect the updated POPPK analysis that included the phase 3 sparse sampling data from infected patients who received the final proposed dose regimen. Essentially, CHMP agreed with the applicant' conclusions regarding the sufficiency of the dose for cUTI and cIAI patients when MICs are up to 8 mg/L. The information available for CAZ efficacy in HAP and the additional PK data from HAP patients provide support for use of CAZ-AVI in this indication.

During the procedure the applicant added three completed studies to the body of evidence. As a result there are two comparative studies vs. meropenem in cIAI and a study vs. doripenem in cUTI (with at least 5 days IV), which showed non-inferiority versus the comparator and support the recommended dose. A fourth study, REPRISE, conducted in patients with cIAI or cUTI due to CAZ-R pathogens, was not powered for inferential testing but it demonstrated numerically comparable efficacy for CAZ-AVI vs. BAT.

Uncertainty in the knowledge about the beneficial effects.

Indication for use in patients with limited therapeutic options

Despite the fact that this indication is supported by the microbiological data, PK-PD analyses and clinical efficacy data in cIAI and cUTI, including efficacy against CAZ-R organisms that express a range of beta-lactamases, CHMP agreed that it is essential that the Zavicefta SmPC fully explains the basis for this indication and the lack of any clinical experience with CAZ-AVI for treating infections at other body sites.

Hospital acquired pneumonia (nosocomial pneumonia)

There are no clinical efficacy data with CAZ-AVI in HAP patients. The updated PTA analyses have included more extensive PK data from patients in REPROVE and have substantiated the adequacy of the plasma exposures, including for patients with ARC. The ELF data are supportive but it is not possible to place undue reliance of the analyses using these data. Although the available data on CAZ alone demonstrate efficacy in the NP indication, it has certain limitations as previously highlighted also in a referral (article 30) procedure. Therefore, although the currently available evidence seems sufficient to allow an indication for HAP, it is essential that the SmPC adequately reflects the basis for this usage. In order to verify the impact on CAZ-AVI use on clinical outcomes in HAP, provision of the full CSR from REPROVE is listed as an annex II condition.

cIAI

RECLAIM was of an adequate design and conduct and nearly 80% of the patients had at least one valid pathogen but the baseline APACHE scores were mostly low. The study met its pre-defined primary endpoint for demonstration of non-inferiority in compliance with CHMP (and FDA) requirements, but CAZ-AVI (plus metronidazole for anaerobic cover) showed almost consistent numerical inferiority to meropenem in each pre-defined analysis population and patient subgroup.

Further analyses investigated the possible reasons for the lower cure rates, especially in the MRIB population and those with APACHE II scores. It seems that the differences were mostly driven by the cure rates in the MRIB group, since removal of these patients from the analyses removed or lessened the differences between treatments. In the MRIB group the cure rates in the MITT and mMITT analysis sets were 48.8% and 45.2% for CAZ-AVI vs. 74.4% and 74.3%, respectively, for meropenem. CAZ and AVI plasma exposures on Day 3 were similar for 35 CAZ-AVI patients with CrCL >30 to ≤50 mL/min vs. those with CrCL > 50 mL/min at baseline. Although day 3 plasma levels suggested appropriate dose adjustment, the patients on CAZ-AVI with rapid recovery in CrCL were more likely to have been temporarily under-dosed than similar patients on meropenem based on the greater % reduction in recommended dose for the former vs. latter. CHMP agreed that this is a plausible explanation, but noted that there are no PK data to substantiate this claim.

In addition, MITT patients with MRIB at baseline (n=84; 41 CAZ-AVI) predominated among the 21 total deaths such that 8/13 CAZ-AVI and 3/8 meropenem deaths involved such patients. Also, among the 9 deaths that were considered to be due to disease progression 5/6 in the CAZ-AVI group and 1/3 in the meropenem group were patients with MRIB.

While the observed differences between CAZ-AVI and meropenem in the MRIB sub-population are of concern the applicant has since revised the dose adjustment schema in an attempt to reduce the risk of potential under-dosing. Nevertheless, CHMP requested that the impact of the treatment responses in the MRIB group on the overall study cure rates is stated in the Zavicefta SmPC.

Overall, taking into account the revised dose adjustment schema for renal impairment, the data are considered sufficient to support an indication for cIAI but the MRIB results and the limitations of the

patient population treated (including the low APACHE II scores), as well as the imbalance in deaths, should be reported in section 4.4 of the SmPC.

cUTI

In support of this indication there are clinical efficacy data from RECAPTURE, in which at least 5 days IV was required before oral switch, and from REPRISE in infections due to CAZ-R pathogens. Nearly half of patients in REPRISE and 72% in RECAPTURE had acute pyelonephritis but the response rates were generally similar to those for the cUTI population.

Although neither study pre-defined a primary endpoint as recommended by CHMP the data from RECAPTURE were re-analysed accordingly and were reassuring regarding the comparative efficacy of CAZ-AVI vs. doripenem. The data from REPRISE were reported for $<10^4$ CFU/mL and for no growth and suggested that CAZ-AVI was at least as efficacious as BAT (noting that this study was not powered for formal inferential testing). REPRISE also provided a substantial body of evidence supporting the CAZ-AVI dose for treatment of CAZ-R pathogens although, due to high drug concentrations predicted in the urinary tract, it cannot necessarily be assumed that the same level of efficacy will be exerted at other sites. It should also be noted that very few pathogens expressing serine carbapenemases have been treated with CAZ-AVI.

Risks

Unfavourable effects

Thus far, the safety profile of CAZ-AVI has generally reflected that already known for CAZ alone. Overall, this is considered to be rather typical of the injectable cephalosporins so that SmPC statements similar to those for CAZ should mostly suffice. Thus, it is appropriate that the CAZ-AVI SmPC should include warnings pertaining to hypersensitivity, antibacterial agent-associated colitis and pseudo-membranous colitis due to *Clostridium difficile*, concurrent treatment with nephrotoxic medicinal products and development of a positive Coombs' test.

Uncertainty in the knowledge about the unfavourable effects

Although the safety database is considered to be adequate in size, it is not possible to draw any definitive conclusions regarding the possible effects of AVI on the ADR profile of CAZ. In addition, since the dose used in CAZ-AVI is the highest intermittent dose recommended for non-CF patients whereas the ADR frequencies reported for CAZ alone reflect broader usage, it is not appropriate to compare frequencies between CAZ-AVI and those reported for CAZ. Other constraints for interpretation of the data include the fact that reasonable comparisons of safety are possible only vs. carbapenems and only in patients with cIAI or cUTI. Hence it is not really so surprising that rates of some AEs more associated with cephalosporins than carbapenems are higher with CAZ-AVI. What is more, all CAZ-AVI patients with cIAI also received metronidazole, which confounds the comparisons made.

After updating of the safety data during the procedure there was only a small imbalance in death rates for CAZ-AVI vs. pooled comparators across indications (37 deaths [21 CAZ-AVI], giving rates of 1.3% for CAZ-AVI vs. 1.0% for pooled comparators). When shown by indication there was a greater imbalance in rates for cIAI patients (18 [2.1%] vs. 12 [1.4%]). This number included 2 CAZ-AVI (both ascribed to disease progression) and 1 meropenem death in RECLAIM3. There were no deaths in RECAPTURE (all cUTI) and very few deaths in REPRISE (mostly UTI), with no imbalance.

In the cIAI patients most deaths occurred before days 14-21 on study. Further exploration of the deaths revealed that in the MRIB/SRIB group 6 CAZ-AVI and 5 comparator patients had AEs with outcome of death but deaths due to disease progression occurred in 7 vs. 1 in respective treatment

groups. It is not possible to ascribe or to rule out a contribution to the imbalance in deaths due to disease progression to temporary under-dosing. It can be observed that baseline APACHE II scores for the patients who died were higher than median baseline APACHE II scores across cIAI CAZ-AVI studies but this finding applied in both treatment groups.

Overall, it remains possible that the remaining imbalance in deaths in cIAI patients occurred by chance and/or reflected at least in part dosing of MRIB patients in the initial phase of treatment and/or an imbalance in adequate surgical management. The imbalance is reflected in section 4.4.of the Zavicefta SmPC.

Across all completed Phase 1 through Phase 3 studies of the CAZ-AVI programme there were 57 subjects/patients (5 AVI, 29 CAZ-AVI +/- MTZ and 23 comparator) who had AEs identified as part of the search strategy used for the Renal disorder Safety Topics of Interest and/or met PCS elevations in creatinine (>2.0 × ULN and >100% increase from baseline). A detailed analysis of these patients and of all PCS values relating to renal function was undertaken.

Of the 57 subjects/patients, 37 could be verified as having laboratory evidence that supported the AEs reported. Another 5 had baseline renal dysfunction and findings that did not suggest a contribution from AVI. In the remaining 32 patients (19 CAZ-AVI) there were 22 (11 CAZ-AVI) with normal function or mild impairment and 10 with MRIB/SRIB (8 CAZ-AVI). However, the information available provided a more likely explanation than CAZ-AVI-related AKI for most cases. The shifts and PCS tables do not suggest an excess risk for CAZ-AVI over comparators.

The SmPC contains the statements and AEs that are based on the information available on ceftazidime, i.e. that CAZ can be associated with nephrotoxicity especially if combined with other nephrotoxic agents. It is not possible from available data to definitively conclude whether adding AVI increases the risk of AKI and whether the resulting rates of AKI exceed those observed with other commonly used antibacterial agents. The matter has been reflected in the RMP.

There was an increased incidence in all categories of AEs with declining renal status. There were very few patients with SRIB. In the MRIB subgroup there were 6 CAZ-AVI patients with renal failure acute [3], renal failure [2] and renal impairment [1] but only one in the comparator group (renal impairment). These patients were investigated as described above.

Other SOCs or PTs for which there was a higher reporting rate in the CAZ-AVI MRIB group were not indicative of AKI. In addition, in the MRIB population the only SOCs that showed higher rates for CAZ-AVI were cardiac disorders (12.9% vs. 8.3%), gastrointestinal disorders (22.7% vs. 14.6%; rates of diarrhoea were comparable between treatments), injury/poisoning/procedural complications (9.1% vs. 4.9%) and renal disorders (8.3% vs. 4.2%).

In Phase 3 studies (except for RECAPTURE), the Coombs seroconversion rate is very high and much higher than what is reported for CAZ alone. In each study the denominator is only a fraction of the total study population but it does seem to be consistent that rates are much higher than reported for CAZ. Further investigation does not suggest that the high rate was driven by an additive effect of AVI. CHMP requested that the actual range of seroconversion rates, and not just the mean across studies, is reported in the Zavicefta SmPC. In addition CHMP noted that agranulocytosis, which is a SAE reported with the use of ceftazidime, was not reported in the clinical trial conducted in cIAI.

The rates of elevated transaminases were further explored. It appears that elevations in AST and ALT are common but again it does not seem that the rates are driven by an additive effect of AVI at the dose used in CAZ-AVI. There have not as yet been any cases that have fully met Hy's Law criteria across all studies with AVI, regardless of the beta-lactam partner. There was no detectable relationship

between plasma exposure to AVI and the risk of transaminase elevations but there was a weak association with CAZ exposures.

Benefit-risk balance

Importance of favourable and unfavourable effects

Taking into account the information already available on CAZ, the clinical efficacy data for CAZ-AVI in cUTI and cIAI, including CAZ-R pathogens, and the PK-PD analyses that support the dose adjustment schema and the application of the same posology to HAP/VAP patients, CHMP agreed that the indications applied for by the applicant are acceptable. Nevertheless, CHMP highlighted that these indications can only be accepted if the various limitations of the data are adequately reflected in the SmPC; the Applicant agreed to the CHMP request. The additional safety data from recently completed comparative studies in cIAI and cUTI have added considerably to the database and for the most part have been reassuring. For those remaining issues on which definitive conclusions could not be drawn, CHMP agreed that an adequate SmPC and RMP would be sufficient at this time point.

Table Effects Table for CAZ-AVI in cIAI

Effect	Short Description	CAZ-AVI +MTZ	Comparator	Uncertainties/ Strength of evidence
Clinical cure in patients with cIAI (overall population)	Proportion of patients with clinical response at TOC RECLAIM MITT	82.5 (429/520)	84.9 (444/523)	• RECLAIM non-inferiority vs meropenem using 10% margin (MITT and CE)
	RECLAIM3 CE	93.8 (166/177)	94.0 (173/184)	• RECLAIM3 non-inferiority vs. meropenem; within -10% for CE and within -12.5% for MITT
	RECLAIM3 MITT	83.2	86.6	
Efficacy in infections caused by CAZ-R pathogens	Clinical response at TOC RECLAIM mMITT	85.0 (68/80)	82.4 (75/91)	• Consistent results for key pathogens
Efficacy in infections caused by CAZ-S pathogens	Clinical response at TOC RECLAIM mMITT	81.3 (270/332)	87.8 (303/345)	• See above.
Efficacy in patients with CrCL ≤50 mL/min	Clinical cure at TOC in patients with moderate renal impairment at baseline (RECLAIM MITT)	48.8 (20/41)	74.4 (32/43)	• Underexposure due to rapid improvement in renal function • Revision of renal dose adjustments

Effect	Short Description	CAZ-AVI +MTZ	Comparator	Uncertainties / Strength of evidence
C. difficile associated diarrhoea (CDAD)	AEs potentially representing CDAD in RECLAIM	0.2 (1/636)	0.2 (1/637)	• Listed in the ceftazidime SmPC
Anaphylaxis and other severe hypersensitivity reactions	AEs potentially representing anaphylaxis and other severe hypersensitivity reactions in RECLAIM	3.1 (20/636)	1.7 (11/637)	• Listed in the ceftazidime SmPC

** Agranulocitosis is a SAE which has been reported with the use of ceftazidime. However, it has not been observed in the clinical trials conducted with CAZ-AVI*

Table Effects Table for CAZ-AVI in cUTI

Effect	Short Description	Unit	CAZ-AVI	Comparator	Uncertainties / Strength of evidence
Eradication ($<10^3$ CFU/mL) cUTI	Eradication at TOC vs. doripenem RECAPTURE	% n/N	76.1 (299/393)	69.8 (291/417)	• Non-inferiority using 10% margin
Eradication ($<10^4$ CFU/mL) cUTI due to CAZ-R pathogens	Eradication at TOC vs. BAT REPRISE cUTI; mMITT population	% n/N	81.9 (118/144)	64.2 (88/137)	• REPRISE used the Phase 3 CAZ-AVI dose regimen • Open label • Not powered for inferential testing
Clinical response in patients with cUTI caused by CAZ-R pathogens	Clinical response at TOC vs. BAT REPRISE cUTI; mMITT population	% n/N	91.7 (132/144)	94.2 (129/137)	
• The highlighted AE observed in the clinical trials conducted with CAZ-AVI in cIAI are also of relevance for the benefit-risk balance in the cUTI indication					

Benefit-risk balance

The benefit-risk balance of Zavicefta is positive for all the indications claimed.

Discussion on the benefit-risk balance

The benefit-risk assessment takes into account the antibacterial spectrum of CAZ-AVI as well as the fact that the beta-lactam agent is well known. The critical issue is to support the adequacy of the AVI dose and its safety profile. Current evidence supports the dose for the indications claimed and does not point to any major safety concerns. However, the SmPC has to adequately reflect the limitation so of the data as well as the imbalances noted in death rates and cure rates in the MRIB and high APACHE score sub-populations.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zavicefta in the treatment of the following infections in adults (see sections 4.4 and 5.1):

- Complicated intra-abdominal Infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)

Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms 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.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Postauthorisation efficacy study (PAES) In order to further investigate the efficacy, safety and tolerability of ceftazidime-avibactam in the treatment of nosocomial pneumonia including ventilator-associated pneumonia in hospitalized adults, the MAH should submit the results of a randomised, multicentre, double-blind, double-dummy, parallel-group study comparing ceftazidime-avibactam to meropenem.	The final study report should be submitted by December 2016

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that constituent of Zavicefta, avibactam sodium, is qualified as a new active substance.