EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/437085/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Zavicefta

International non-proprietary name: ceftazidime / avibactam

Procedure No. EMEA/H/C/004027/II/0019

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation or special term	Definition
50%*f*T	50% of the dosing interval
ADR	Adverse drug reaction
AE	Adverse event
APACHE	Acute Physiology and Chronic Health Evaluation
BAT	Best available therapy
BMI	Body mass index
CAZ-AVI	Ceftazidime-avibactam
CC	Clinical cure
CF	Clinical failure
CFU	Colony-forming unit
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CrCl[1]	Creatinine clearance
CSR	Clinical Study Report
cUTI	Complicated urinary tract infection
ECG	Electrocardiogram
EOT	End of treatment
ESBL	Extended spectrum β-lactamases
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed dose combination
HAP	Hospital-acquired pneumonia
HLT	Higher Level Term
ICH	International Council for Harmonisation
IB	Investigator's Brochure
IP	Investigational product
IV	Intravenous
LLN	Lower limit of normal
KPC	*Klebsiella pneumoniae* carbapenemases
MD	Multiple dose
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
mMITT	Microbiological modified intent-to-treat
MTZ	Metronidazole
NEC	Not elsewhere classified

Abbreviation or special term	Definition
NP	Nosocomial pneumonia
PCS	Potentially clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
q8h	quaque octa hora (every 8 hours)
RMP	Risk Management Plan
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SD	Standard deviation
SI	International System of Units
SmPC	Summary of Product Characteristics
SOC	System organ class
STOI	Safety topic of interest
TOC	Test of cure
ULN	Upper limit of normal
US	United States
VAP	Ventilator-associated pneumonia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Ireland Pharmaceuticals submitted to the European Medicines Agency on 13 November 2019 an application for a variation.

The following variation was requested:

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

Extension of Indication to include bacteraemia (in association with, or suspected to be associated with, the currently approved indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)) for Zavicefta; as a consequence, sections 4.1 and 4.2 of the SmPC are updated in order to add this indication and the posology. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The Package Leaflet is updated in accordance.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0340/2018 on the agreement of a paediatric investigation plan (PIP). Although the current indication bacteraemia is not specifically mentioned in the PIP, the relevant data in this application are based on the studies in this PIP.

At the time of submission of the application, the PIP EMEA-001313-PIP01-12-M08 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 MAH 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 indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bjorg Bolstad Co-Rapporteur: Simona Stankeviciute

Timetable	Actual dates
Submission date	13 November 2019
Start of procedure:	30 November 2019
CHMP Co-Rapporteur Assessment Report	9 January 2020
CHMP Rapporteur Assessment Report	24 January 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	2 June 2020
CHMP members comments	15 Jun 2020
Updated CHMP Rapporteur Assessment Report	18 Jun 2020
Opinion	25 Jun 2020

2. Scientific discussion

2.1. Introduction

Bacteraemia due to Gram-negative pathogens is associated with significant morbidity and mortality. Nearly 2 million episodes of bloodstream infection in North America and Europe annually led to ~250,000 deaths and nearly half of community-acquired and one third of healthcare associated cases were caused by Gram-negative bacteria. Infections associated with bacteraemia may be severe, require hospitalisation and have the potential to be life-threatening. Bacteraemia due to resistant pathogens is increasing in frequency and associated with more adverse effects. Prompt administration of effective antibiotics is therefore critical for a favorable outcome.

Zavicefta - Ceftazidime-avibactam (CAZ-AVI) - is a fixed dose combination (FDC) that has been developed as an intravenously administered compound for treatment of patients with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime.

Ceftazidime is a cephalosporin that has been approved for many years in several member states. As a result from an Article 30 referral procedure (EMEA/H/A-30/001006, EC decision date 13/01/2011) ceftazidime (brand leader Fortum) was approved for the following indications: the treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), nosocomial pneumonia (NP), *including treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above*. In addition, a range of other infections were also approved in the referral procedure, however these are not mentioned here. Ceftazidime has no noticeable antibacterial activity against Gram-positive pathogens, with the exception of some streptococci, or anaerobes.

Avibactam is a novel non-betalactam-lactamase inhibitor with a spectrum of beta-lactamases of class A and class C, including ESBLs and serine-based carbapenemases (KPCs). It also inhibits class D beta-lactamases (e.g. OXA-48 type carbapenemase). Avibactam has no inhibitory effect on class B metallo-beta-lactamases.

CAZ-AVI is currently approved for use in EU, under the trade name Zavicefta, for the treatment of adults with cIAI, cUTI including pyelonephritis, hospital-acquired pneumonia (HAP) including ventilator associated pneumonia (VAP), and infections due to aerobic Gram-negative organisms in patients with limited treatment options. Zavicefta was first made commercially available in the EU in 2016.

Zavicefta is currently only approved for adults, however, a Type II variation to extend the indication of Zavicefta to include paediatric patients aged 3 months to less than 18 years for the treatment of cIAI and cUTI is ongoing at the time of the adoption of this assessment report (EMEA/H/C/004027/II/0015).

This Type II variation concerns an extension of the indication to include treatment of bacteraemia (in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP) in Section 4.1 of the SmPC.

The clinical development program for CAZ-AVI included patients with bacteraemia at baseline in all of the 5 completed Phase 3 studies that were conducted to support the currently approved indications of cIAI, cUTI and HAP/VAP (this includes also the indication related to aerobic Gram-negative organisms in patients with limited treatment options). A brief overview of these studies are presented in Table 1 below. No new studies have been submitted for the current application.

This Type II variation for the extension of the indication to include treatment of bacteraemia (in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP) is based on:

- Post-hoc analysis of efficacy and safety data from the sub-group of patients who had bacteraemia at baseline across these 5 studies mentioned above.
- Relevant post-marketing (PM) safety data.

The CHMP acknowledged that this proposed indication extension for the addition of bacteraemia associated with the currently approved indication in adults is mainly based on post-hoc analysis of efficacy and safety data from the sub-group of patients who had bacteraemia at baseline across the previously assessed 5 Phase 3 studies. These studies (RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE) were conducted to support the currently approved indications of cIAI, cUTI and HAP/VAP. No new documentation to support the indication extension to include bacteraemia was submitted. The Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013) states the following regarding non-pathogen-specific bacteraemia: *„It may be possible to accumulate sufficient clinical data to support an indication for use of an antibacterial agent in the treatment of bacteraemia that is associated with specific types of infection, with or without restriction to certain pathogens. For example, in the case of agents that have been in use for many years and are indicated for use in a broad range of infections the total evidence may be considered sufficient for an indication that reads: Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above (i.e. referring to the list of indications approved). If the antibacterial agent has been evaluated in several indications and the total number of bacteraemic patients treated across these indications is deemed sufficient (e.g. ~50 or more) to support a conclusion that efficacy is comparable to that in other patients or, at least, comparable to that of other treatments, then the addition of the sentence could be considered appropriate."*

The MAH's approach is therefore considered acceptable and in line with the current AB-guideline as well as in accordance with the CHMP-decisions for older antibiotics that have been going through referral harmonisations, e.g. ceftazidime (Article 30 referral procedure, EMEA/H/A-30/001006).

Of main importance when evaluating this extension of the indication for Zavicefta is the fact that during the aforementioned Article 30 procedure of ceftazidime in 2011 (EMEA/H/A-30/001006), treatment of patients with bacteraemia in association with, or suspected to be associated with, the approved adult indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP) was added to the EU SmPC of ceftazidime. The additional data submitted for the Fixed Dose Combination Zavicefta, which is further described below, are merely supplementary.

2.2. Non-clinical aspects

This Type II variation concerns an extension of the indication to include treatment of bacteraemia in adults associated with, or suspected to be associated with, the currently approved indications cIAI, cUTI and HAP/VAP. No new non-clinical data have been submitted with this application, which was considered acceptable by the CHMP. In view of that the proposed posology and route of administration in patients with bacteraemia are identical as for the approved indications, update of the initial non-clinical safety assessment is not warranted.

Non-clinical data within previous submissions of MAA for Zavicefta reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproduction toxicity or genotoxicity. Carcinogenicity studies have not been conducted with ceftazidime and avibactam, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Introduction

Zavicefta is indicated for the treatment of the following infections in adults;

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

The current indication extension seeks to include 'treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above'.

The active ingredients in Zavicefta are ceftazidime and avibactam. The recommended dosage of Zavicefta for patients with estimated creatinine clearance ≥51 mL/min is 1 vial containing 2000 mg ceftazidime and 500 mg avibactam administered by intravenous (IV) infusion. Treatment will be repeated every 8 hours, i.e. a maximum of 3 vials per 24-hour period. Hence, the maximum daily dose is 6000 mg/day and 1500 mg/day of ceftazidime and avibactam, respectively. Treatment duration is normally from 5 to 14 days. For the paediatric population, the recommended maximum dosage is similar to the adult population.

Zavicefta was first approved in Europe in 2016. In 2019, an application for extension of the indication to include paediatric use for the indications cIAI and cUTI was submitted, which was pending at the time of adoption of this AR.

The environmental risk assessment (ERA) is divided into an ERA for ceftazidime (Phase I and Phase II: Tier A and Tier B) and an ERA for avibactam (Phase I and Phase II: Tier A and B).

Ceftazidime

PEC calculation ceftazidime

The Fpen of ceftazidime is refined by taking into account the consumption data of ceftazidime in Italy in 2016 (4268 kg), a maximum daily dose of 6000 and a population in Italy in 2016 of 59,290,969:

$$refined\ Fpen = \frac{4268x10^6}{6000\ x\ 50{,}968{,}694\ x\ 365} = 4{,}0\ x10^{-5}$$

This Fpen reflects existing approved indications, but not necessarily bacteraemia. Based on the ECDC 2016-17 point prevalence survey, approximately 5.5% of patients in the EU were diagnosed with at least one healthcare associated infection (HAI) during 2016-2017. This ECDC data estimates the total annual number of people acquiring one HAI is about 3.8 million. The same survey reported 10.8% of HAIs across the EU countries are attributed to blood stream infections or bacteraemia.

Therefore, the EU prevalence (Fpen) for bacteremia may be determined as follows:

$$\text{Refined } fpen = \frac{HAI\ patients\ \times 0.108}{EUpopulation}$$

fpen (market penetration bacteremia)	-
Number of HAI in EU (2016-2017)	3.8 million
EU population in 2016 (Eurostat)[7]	511.8 million
HAIs associated with bloodstream (bacteremia)	10.8%

$$\text{Refined } fpen = \frac{3.8 \times 10^6\ patients\ \times 0.108}{511{,}800{,}000}$$

$$\text{Refined } fpen\ bacteremia = 0.00080$$

Total fpen based on consumption and bacteremia:

	Ceftazidine fpen	Avibactam fpen
Approved indications (consumption-Appendix 1)	3.8×10^{-5}	2.0×10^{-6}
Bacteremia (prevalence)	8.0×10^{-4}	8.0×10^{-4}
Total fpen	**8.4×10^{-4}**	**8.0×10^{-4}**

In addition, the MAH has used US hospital data (Optum de-identified Electronic Health Record (EHR) dataset 2007-2019) to recalculate the daily dose consumed per inhabitant, in order to cover the possible scenario that a patient could receive more than one course of treatment per year. EHR data includes more than 700 hospitals and 7000 clinics in US and show that approximately 15% of patients receive more than

one course of treatment within a 12 month period. There are no similar European data available. The revised $Dose_{ai}$ is thus 267.7 mg/day for ceftazidime, and 66.2 mg/day for avibactam.

$$\text{Refined } PECsw = \frac{264.7\ mg \times 0.00084}{200\ L/(inh \cdot d) \times 10}$$

$$\text{Refined } PECsw = 1.11 \times 10^{-4}\ mg/L = 0.111\ \mu g/L$$

The refined PEC_{sw} value is above the threshold of 0.01 µg/L, and a Phase II assessment is provided.

Phase II Tier A, ceftazidime

The Phase II Tier A assessment for ceftazidime was assessed during the initial marketing authorisation procedure.

Table 1: Updated Risk calculations ceftazidime

$PEC_{surfacewater}$ $PNEC_{surfacewater}$ **$PEC/PNEC_{surfacewater}$**	0.111 1.3 0.085	µg/L µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{groundwater}$ $PNEC_{groundwater}$ **$PEC/PNEC_{groundwater}$**	0.028 920 0.00003	µg/L µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{microorganisms}$ $PNEC_{microorganisms}$ **$PEC/PNEC_{microorganisms}$**	0.111 32 000 3.5×10^{-6}	µg/L µg/L	Unlikely to represent a risk to wastewater micro-organisms
$PEC_{sediment}$ $PNEC_{sediment}$ **$PEC/PNEC_{sediment}$**	1.29 3030 0.00043	µg/kg µg/kg	Unlikely to represent a risk to sediment dwelling organisms

For the calculation of the PNEC of all three compartments, an assessment factor (AF) of 10 is used.

The risk quotient (RQ) for all compartments are under the action limit (table 1), therefore a Tier B is not triggered. However, in the water-sediment study greater than 10% of the applied radioactivity was associated with the sediment phase, therefore the effect of ceftazidime on the sediment dwelling organism *Chironomus riparius* was investigated in Tier B.

Phase II Tier B, ceftazidime

The Tier B study on sediment-water toxicity in Chironomids has been assessed previously: LOEC (28d) >100 mg/kg dw, NOEC 100 mg/kg dw, recalculated to standard sediment: $NOEC_{standard\ sediment}$ 303 mg/kg, and using an AF of 10, results in a PNEC of 3030 µg/kg.

The $RQ_{sediment}$ is 0.00043, which is under the action limit of 1 and no further testing is required.

The CHMP considered that the study on ceftazidime transformation in water/sediment systems (OECD 308) shows that both main transformation products M1 and M3 are very persistent considering the DT50 values of 101.0 d and 118.0 d at 20°C for M1 and M3, respectively in water/sediment. Criteria for classification as PBT or vPvB are, however, not met (not B or T).

Avibactam

PEC calculation avibactam

$$\text{Refined } PECsw = \frac{66.2\ mg \times 0.00080}{200\ L/(inh \cdot d) \times 10}$$

$$\text{Refined } PECsw = 2.65 \times 10^{-5}\ mg/L = 0.027\ \mu g/L$$

The refined PEC_{sw} value for avibactam is above the threshold of 0.01 µg/L, and a Phase II assessment is provided.

Phase II Tier A, avibactam

The Phase II Tier A assessment for avibactam was assessed during the initial marketing authorisation procedure.

Table 2: Updated Risk Calculations avibactam

$PEC_{surfacewater}$ $PNEC_{surfacewater}$ **$PEC/PNEC_{surfacewater}$**	0.2027 200 0.00014	µg/L µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{groundwater}$ $PNEC_{groundwater}$ **$PEC/PNEC_{groundwater}$**	0.0068 10 000 0.0000068	µg/L µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{microorganisms}$ $PNEC_{microorganisms}$ **$PEC/PNEC_{microorganisms}$**	0.027 100 0.00027	µg/L µg/L	Unlikely to represent a risk to wastewater micro-organisms
$PEC_{sediment}$ $PNEC_{sediment}$ **$PEC/PNEC_{sediment}$**	0.14 11,110 0.000012	µg/kg µg/kg	Unlikely to represent a risk to sediment dwelling organisms

For the calculation of the PNEC of all three compartments, an assessment factor (AF) of 10 is used.

The risk quotient (RQ) for all compartments are under the action limit (table 2), therefore a Tier B is not triggered. However, in the water-sediment study greater than 10% of the applied radioactivity was associated with the sediment phase, therefore the effect of avibactam on the sediment dwelling organism *Chironomus riparius* was investigated in Tier B.

Phase II Tier B, avibactam

The Tier B study on sediment-water toxicity in Chironomids has been assessed previously: LOEC (28d) >300 mg/kg dw, NOEC 300 mg/kg dw, recalculated to standard sediment: $NOEC_{standard\ sediment}$ 1111 mg/kg, and using an AF of 100, results in a PNEC of 11,110 µg/kg.

The $RQ_{sediment}$ is 0.000012, which is under the action limit of 1 and no further testing is required.

Consumption based refinement of Fpen values was considered acceptable by CHMP as part of the ongoing extension of indication procedure to include the paediatric population (Zavicefta Module 1.6.1 ERA dated 23 October 2019). In addition, the MAH refined $Dose_{ai}$ for ceftazidime and avibactam to reflect the possibility of patients receiving more than one course of treatment per year, in line with the CHMP request made during this assessment. The source for data and the estimate is considered appropriate to use for PEC calculation.

2.2.2. Discussion on non-clinical aspects

The MAH did not propose any changes to section 4.6 (Fertility, pregnancy and lactation) or 5.3 (Preclinical safety data) of the SmPC, or in corresponding parts of the PL. This is considered adequate and acceptable by the CHMP.

2.2.3. Conclusion on the non-clinical aspects

There are no objections to approval of the proposed extension of indication from a non-clinical point of view.

Ceftazidime and avibactam as combined in the product Zavicefta are not expected to pose a risk to the environment

2.3. Clinical aspects

2.3.1. Introduction

No new clinical pharmacology data was submitted for this extension of indication variation. This however was acceptable to the CHMP as a previously submitted population PK, PK/PD and PK/PD target attainment analyses report, CAZ-MS-09, was used to justify the posology in patients with bacteraemia. Refer to Section 2.3.4 on PK/PD modelling for discussion on the topic.

- Tabular overview of the 5 completed clinical Phase 3 studies that were conducted to support the indications of cIAI, cUTI and HAP/VAP:

Table 3. Overview of Phase 3 Studies by Indication - (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Study [Study Number] Title	CAZ-AVI Dosage regimen	Comparator Dosage regimen	Overall Set		Bacteraemia Subset	
			CAZ-AVI ± MTZ n/N	Comparator n/N	CAZ-AVI ± MTZ n/N	Comparator n/N
cIAI						
RECLAIM (Global) **[D4280C00001/5]** A Phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of ceftazidime-avibactam (CAZ-AVI) plus metronidazole (MTZ) vs meropenem in the treatment of complicated intra-abdominal infections (cIAIs) in hospitalised adults	CAZ-AVI (ceftazidime 2000 mg + avibactam 500 mg; 2-hour IV infusion) followed by MTZ 500 mg (1-hour IV infusion) q8h for 5 to 14 days	Meropenem 1000 mg; 30-minute IV infusion q8h for 5 to 14 days	270 / 529	294 / 529	9 / 22	4 / 14
RECLAIM3 (Asia) **[D4280C00018]** A Phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of ceftazidime-avibactam (CAZ-AVI) plus metronidazole vs meropenem in the treatment of complicated intra-abdominal infections (cIAIs) in hospitalised adults	CAZ-AVI (ceftazidime 2000 mg + avibactam 500 mg; 2-hour IV infusion) followed by MTZ 500 mg (1-hour IV infusion) q8h for 5 to 14 days	Meropenem 1000 mg; 30-minute IV infusion q8h for 5 to 14 days	100 / 215	119 / 217	2 / 5	6 / 10
REPRISE/cIAI **[D4280C00006]** An open-label, randomised, multicentre, Phase 3 study of ceftazidime-avibactam (CAZ-AVI) and the best available therapy for the treatment of infections due to ceftazidime-resistant Gram-negative pathogens	CAZ-AVI (ceftazidime 2000 mg + avibactam 500 mg); 2-hour IV infusion q8h for 5 to 21 days Patients with cIAI also receive MTZ 500 mg 1 hr IV q8h following completion of CAZ-AVI infusion for 5 to 21 days.	Investigator's BAT choice for 5 to 21 days Preferred choices for cIAI: meropenem, imipenem, doripenem, tigecycline, and colistin with MTZ for anaerobic coverage	8 / 12	5 / 15	0 / 0	0 / 0
Total cIAI			**378 / 756**	**418 / 761**	**11 / 27**	**10 / 24**
cUTI						
RECAPTURE (Global) **[D4280C00002/4]** A Phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of ceftazidime-avibactam (CAZ-AVI, formerly CAZ104) vs doripenem followed by appropriate oral therapy in the treatment of complicated urinary tract infections, including acute pyelonephritis, with a Gram-negative pathogen in hospitalised adults	CAZ-AVI (ceftazidime 2000 mg + avibactam 500 mg; 2-hour IV infusion) q8h for 5 to 14 days	Doripenem 500 mg; 1-hour IV infusion q8h for 5 to 14 days	292 / 511	311 / 509	25 / 43	24 / 36
REPRISE/cUTI **[D4280C00006]** An open-label, randomised, multicentre, Phase 3 study of ceftazidime-avibactam (CAZ-AVI) and the best available therapy for the treatment of infections due to ceftazidime-resistant Gram-negative pathogens	CAZ-AVI (ceftazidime 2000 mg + avibactam 500 mg); 2-hour IV infusion q8h for 5 to 21 days.	Investigator's BAT choice for 5 to 21 days Preferred choices for cUTI: meropenem, imipenem, doripenem and colistin	131 / 152	124 / 153	3 / 5	5 / 6
Total cUTI			**423 / 663**	**435 / 662**	**28 / 48**	**29 / 42**

NP						
REPROVE [D4281C00001] Phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group comparative study to determine the efficacy, safety, and tolerability of ceftazidime-avibactam (CAZ-AVI) vs meropenem in the treatment of nosocomial pneumonia (NP) including ventilator-associated pneumonia (VAP) in hospitalised adults	CAZ-AVI (ceftazidime 2000 mg + avibactam 500 mg); 2-hour IV infusion q8h for 7 to 14 days	Meropenem 1000 mg; 30 minute IV infusion q8h for 7 to 14 days	125 / 436	131 / 434	15 / 24	8 / 18
Total NP			**125 / 436**	**131 / 434**	**15 / 24**	**8 / 18**
Total Number of Patients in the Overall set			**926 / 1855**	**984 / 1857**	-	-
Total Number of Patients in the Bacteraemia subset			-	-	**54 / 99**	**47 / 84**

BAT = best available therapy; q8h = every 8 hours; VAP = ventilator-associated pneumonia n = the number of subjects in the efficacy population i.e. the Gram-negative extended ME at TOC population N = the number of subjects in the safety population. For the Overall set this is the overall Phase 2/3 pooled safety analysis population and for the Bacteraemia subset this is the pooled safety analysis population of the patients that had bacteraemia at baseline in the 5 Phase 3 studies.

2.3.2. Pharmacokinetics

Reference is made to the initial MAA (EMEA/H/C/4027) and other extension of indications procedures EMEA/H/C/004027/II/0002 and EMEA/H/C/004027/II/0015 for details on pharmacokinetics.

2.3.3. Pharmacodynamics

Reference is made to the initial MAA (EMEA/H/C/4027) and other extension of indications procedures EMEA/H/C/004027/II/0002 and EMEA/H/C/004027/II/0015 for details on pharmacodynamics.

2.3.4. PK/PD modelling

- The ceftazidime (CAZ) dataset comprised 9155 observations from 1975 individuals, including 86 (4.4%) healthy volunteers, 696 (35.2%) cUTI patients, 781 (39.5%) cIAI patients and 412 (20.9%) with HAP/VAP.
- The avibactam (AVI) dataset included 13735 observations from 2249 individuals, including 345 (15.3%) healthy volunteers, 705 (31.3%) cUTI patients, 786 (34.9%) cIAI patients and 413 (18.4%) with HAP/VAP.

There is a difference between the number of Phase 3 patients in the two datasets (n=1747 CAZ, n=1762 AVI) because 16 patients did not have CAZ concentrations and one did not have AVI concentrations available.

The PK data for each analyte were well described by 2-compartment PK models with first-order disposition and elimination. Of the covariates evaluated (including CrCL, age, body weight, sex, race, indication and geographic region) only CrCL had sufficiently large effects on exposures to warrant dose adjustment and only for patients with CrCL<50 mL/min. The CL of CAZ and AVI were correlated with CrCL. The relationship was close to proportional at CrCL <100 mL/min. Above this level, CL was found to increase slowly with increasing CrCL, such that an increase of 100 mL/min in CrCL led to a 27.9% increase in AVI CL and a 12.5% increase in CAZ CL.

The final POPPK models included a number of other covariate effects that did not warrant dose adjustment. Typically, covariate effects were retained in the final models if the associated impact on

either CL or Vc was on the order of ± 20%. However, in some instances, covariate effects with smaller magnitudes were retained for informational purposes as deemed appropriate.

Individual Etas for CL and Vc, stratified by bacteraemia status, for the CAZ model are presented in Figure 1 and Figure 2, respectively. Etas for CL and Vc for the AVI model are presented in Figure 3 and Figure 4, respectively.

Figure 1. Individual estimates of ceftazidime ETA-CL in individuals with and without bacteraemia. Source: CAZ-09-MS, Post-Text_Figure 8. Parameter shrinkage was 11.4% (CAZ-09-MS, Table 7)

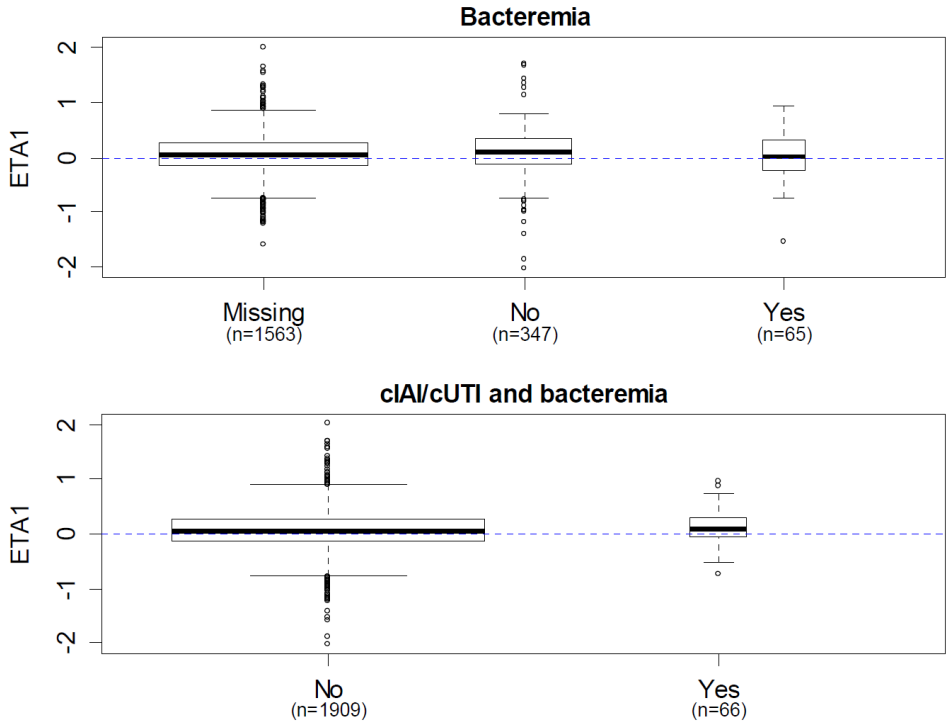


Figure 2. Individual estimates of ceftazidime ETA-Vc in individuals with and without bacteraemia. Source: CAZ-09-MS, Post-Text_Figure 9. Parameter shrinkage was 31.2% (CAZ-09-MS, Table 7)

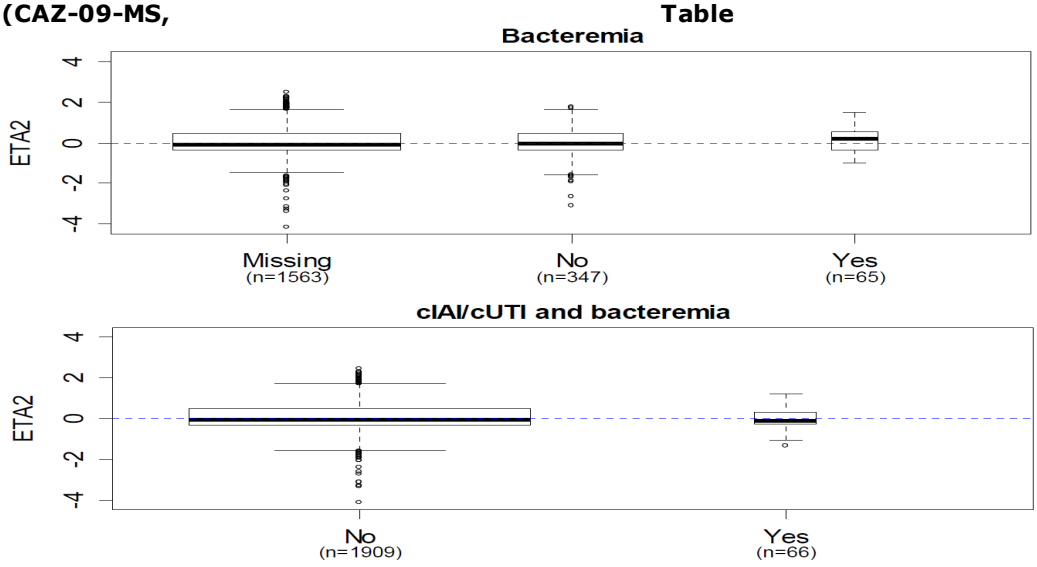


Figure 3. Individual estimates of avibactam ETA-CL in individuals with and without bacteraemia. Source: CAZ-09-MS, Appendix 14.14.2. Parameter shrinkage was 7.29% (CAZ-09-MS, Table 11)

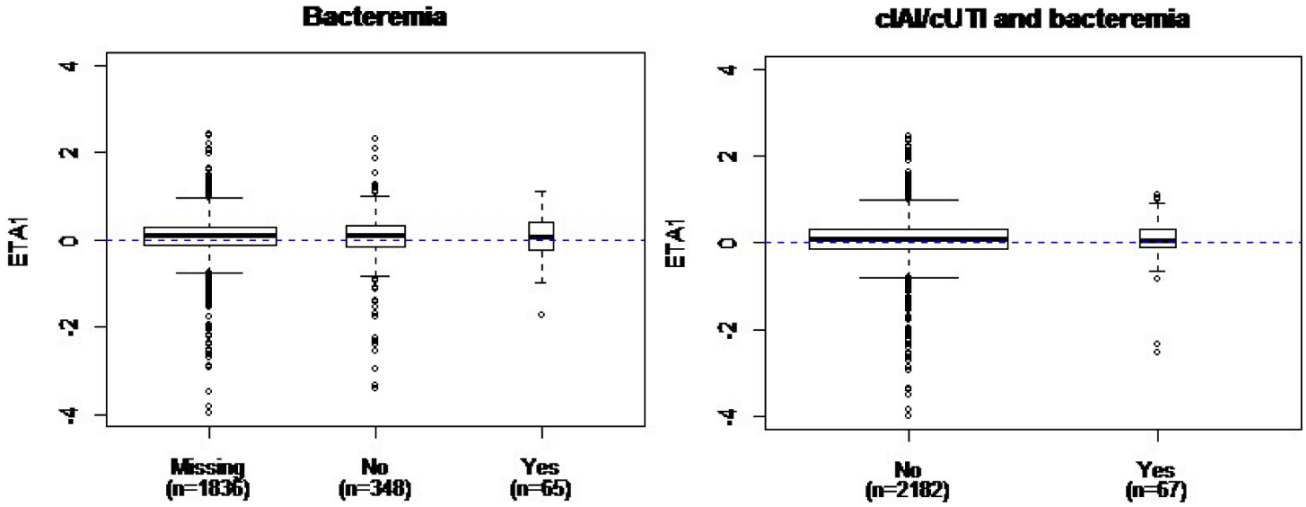
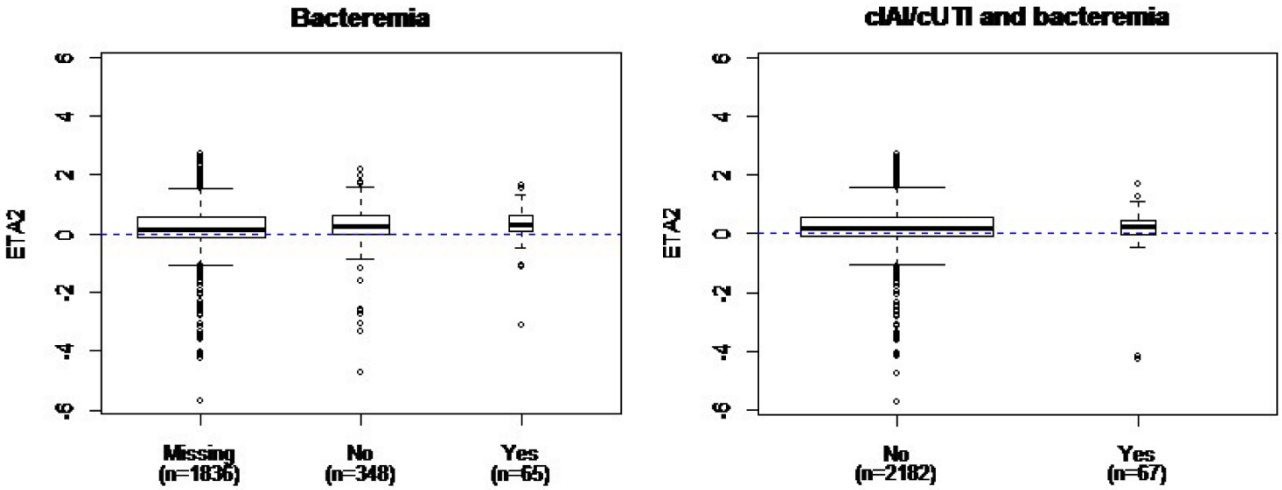


Figure 4. Individual estimates of avibactam ETA-V_c in individuals with and without bacteraemia. Source: CAZ-09-MS, Appendix 14.14.2. Parameter shrinkage 28.15% (CAZ-09-MS, Table 11)



The final POPPK models performed well on visual predictive testing (pcVPC) in subgroups such as patients with high and low CrCL, obese patients and elderly patients (figures not shown here).

Exposure and joint probability of target attainment defined as the probability of PK/pharmacodynamic (PD) target attainment for the joint PK/PD targets of free CAZ concentrations that exceed the CAZ-AVI minimum inhibitory concentration (MIC) for 50% of the dosing interval, denoted 50%*f*T > MIC, and simultaneously, free AVI concentrations that exceed the threshold concentration (C_T) of 1 mg/L for 50%fT > C_T were comparable among patients with and without baseline bacteraemia. The joint probability of PK/PD target attainment at CAZ-AVI MIC=8 mg/L were >98% in patients with and without concurrent bacteraemia (Table 4).

Table 4. Comparison of geometric mean (CV%) of $C_{max,ss}$, $AUC_{ss,0-24}$ and rates of the joint target attainment in patients with- and without baseline bacteraemia for Phase III cIAI, cUTI, and NP, including VAP and non-VAP patients. Source: CAZ-MS-09, Table 13

		Ceftazidime		Avibactam		
Baseline bacteraemia	N	$C_{max,ss}$ (CV%)	$AUC_{ss,0-24}$ (CV%)	$C_{max,ss}$ (CV%)	$AUC_{ss,0-24}$ (CV%)	Probability of target attainment*, % (95% CI)
No	1465	71.9 (116.1)	881 (126)	12.6 (157)	141 (161)	98.6 (98.0, 99.2)
Yes	88	73.6 (102.8)	919 (120)	14.2 (164)	161 (161)	100 (NA)

$AUC_{ss,0-24}$; area under the plasma concentration versus time curve at steady state, cIAI; complicated intra-abdominal infections, $C_{max,ss}$; maximum plasma concentration at steady state, cUTI; complicated urinary tract infections, CV%; coefficient of variation, NP; nosocomial pneumonia, VAP; ventilator associated pneumonia

*PTA was calculated for the joint PK/PD target of the free CAZ concentration above the MIC for 50% of the dosing interval (50%fT > MIC) and free avibactam concentrations exceeding the threshold concentration (C_T) of 1 mg/mL for (50%fT > C_T) at CAZ-AVI MIC of 8 mg/L.

The CHMP noted that the CAZ-MS-09 study report was submitted as part of a previous type II variation (EMEA/H/C/4027/II/002). The presented models in the report were assessed as part of that procedure.

The PK/PD modelling presented in CAZ-09-MS report was not conducted specifically to investigate the impact of bacteraemia on CAZ and AVI exposure. This has led to some limitations in the presented analyses:

- Bacteraemia status is not included in the tables describing the baseline demographics in subjects included in the CAZ- and AVI models (Table 5 and Table 9 in CAZ-09-MS). This has led to some uncertainty regarding the bacteraemia status in the patients included in the exposure/target attainment analyses. In Table 4, there are n=88 patients with status "yes" and n=1465 with "no". Conflictingly, as shown in the Eta plots in e.g. Figure 1, there were n=65 patients with bacteraemia status "yes", n=347 with status "no" and n=1563 with status "missing". In addition, there is also a discrepancy in the number of patients with bacteraemia status "yes", with n=88 in the exposure/target attainment analyses versus n=65/66/67 in the eta plots.

- The report did not contain diagnostic plots (pcVPCs) confirming that the models predicted exposure adequately across bacteraemia status.

The above-mentioned issues were however not further pursued, since bacteraemia status had no apparent effect on the CL or Vc for neither CAZ nor AVI, as shown in Figure 1, Figure 2, Figure 3 and Figure 4. These plots are considered sufficiently reliable due to the low parameter shrinkage for CL (<12%) and moderate shrinkage for Vc (28-31%). There was no apparent difference in $C_{max,ss}$ or $AUC_{ss,0-24}$ of CAZ and AVI between patients with and without bacteraemia. The joint target attainment of CAZ and AVI was also comparable in patients with and without bacteraemia. Finally, bacteraemia per se is not expected to influence pharmacokinetic processes.

2.3.5. Discussion on clinical pharmacology

No new clinical pharmacology data were submitted. This however was acceptable to the CHMP as the posology is supported by a previously submitted modelling report (CAZ-09-MS), which indicated that

patients with bacteraemia have similar pharmacokinetics and therefore similar joint target attainment of CAZ and AVI as patients without bacteraemia.

CAZ monotherapy is currently approved for the treatment of bacteraemia associated, or expected to be associated, with cUTI, cIAI and nosocomial pneumonia (HAP/VAP) (EMEA/H/A-30/1006). No CAZ dose adjustments are needed for patients with bacteraemia in comparison to non-bacteraemic patients.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics and the joint target attainment for CAZ and AVI appear similar in patients with and without bacteraemia. Similar posology in these patient populations is endorsed.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

N/A

2.4.2. Main studies

The 5 main studies (**RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE**) were conducted to support the currently approved indications for Zavicefta. These five Phase 3 studies were used for a pooled analysis to support an extension of the adult cIAI, cUTI, and HAP/VAP indications to patients with bacteraemia associated with, or is suspected to be associated with, any of these infections. The MAH presented post-hoc analyses of results across these studies from the sub-group of patients in the Gram-negative extended ME at TOC population who had bacteraemia at baseline (54 patients in the CAZ-AVI +/-MTZ treatment group and 47 patients in the pooled comparator treatment group). In the analysis performed for this submission, bacteraemia was defined as any patient who had 1 or more bacteria identified from a blood culture at baseline for all studies, except for 1 of the cUTI studies (RECAPTURE), which also required the same pathogen to be identified in a urine sample at $>10^5$ colony-forming units (CFUs)/ml.

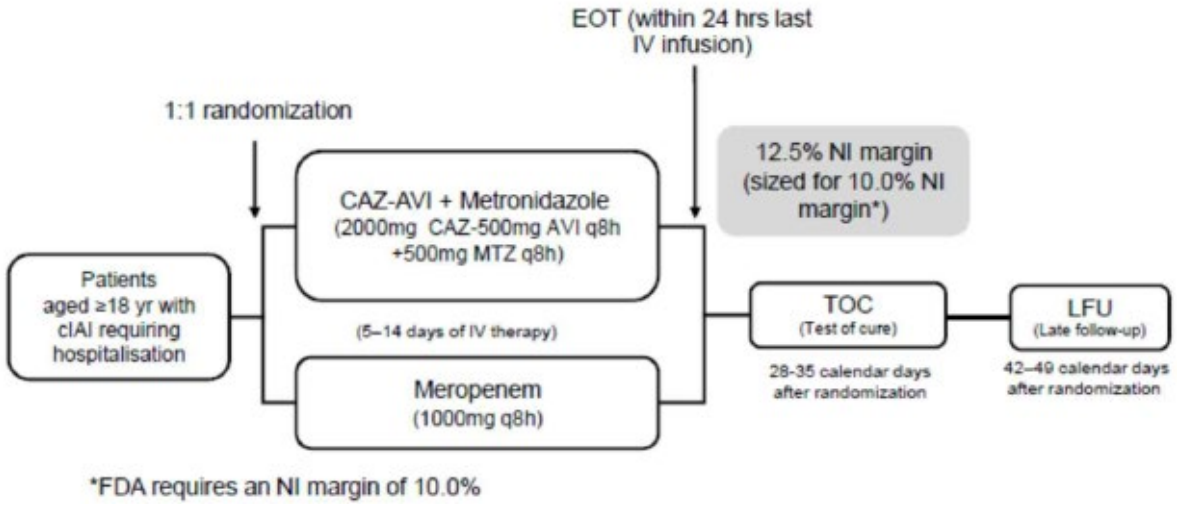
The CHMP considered that 5 adult Phase 3 main studies (RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE) have been presented, and assessed before, in connection with previous applications for Zavicefta (i.e., EMEA/H/C/004027/0000 – initial MAA and EMEA/H/C/004027II/0002 - Type II variation application to provide the results from the finalized REPROVE study). Therefore, the methods and results for these studies are only briefly described in this assessment report. The main focus will be on the post-hoc analysis of efficacy data from the sub-group of patients who had bacteraemia at baseline across these 5 studies.

A brief overview of the overall study designs for each of the 5 adult Phase 3 studies is presented below, and in Table 1 above. The primary endpoint results and analysis populations presented are those corresponding to the ROW (rest of world, including EU) analyses in each original Clinical Study Report (CSR). Of note, randomisation was not stratified by bacteraemia status at baseline in any of these studies.

RECLAIM and RECLAIM3 were both prospective, randomised, multi-centre, double-blind, double-dummy, comparative studies to determine the efficacy, safety and tolerability of CAZ-AVI plus

metronidazole (MTZ) versus meropenem in the treatment of hospitalised adults with cIAI. RECLAIM was conducted in predominantly Western patients whereas RECLAIM3 was conducted at sites in the Asia-Pacific region. Patients were stratified by baseline severity of disease and region. The primary objective was to assess the non-inferiority of CAZ-AVI plus MTZ compared to meropenem with respect to clinical cure at the TOC visit for the modified intent-to-treat (MITT) analysis population (RECLAIM) and the clinically evaluable (CE) analysis population (both RECLAIM and RECLAIM 3):

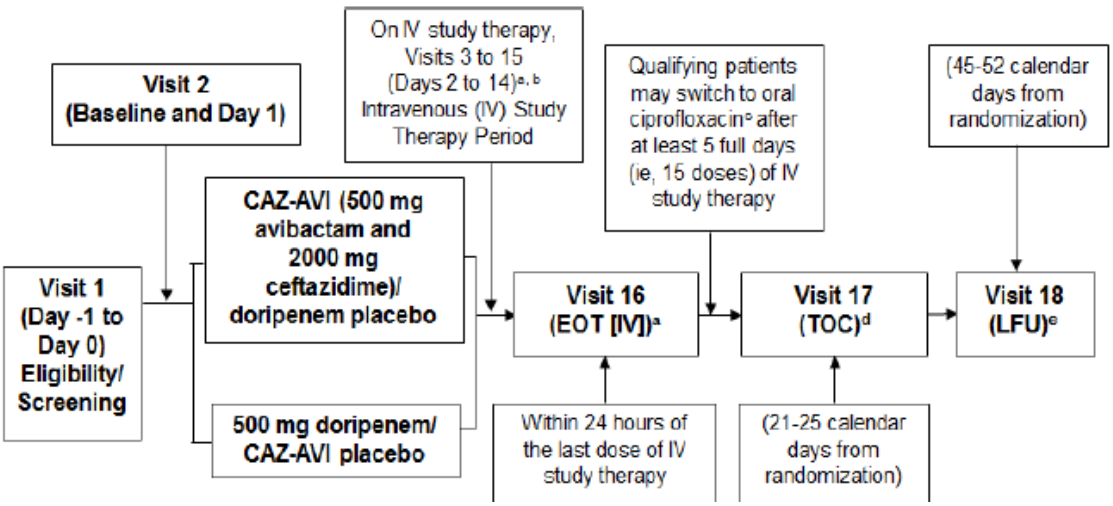
Figure 5. RECLAIM (cIAI- Global) and RECLAIM3 (cIAI- Asia)



LFU Late follow Up. NI Non-Inferiority

RECAPTURE was a prospective, randomised, multi-centre, double-blind, double-dummy, comparative study to determine the efficacy, safety, and tolerability of CAZ-AVI compared with doripenem in the treatment of hospitalised patients with cUTIs. Patients were stratified by type of infection at baseline and region. The primary objective for the ROW analysis was to assess the non-inferiority of CAZ-AVI compared to doripenem with respect to the per-patient microbiological response at the TOC visit in the mMITT analysis population:

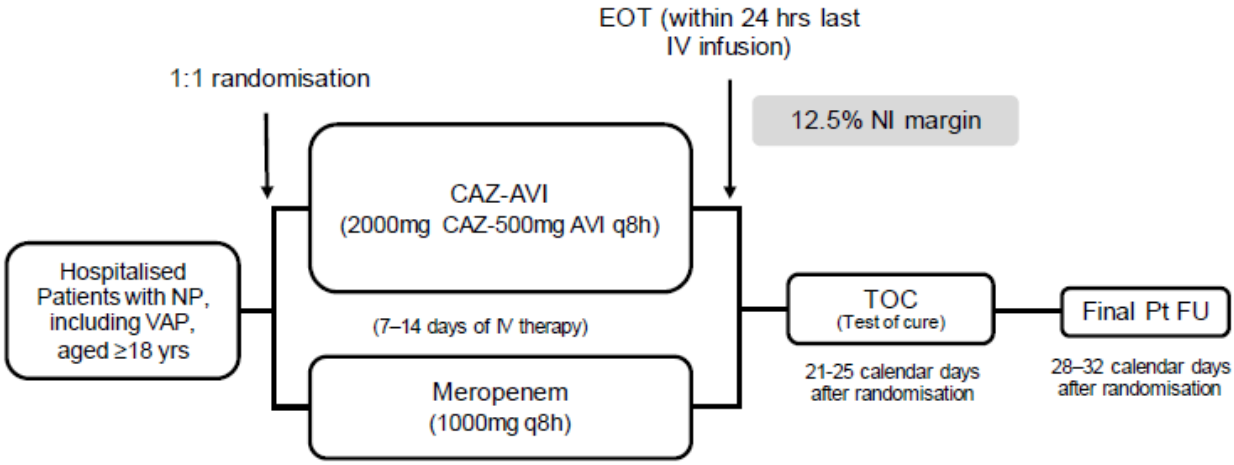
Figure 6. RECAPTURE (cUTI)



LFU Late follow Up. NI Non-Inferiority

REPROVE was a prospective, randomised, multi-centre, double-blind, double-dummy, comparative study designed to evaluate the efficacy, safety, and tolerability of CAZ-AVI versus meropenem in the treatment of nosocomial pneumonia (NP) including ventilator-associated pneumonia (VAP), in hospitalised adult patients. Patients were stratified by type of infection (VAP/non-VAP) and geographical region. The primary objective was to assess the non-inferiority of CAZ-AVI compared to meropenem with respect to clinical cure at the TOC visit for the clinically modified intent-to-treat (cMITT) and clinically evaluable (CE) analysis populations:

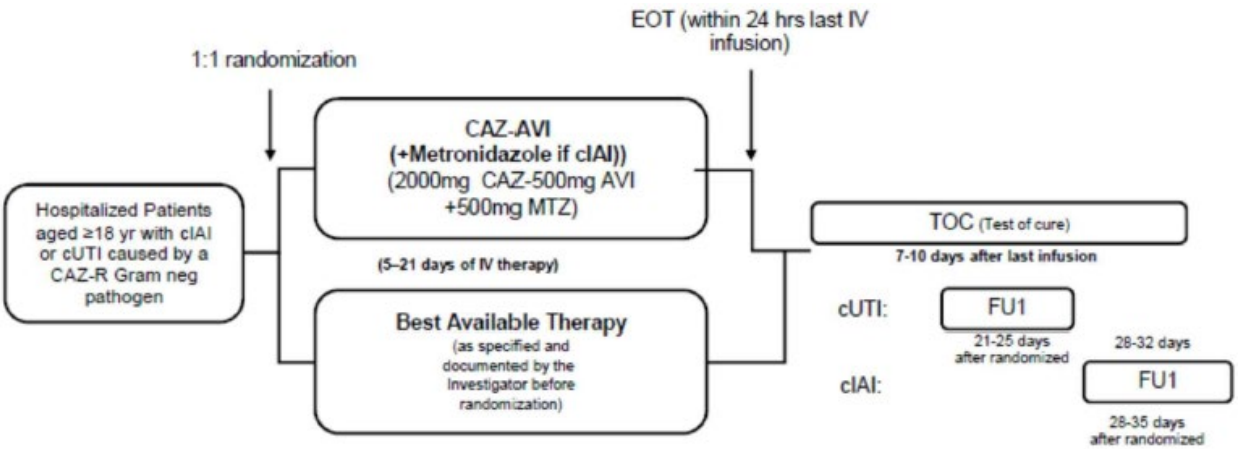
Figure 7. REPROVE (HAP)



LFU Late follow Up. NI Non-Inferiority

REPRISE was a prospective, randomised, multi-centre, open-label, non-comparative study to evaluate the efficacy, safety, and tolerability of CAZ-AVI and Best Available Therapy (BAT) in the treatment of hospitalised adults with cIAIs and cUTIs caused by CAZ-resistant Gram-negative pathogens. Patients were stratified by entry diagnosis and region. The substantial majority (306/333 patients) had cUTI at baseline and therefore REPRISE principally provided supportive evidence of efficacy against CAZ-resistant pathogens in the cUTI indication. The primary objective was to estimate the per-patient overall clinical response to CAZ-AVI and BAT at TOC in the mMITT analysis population:

Figure 8. REPRISE (CAZ-Resistant Gram-Negative Pathogens)



FU Follow Up

The primary endpoint results for each of the 5 adults Phase 3 studies are presented in the table below.

Table 5. Primary Endpoint Results for the 5 Adult Phase 3 Studies (RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Indication Study	Primary Endpoint (Analysis Population)	CAZ-AVI[a] n/N (%)	Comparator[b] n/N (%)	% Difference (95% CI)	Non-inferiority test p-value for a -12.5% margin[c]
cIAI RECLAIM 1&2	Clinical cure at TOC (MITT)	429/520 (82.5)	444/523 (84.9)	-2.4 (-6.9, 2.10)	<0.001
	Clinical cure at TOC (CE)	376/410 (91.7)	385/416 (92.5)	-0.8 (-4.61, 2.89)	<0.001
cIAI RECLAIM 3	Clinical cure at TOC (CE)	166/177 (93.8)	173/184 (94.0)	-0.2 (-5.53, 4.97)	<0.001
cUTI RECAPTURE 1&2	Favourable microbiological response at TOC (mMITT)	304/393 (77.4)	296/417 (71.0)	6.4 (0.33, 12.36)	<0.0001
NP REPROVE	Clinical response at TOC (cMITT)	245/356 (68.8)	270/370 (73.0)	-4.2 (-10.76, 2.46)	0.007
	Clinical cure at TOC (CE)	199/257 (77.4)	211/270 (78.1)	-0.7 (-7.86, 6.39)	<0.001
Resistant pathogens[d] REPRISE [CAZ-R cIAI or cUTI]	Overall clinical cure at TOC (mMITT) (cIAI + cUTI)	140/154 (90.9)	135/148 (91.2)	ND	ND

[a] Plus metronidazole for cIAI studies.
[b] Meropenem for cIAI and HAP; doripenem for cUTI; best available therapy for resistant pathogen study (REPRISE).
[c] P-value for 1-sided test at test of cure (TOC) with a -12.5% non-inferiority margin, i.e. H0: diff ≤ -12.5%.
[d] Not formally powered or analysed for non-inferiority.
ND Not done
Sources: Table 11.2.1.2 RECLAIM CSR, Table 11.2.1.2 RECLAIM3 CSR, Table 11.2.1.1.6 RECAPTURE CSR, Table 11.2.1.2 REPROVE CSR, and Table 11.2.1.1 REPRISE CSR.

The table below presents the results observed for the primary efficacy endpoint in each study for the subset of patients with bacteraemia at baseline, that were analysed as a pre-specified descriptive sub-group analysis in 4 of the 5 adult Phase 3 studies (RECLAIM, RECLAIM3, RECAPTURE and REPROVE). These results were presented in the individual CSRs, and assessed in connection with previously submitted applications for Zavicefta (initial MAA and EMEA/H/C/004027/II/0002).

Table 6. Favourable Response Rates for the Bacteraemia Subsets in the Adult Phase 3 Studies (RECLAIM, RECLAIM3, RECAPTURE, REPROVE)

Indication Study	Primary Endpoint (Analysis Population)	CAZ-AVI[a] n/N (%)	Comparator[b] n/N (%)	% Difference (95% CI)
cIAI RECLAIM 1&2	Clinical cure at TOC (MITT)	17/22 (77.3)	10/14 (71.4)	5.8 (-22.28, 36.44)
	Clinical cure at TOC (CE)	15/17 (88.2)	9/10 (90.0)	-1.8 (-27.45, 31.39)
cIAI RECLAIM 3	Clinical cure at TOC (CE)	4/4 (100.0)	7/8 (87.5)	12.5 (-41.70, 48.68)
cUTI RECAPTURE 1&2	Per-patient microbiological favourable response at TOC (mMITT)	31/38 (81.6)	24/33 (72.7)	8.9 (-10.9, 28.9)
cUTI REPRISE[c]	N/A	N/A	N/A	N/A
NP REPROVE	Clinical cure at TOC (cMITT)	13/19 (68.4)	9/15 (60.0)	8.4 (-23.35, 39.62)
	Clinical cure at TOC (CE)	12/17 (70.6)	7/10 (70.0)	0.6 (-32.38, 37.28)

[a] Plus metronidazole for cIAI studies.
[b] Meropenem for cIAI and HAP; doripenem for cUTI; best available therapy for resistant pathogen study (REPRISE).
c This study did not include a pre-specified sub-group analysis of patients with Bacteraemia.
Sources Table 11.2.3.2.1 RECLAIM CSR, Table 11.2.3.2.3 RECLAIM CSR, Table 11.2.3.2.3 RECLAIM3 CSR, Table 11.2.2.3.2 RECAPTURE CSR, and Table 11.2.3.2.1

Zavicefta was granted a marketing authorisation in adults for the treatment of complicated intra-abdominal and urinary tract infections, hospital-acquired pneumonia (including VAP) as well as infections due to aerobic Gram-negative organisms where treatment options are limited, primarily based on the outcome of the main studies as show in Table 2 and Table 3 above.

The CHMP acknowledged that patients with bacteremia were included from five Phase 3 studies (RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE) and the MAH submitted a pooled analysis of results across studies.

Overall features of the studies are presented below in Table 2.

Table 2. Overview of studies included in the pooled analysis.

	RECLAIM (global) and RECLAIM3 (Asian)	**RECAPTURE**	**REPROVE**	**REPRISE**
Study design	Prospective, randomized, multi-centre, double-blind, double-dummy, comparative studies	Prospective, randomized, multi-centre, double-blind, double-dummy, comparative study	Prospective, randomized, multi-centre, double-blind, double-dummy, comparative study	Prospective, randomised, multi-centre, open-label, non-comparative study
Study drug	CAZ AVI plus MTZ	CAZ AVI	CAZ AVI	CAZ AVI
Comparator	Meropenem	Doripenem	Meropenem	BAT
Indication	The treatment of hospitalised adults with cIAI	The treatment of hospitalized patients with cUTIs	The treatment of NP (HAP) including VAP in hospitalized patients	The treatment of hospitalized adults with cIAIs and cUTIs caused by CAZ-resistant Gram-negative pathogens
Primary objective/ endpoints	To assess the non-inferiority of CAZ-AVI plus MTZ compared to meropenem with respect to clinical cure at the TOC visit for the MITT the CE analysis populations	To assess the non-inferiority of CAZ-AVI compared to doripenem with respect to the per-patient microbiological response at the TOC visit in the mMITT analysis population	To assess the non-inferiority of CAZ-AVI compared to meropenem with respect to clinical cure at the TOC visit for the clinically modified intent-to-treat (cMITT) and CE analysis populations	To estimate the per-patient overall clinical response to CAZ-AVI and BAT at TOC in the mMITT analysis population
Stratification	Patients were stratified by baseline severity of disease and	Patients were stratified by type of infection at baseline and	Patients were stratified by type of infection (VAP/non-VAP) and	Patients were stratified by entry diagnosis and region

	region	region	geographical region	
Analysis population	The MITT analysis population included all randomised patients who met the disease definition of cIAI and had at least 1 identified pathogen. The CE analysis population includes all patients who had an appropriate diagnosis of cIAI and excluded patients with a bacterial species typically not expected to respond to both study drugs.	The mMITT analysis population includes all randomised patients who received at least 1 dose of study drug and had a study qualifying pre-treatment urine culture containing ≥105 CFUs/mL of ≥1 uropathogen	The cMITT analysis population includes patients who had properly obtained baseline respiratory or blood cultures demonstrating Gram negative pathogens, with or without concomitant Gram positive pathogens, excluding patients with Gram negative pathogens not expected to respond to either study treatment (ie, patients with only the following monomicrobial Gram negative infections. The cMITT also includes patients in whom no etiologic pathogens were identified from respiratory or blood cultures at baseline. The CE analysis population is a subset of the cMITT analysis population in which patients were required to have either received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered, or for <48 hours before discontinuing treatment due to an AE.	The mMITT analysis population includes all patients who had a diagnosis of cIAI or cUTI with a ceftazidime-resistant Gram-negative pathogen on the study-qualifying culture and who received at least 1 dose of study therapy.
EOT	The period within 24 hours following the last IV infusion			
Time of TOC visit	28 to 35 calendar days from	21 to 25 calendar days	21 to 25 days from randomisation	7 to 10 days after the last infusion of therapy

	randomisation	from randomisation		
Number of patients included to the pooled analysis from each study (extended ME at TOC population)	Global CAZ-AVI 9 Comparator 4 Asian CAZ-AVI 2 Comparator 6	CAZ-AVI 25 Comparator 24	CAZ-AVI 15 Comparator 8	CAZ-AVI 3 Comparator 5
CAZ AVI – ceftazidime/avibactam; MTZ – metronidazole; BAT – best available therapy; cIAI – complicated intraabdominal infection; cUTI – complicated urinary tract infection; NP – nosocomial pneumonia; HAP – hospital-acquired pneumonia; VAP – ventilator-associated pneumonia; TOC – test of cure; MITT – modified intent to treat; CE – clinically evaluable; mMITT – microbilogically modified intent to treat; cMITT – dinically modified intent to treat; EOT – end of treatment				

Comparison and analyses of results across studies - pooled analysis of efficacy

Results for the subset of patients with bacteraemia at baseline who were enrolled in the 5 Phase 3 studies are summarised in the sections below. Patients with bacteraemia at baseline are referred to as the Bacteraemia subset(s) and all patients enrolled in any of the 5 Phase 3 studies are referred to as the "Overall set".

Summaries were presented according to the following indications:

- cIAI: includes patients enrolled from RECLAIM, RECLAIM3 and REPRISE/cIAI;
- cUTI: includes patients enrolled from RECAPTURE and REPRISE/cUTI;
- NP: includes patients enrolled from REPROVE. For this study, patients with moderate or severe renal impairment at baseline who enrolled prior to amendment 3 and who received the original dosing were excluded from the pooled efficacy analysis because they were not part of the primary efficacy analyses presented in the CSR for the REPROVE study in the initial MAA.
- All Indications (cIAI, cUTI and NP): includes patients enrolled from any of the above studies (RECLAIM, RECLAIM3, RECAPTURE, REPRISE and REPROVE).

Methods

Study participants – population included in the pooled analysis

A total of 101 patients in the Bacteremia subset (i.e., 54 patients in the CAZ-AVI ± MTZ treatment group and 47 patients in the pooled comparator treatment group) were included in the Gram-negative extended ME at TOC population. Within each indication in total 21 patients, 57 patients and 23 patients were included in the following diagnosis categories cIAI, cUTI and HAP/VAP, respectively.

Treatments

A brief description of the treatments in the different treatment groups in the main studies are presented in Table 1 and under section "Main studies" above.

The comparators used in the main studies (which also included patients with bacteraemia) were already considered appropriate by the CHMP in the context of the assessment of the initial MAA for use in the treatment of cIAI, cUTI and HAP (including VAP) as well as infections due to aerobic Gram-negative organisms where treatment options are limited (EMEA/H/C/004027/0000 and EMEA/H/C/004027II/0002). Furthermore, meropenem, the main comparator in the studies concerning cIAI and HAP/VAP, is approved in EU for treatment of bacteraemia in association with these indications. For doripenem, the main comparator in the cUTI studies, no restriction with respect to the use in patients with bacteraemia is included in its EU SmPC.

Outcomes/endpoints

Efficacy endpoints were assessed in relation to the primary diagnosis, according to the definitions of response utilised in each of the individual studies (see above under section "Main study", table 3). The efficacy results for each set (i.e. the Bacteraemia subset and the Overall set) were presented for CAZ-AVI ± MTZ and comparator for the following endpoints:

- Clinical response at TOC and at EOT (favourable clinical response at TOC was considered the efficacy endpoint of interest of this pooled analysis of efficacy)
- Per-pathogen microbiological response at TOC
- Per-patient microbiological response at TOC and at EOT
- Emergent infections

Statistical methods

No formal statistical hypotheses testing was performed. Efficacy data in the Bacteraemia Subset, and Overall Set, presented for CAZ-AVI±MTZ and comparator, were summarised descriptively for the three indications (cIAI, cUTI, NP) separately and combined.

Descriptive statistics for age, sex and race for the Bacteraemia subset and Overall set were presented.

Analysis population

The Gram-negative extended ME at TOC population (see definition of populations below) is considered the main analysis population, since, for the Bacteraemia subset, this population is limited to patients with the most relevant pathogens (i.e., aerobic Gram-negative bacteria - either *Enterobacteriaceae* or aerobic Gram-negative pathogens other than *Enterobacteriaceae*) isolated from the blood at baseline. For the purposes of this application, data presentations are focused on the Gram-negative extended ME at TOC population.

Definitions for each of the analysis populations used for the pooled efficacy analyses are as follows:

Extended ME at TOC population. The ME and extended ME at TOC analysis sets was not included as formal analysis sets in this submission, but are defined here to aid the definition of the Gram-negative extended ME population below.

- The ME analysis set across the pivotal Phase 3 studies included patients who were compliant with

the protocol (as defined in each of the individual studies), had an evaluable clinical response (i.e., not indeterminate), and had a study-qualifying Gram-negative pathogen at baseline. The REPRISE study did not have an ME analysis set defined.

- The definition of the extended ME analysis set was the same as the ME analysis set but without a requirement for susceptibility of the baseline pathogen to study treatment. For the REPRISE study, the extended ME analysis set was a subset of the mMITT analysis set and comprised patients who also received a minimum duration of study treatment and had no major protocol deviations that would affect the assessment of efficacy.

Gram-Negative Extended ME population at TOC. For the Overall set, the Gram-negative extended ME population was defined as a subset of the extended ME population as defined in each individual study, limited to patients with aerobic Gram-negative bacteria (either *Enterobacteriaceae* or aerobic Gram-negative pathogens other than *Enterobacteriaceae*) isolated from the primary site of infection and/or blood. For the Bacteraemia subset, this population was further limited to subjects with Gram-negative pathogens isolated from the blood at baseline.

mMITT population. The mMITT population across the Phase 3 studies was defined as patients who received 1 dose of study drug, met the protocol-specific disease definition, and who had at least 1 etiologic pathogen at baseline at the primary site of infection and/or in blood, excluding those that were not expected to respond to either study treatment (i.e., patients with only the monomicrobial Gram-negative infections against which CAZ-AVI has no activity, such as any of the *Acinetobacter* species, any of the *Legionella* species, *Stenotrophomonas maltophilia*, or *Elizabethkingia meningoseptica)*. **RECAPTURE** 1 & 2 also required the same pathogen to be identified in a urine sample at $>10^5$ CFUs/ml. For the **REPRISE** study, the mMITT analysis set included all patients who met the protocol-specific disease definition, had a ceftazidime-resistant Gram-negative pathogen on the study-qualifying culture, and received at least 1 dose of study therapy.

Results

Baseline data

The MAH stated that compared with the Overall set, patients in the Bacteraemia subset were slightly older, had a higher proportion of females and Asian patients and higher mean baseline APACHE II scores (Acute Physiology, Age, Chronic Health Evaluation). The mean creatinine clearance (CrCL) was lower in the Bacteraemia subset than the Overall set.

Demographic and disease characteristics for the Bacteremia subset are presented in the tables below.

Table 7. Demographic Characteristics (Age, Sex, and Race) for Patients with Bacteraemia: Gram-Negative Extended ME at TOC Population (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

		Number (%) of Patients with Bacteraemia							
		cIAI		cUTI		NP		All Indications	
		CAZ-AVI+MTZ (N=11)	Comparator (N=10)	CAZ-AVI (N=28)	Comparator (N=29)	CAZ-AVI (N=15)	Meropenem (N=8)	CAZ-AVI+/-MTZ (N=54)	Comparator (N=47)
Age (years)	n	11	10	28	29	15	8	54	47
	Mean	61.5	53.7	57.4	64.2	65.3	65.8	60.4	62.2
	SD	19.80	16.83	20.27	14.93	11.09	13.33	18.10	15.44
	Median	62.0	54.0	63.5	66.0	65.0	65.5	64.0	65.0
	Minimum	24	19	19	26	45	49	19	19
	Maximum	83	75	79	84	86	86	86	86
Age group (years) n(%)	>=18 - 45	2 (18.2)	3 (30.0)	7 (25.0)	3 (10.3)	1 (6.7)	0 (0.0)	10 (18.5)	6 (12.8)
	46 - 64	4 (36.4)	4 (40.0)	9 (32.1)	9 (31.0)	5 (33.3)	3 (37.5)	18 (33.3)	16 (34.0)
	65 - 74	1 (9.1)	2 (20.0)	5 (17.9)	10 (34.5)	6 (40.0)	3 (37.5)	12 (22.2)	15 (31.9)
	>=75 - <=90	4 (36.4)	1 (10.0)	7 (25.0)	7 (24.1)	3 (20.0)	2 (25.0)	14 (25.9)	10 (21.3)
	Total	11 (100)	10 (100)	28 (100)	29 (100)	15 (100)	8 (100)	54 (100)	47 (100)
Sex n(%)	Female	7 (63.6)	4 (40.0)	25 (89.3)	23 (79.3)	6 (40.0)	2 (25.0)	38 (70.4)	29 (61.7)
	Male	4 (36.4)	6 (60.0)	3 (10.7)	6 (20.7)	9 (60.0)	6 (75.0)	16 (29.6)	18 (38.3)
	Total	11 (100)	10 (100)	28 (100)	29 (100)	15 (100)	8 (100)	54 (100)	47 (100)
Race n(%)	White	7 (63.6)	3 (30.0)	15 (53.6)	18 (62.1)	10 (66.7)	5 (62.5)	32 (59.3)	26 (55.3)
	Black or African American	0 (0.0)	0 (0.0)	1 (3.6)	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.1)
	Asian	4 (36.4)	7 (70.0)	11 (39.3)	6 (20.7)	5 (33.3)	2 (25.0)	20 (37.0)	15 (31.9)
	Other	0 (0.0)	0 (0.0)	1 (3.6)	4 (13.8)	0 (0.0)	1 (12.5)	1 (1.9)	5 (10.6)
	Total	11 (100)	10 (100)	28 (100)	29 (100)	15 (100)	8 (100)	54 (100)	47 (100)

n Number of patients in category or analysis. SD Standard deviation. ME Microbiologically evaluable. TOC Test of cure. Percentages are based on the total number of patients in the treatment group (N).

Table 8. Disease Characteristics (APACHE II, Prior Treatment Failure, Estimated CrCl, Renal Status) at Baseline for Patients with Bacteremia: Gram-Negative Extended ME at TOC population (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

		Number (%) of Patients with Bacteraemia							
		cIAI		cUTI		NP		All Indications	
		CAZ-AVI+MTZ (N=11)	Comparator (N=10)	CAZ-AVI (N=28)	Comparator (N=29)	CAZ-AVI (N=15)	Meropenem (N=8)	CAZ-AVI+/-MTZ (N=54)	Comparator (N=47)
APACHE II score (from eCRF) [a]	n	11	10	0	0	15	8	26	18
	Mean	9.5	9.7	-	-	16.1	15.1	13.3	12.1
	SD	6.06	6.24	-	-	5.03	3.76	6.31	5.84
	Median	10.0	8.5	-	-	15.0	15.0	13.5	11.5
	Minimum	1	3	-	-	10	10	1	3
	Maximum	19	24	-	-	29	20	29	24
APACHE II (from eCRF) n (%)	<10	5 (45.5)	5 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (9.3)	5 (10.6)
	10 - 19	6 (54.5)	4 (40.0)	0 (0.0)	0 (0.0)	12 (80.0)	6 (75.0)	18 (33.3)	10 (21.3)
	20 - 30	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	3 (20.0)	2 (25.0)	3 (5.6)	3 (6.4)
	Missing/Not done	0 (0.0)	0 (0.0)	28 (100)	29 (100)	0 (0.0)	0 (0.0)	28 (51.9)	29 (61.7)
	Total	11 (100)	10 (100)	28 (100)	29 (100)	15 (100)	8 (100)	54 (100)	47 (100)
Prior treatment failure n (%)	Yes	1 (9.1)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.1)
	No	10 (90.9)	9 (90.0)	3 (10.7)	5 (17.2)	0 (0.0)	0 (0.0)	13 (24.1)	14 (29.8)
	Missing/Not done	0 (0.0)	0 (0.0)	25 (89.3)	24 (82.8)	15 (100)	8 (100)	40 (74.1)	32 (68.1)
	Total	11 (100)	10 (100)	28 (100)	29 (100)	15 (100)	8 (100)	54 (100)	47 (100)
Estimated CrCl (mL/min) [b]	n	11	10	28	29	15	8	54	47
	Mean	81.17	80.19	74.79	60.08	86.47	113.48	79.33	73.45
	SD	34.050	31.791	26.978	22.927	25.736	103.558	28.116	50.507
	Median	77.00	78.01	71.36	55.36	85.50	64.35	77.05	58.00
	Minimum	31.3	34.0	22.5	26.4	50.7	41.2	22.5	26.4
	Maximum	129.8	143.2	131.0	115.0	138.0	355.9	138.0	355.9
Renal status n (%)	<=30	0 (0.0)	0 (0.0)	1 (3.6)	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.1)
	31-50	2 (18.2)	3 (30.0)	3 (10.7)	7 (24.1)	0 (0.0)	1 (12.5)	5 (9.3)	11 (23.4)
	51-80	4 (36.4)	3 (30.0)	14 (50.0)	17 (58.6)	7 (46.7)	4 (50.0)	25 (46.3)	24 (51.1)
	>=81	5 (45.5)	4 (40.0)	10 (35.7)	4 (13.8)	8 (53.3)	3 (37.5)	23 (42.6)	11 (23.4)
	Total	11 (100)	10 (100)	28 (100)	29 (100)	15 (100)	8 (100)	54 (100)	47 (100)

[a] APACHE II score is calculated programmatically using data obtained at the site and reported in the eCRF. [b] As reported by the site using the Cockcroft Gault method (Cockcroft and Gault 1976) method based on local laboratory data n Number of patients in category or analysis. SD Standard deviation.

Percentages are based on the total number of patients in the treatment group (N). eCRF Electronic case report form. ME Microbiologically evaluable. TOC Test of cure.

Prior systemic antibiotic use

In the Bacteraemia subset, for all indications combined, almost half of the subjects had prior systemic antibiotic use (42.6% for the CAZ-AVI ± MTZ treatment group and 46.8% for the comparator treatment group). Most of the prior systemic antibiotic use was reported for patients in the cIAI studies (63.6% for the CAZ-AVI + MTZ treatment group and 80.0% for the comparator treatment group) and the NP study (66.7% for the CAZ-AVI treatment group and 75.0% for the meropenem treatment group).

In the Overall set 45.4% of the CAZ-AVI ± MTZ treatment group and 45.8% of the comparator treatment group had prior systemic antibiotic use with patients in the cIAI and NP studies reporting the most prior systemic antibiotic use.

The CHMP noted that a comparison of demographic and disease characteristics for the Bacteraemia and the Overall set had not been provided by the MAH. However, according to the MAH, compared with the Overall set, patients in the Bacteraemia subset were slightly older, had a higher proportion of females and

Asian patients and higher mean baseline APACHE II scores. The mean creatinine clearance (CrCL) was lower in the Bacteraemia subset than the Overall set. As illustrated in the tables above, although some differences within each indications were observed for the Bacteraemia subset, the distribution of patients according to baseline demographic and disease characteristics were largely similar between treatment groups for the Bacteraemia subset, by indication and across all indications. Considering the small numbers in the Bacteraemia subset for each diagnosis included in these post-hoc analyses, no meaningful conclusions based on these differences can be drawn. These considerations were acceptable to the CHMP.

Baseline microbiology

The most commonly isolated pathogens in CAZ-AVI treated patients with bacteremia (Bacteraemia subset), were *E. coli* (68.5%), followed by *P. aeruginosa* (20.4%), *K. pneumonia* (18.5%), and *E. cloacae* (7.4%) (Table 9).

Table 9. Pathogens Per Species at Baseline: Gram-Negative Extended ME at TOC Population in the Bacteraemia Subset and in the Overall Set – (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Baseline pathogen	Number (%) of Patients with Bacteraemia							
		cIAI		cUTI		NP		All Indications	
		CAZ-AVI + MTZ (N=11)	Comparator (N=10)	CAZ-AVI (N=28)	Comparator (N=29)	CAZ-AVI (N=15)	Meropenem (N=8)	CAZ-AVI ± MTZ (N=54)	Comparator (N=47)
Enterobacteriaceae		11 (100.0)	9 (90.0)	28 (100.0)	28 (96.6)	11 (73.3)	8 (100.0)	50 (92.6)	45 (95.7)
	Enterobacter Cloacae	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	4 (26.7)	0 (0.0)	4 (7.4)	1 (2.1)
	Escherichia coli	11 (100.0)	6 (60.0)	23 (82.1)	23 (79.3)	3 (20.0)	4 (50.0)	37 (68.5)	33 (70.2)
	Klebsiella Pneumoniae	0 (0.0)	4 (40.0)	5 (17.9)	4 (13.8)	5 (33.3)	3 (37.5)	10 (18.5)	11 (23.4)
Gram negative pathogens other than *Enterobacteriaceae*		4 (36.4)	2 (20.0)	0 (0.0)	1 (3.4)	9 (60.0)	3 (37.5)	13 (24.1)	6 (12.8)
	Pseudomonas aeruginosa	4 (36.4)	2 (20.0)	0 (0.0)	1 (3.4)	7 (46.7)	3 (37.5)	11 (20.4)	6 (12.8)
	Baseline pathogen	Number (%) of Patients Overall							
		cIAI		cUTI		NP		All Indications	
		CAZ-AVI + MTZ (N=378)	Comparator (N=418)	CAZ-AVI (N=423)	Comparator (N=435)	CAZ-AVI (N=125)	Meropenem (N=131)	CAZ-AVI ± MTZ (N=926)	Comparator (N=984)
Enterobacteriaceae		361 (95.5)	400 (95.7)	399 (94.3)	411 (94.5)	87 (69.6)	94 (71.8)	847 (91.5)	905 (92.0)
	Enterobacter Cloacae	15 (4.0)	18 (4.3)	14 (3.3)	17 (3.9)	21 (16.8)	11 (8.4)	50 (5.4)	46 (4.7)
	Escherichia coli	290 (76.7)	316 (75.6)	267 (63.1)	277 (63.7)	11 (8.8)	18 (13.7)	568 (61.3)	611 (62.1)
	Klebsiella Pneumoniae	62 (16.4)	67 (16.0)	85 (20.1)	102 (23.4)	37 (29.6)	49 (37.4)	184 (19.9)	218 (22.2)
Gram negative pathogens other than *Enterobacteriaceae*		57 (15.1)	64 (15.3)	27 (6.4)	24 (5.5)	57 (45.6)	54 (41.2)	141 (15.2)	142 (14.4)
	Pseudomonas aeruginosa	46 (12.2)	49 (11.7)	26 (6.1)	23 (5.3)	42 (33.6)	35 (26.7)	114 (12.3)	107 (10.9)

A patient can have more than 1 pathogen. Multiple isolates of the same species from the same patient are counted only once.
Percentages are based on the total number of patients in the treatment group (N).

For All Enterobacteriaceae isolated in the CAZ-AVI ± MTZ treatment group (n=38, the Bacteraemia subset), the CAZ-AVI MIC range was 0.015 to 2 µg/mL with an MIC_{90} of 0.25 µg/mL.

For *P. aeruginosa* isolated in the CAZ-AVI ± MTZ treatment group (n=10, the Bacteraemia subset), the CAZ-AVI MIC range was 1 to >256 µg/mL with an MIC_{90} of 8 µg/mL.

The MAH stated that CAZ-AVI MICs were generally low in the Bacteraemia subset, and in general, the distribution of baseline MICs of Gram-negative pathogens were balanced across treatment arms and across all indications.

For the Bacteraemia subset, CAZ-resistant Enterobacteriaceae pathogens were identified in 18.5% (n=10) of patients in the CAZ-AVI ± MTZ group and in 38.3% (n=18) of patients in the comparator group. The number of CAZ-resistant *P. aeruginosa* was very limited in both treatment arms. A summary of CAZ-resistant isolates by pathogen are presented for the Gram-negative extended ME at TOC population is presented in Table 10.

Table 10. Ceftazidime-Resistant Gram-Negative Pathogens per Species at Baseline for Patients with Bacteraemia – Gram-negative Extended ME at TOC Population (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Baseline pathogen	Number (%) of Patients with Bacteraemia							
	cIAI		cUTI		NP		All Indications	
	CAZ-AVI + MTZ (N=11)	Comparator (N=10)	CAZ-AVI (N=28)	Comparator (N=29)	CAZ-AVI (N=15)	Meropenem (N=8)	CAZ-AVI ± MTZ (N=54)	Comparator (N=47)
All *Enterobacteriaceae*	**2 (18.2)**	**3 (30.0)**	**4 (14.3)**	**11 (37.9)**	**4 (26.7)**	**4 (50.0)**	**10 (18.5)**	**18 (38.3)**
Enterobacter cloacae	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.9)	1 (2.1)
Escherichia coli	2 (18.2)	2 (20.0)	1 (3.6)	8 (27.6)	1 (6.7)	2 (25.0)	4 (7.4)	12 (25.5)
Klebsiella pneumoniae	0 (0.0)	0 (0.0)	3 (10.7)	2 (6.9)	2 (13.3)	3 (37.5)	5 (9.3)	5 (10.6)
Morganella morganii	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Providencia rettgeri	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Gram negative pathogens other than *Enterobacteriaceae*	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (6.7)**	**1 (12.5)**	**1 (1.9)**	**1 (2.1)**
Pseudomonas aeruginosa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (12.5)	1 (1.9)	1 (2.1)

A patient can have more than 1 pathogen. Multiple isolates of the same species from the same patient are counted only once.
Percentages are based on the total number of patients in the treatment group (N).

Comparison of efficacy results of all studies

For this submission, clinical cure (as related to the primary diagnosis) at the TOC visit was presented for each indication and for all indications combined as the main efficacy analysis. Clinical cure at TOC corresponds to the primary efficacy parameter, which was assessed in the primary analysis populations for the majority of the Phase 3 studies. For the RECAPTURE study, the primary efficacy endpoint was per-patient microbiological response at TOC in the Gram-negative extended ME at TOC population. Therefore, this endpoint is additionally presented below for the cUTI indication in the Bacteraemia subset.

Efficacy outcomes

Clinical response at TOC

Table 11. Clinical Cure Rates at TOC in the Gram-Negative Extended ME at TOC Population at each Indication, for the Bacteremia Subset and the Overall Set (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Indication	Bacteraemia Subset			Overall Set		
	CAZ-AVI ± MTZ n/N (%)	Comparator n/N (%)	Difference (%)[a] (95% CI)	CAZ-AVI ± MTZ n/N (%)	Comparator n/N (%)	Difference (%) (95% CI)
cIAI	9/11 (81.8)	9/10 (90.0)	-8.2 (-41.16, 27.12)	349/378 (92.3)	396/418 (94.7)	- 2.4 (-6.03, 1.02)
cUTI	28/28 (100.0)	25/29 (86.2)	13.8 (0.71, 30.74)	409/423 (96.7)	418/435 (96.1)	0.6 (-2.01, 3.24)
HAP	10/15 (66.7)	5/8 (62.5)	4.2 (-33.32, 43.99)	96/125 (76.8)	103/131 (78.6)	-1.8 (-12.13, 8.41)
All indications	47/54 (87.0)	39/47 (83.0)	4.1 (-10.21, 19.09)	854/926 (92.2)	917/984 (93.2)	-1.0 (-3.34, 1.37)

Source: Table 3.16b and Table 3.16d
CI: confidence interval
a: difference in clinical cure rates of CAZ-AVI ± MTZ treatment group minus comparator treatment group, along with 95% CI for the difference.

Clinical response at EOT

Table 12. Clinical Cure Rates at EOT in the Gram-negative Extended ME at TOC Population at each Indication, for the Bacteremia Subset and the Overall Set (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Bacteraemia Subset			Overall Set		
Indication	CAZ-AVI ± MTZ n/N (%)	Comparator n/N (%)	Difference (%)[a] (95% CI)	CAZ-AVI ± MTZ n/N (%)	Comparator n/N (%)	Difference (%) (95% CI)
cIAI	9/11 (81.8)	9/10 (90.0)	-8.2 (-41.16, 27.12)	356/378 (94.2)	404/418 (96.7)	-2.5 (-5.64, 0.43)
cUTI	28/28 (100.0)	29/29 (100.0)	0.0 (-12.25, 11.88)	421/423 (99.5)	434/435 (99.8)	-0.2 (-1.50, 0.86)
HAP	13/15 (86.7)	6/8 (75.0)	11.7 (-20.64, 49.42)	107/125 (85.6)	115/131 (87.8)	-2.2 (-10.82, 6.28)
All indications	50/54 (92.6)	44/47 (93.6)	-1.0 (-12.26, 10.82)	884/926 (95.5)	953/984 (96.8)	-1.4 (-3.19, 0.34)

Source: Table 3.21b and Table 3.21d
CI: confidence interval
a: difference in clinical cure rates of CAZ-AVI ± MTZ treatment group minus comparator treatment group, along with 95% CI for the difference.

The CHMP considered that, for all indications combined, the clinical cure rate at TOC was 87.0% (47/54) for patients in the CAZ-AVI ± MTZ treatment group vs. 83.0% (39/47) in the comparator treatment group. The difference in clinical cure rates at TOC of CAZ-AVI ± MTZ treatment group minus comparator treatment group was 4.1% (95% CI: -10.21, +19.09).

Despite the limited number of patients in each specific diagnosis category (cIAI, cUTI, HAP/VAP) included in the post-hoc analyses; generally, the presented results indicate a favourable clinical response at TOC for CAZ-AVI patients with bacteraemia at baseline. Overall, these results were comparable to those seen in the comparator group as well as in the overall population for each of the 3 indications

In total, there were no substantial differences in the mMITT analysis set (not shown) compared to the Gram-negative extended ME at TOC analysis set.

Per-pathogen clinical response at TOC

Table 13. Clinical Response at TOC by Baseline Pathogen for the 4 most Commonly Isolated Pathogens for All Indications – Gram-negative Extended ME at TOC Population for the Bacteraemia Subset and Overall Set (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Baseline pathogen	CAZ-AVI ± MTZ			Comparator			Comparison between groups	
	Cure Rate (%)	n	N1	Cure Rate (%)	n	N1	Difference[a] (%)	95% CI[b] for % difference
Bacteraemia Subset All Indications		**N=54**			**N=47**			
All	**79.4**	**27**	**34**	**82.4**	**28**	**34**	**-2.9**	**(-22.29, 16.45)**
Enterobacteriaceae	81.3	26	32	81.3	26	32	0.0	(-19.91, 19.91)
Enterobacter cloacae	100.0	4	4	100.0	1	1	0.0	(-54.55, 82.76)
Escherichia coli	81.0	17	21	87.0	20	23	-6.0	(-29.72, 16.99)
Klebsiella pneumoniae	100.0	7	7	77.8	7	9	22.2	(-18.78, 55.74)
Gram-negative pathogens other than *Enterobacteriaceae*	72.7	8	11	83.3	5	6	-10.6	(-46.80, 36.35)
Pseudomonas aeruginosa	72.7	8	11	83.3	5	6	-10.6	(-46.80, 36.35)
Overall set All Indications		**N=926**			**N=984**			
All	**88.7**	**441**	**497**	**91.1**	**499**	**548**	**-2.3**	**(-6.08, 1.33)**
Enterobacteriaceae	90.0	412	458	91.9	468	509	-2.0	(-5.72, 1.63)
Enterobacter cloacae	97.2	35	36	82.8	24	29	14.5	(0.24, 32.38)
Escherichia coli	90.9	280	308	94.2	327	347	-3.3	(-7.60, 0.69)
Klebsiella pneumoniae	91.1	92	101	88.1	104	118	3.0	(-5.61, 11.30)
Gram negative pathogens other than *Enterobacteriaceae*	78.0	71	91	87.5	77	88	-9.5	(-20.69, 1.70)
Pseudomonas aeruginosa	77.3	68	88	87.1	74	85	-9.8	(-21.31, 1.74)

[a] Difference = Difference in clinical cure rates (For All Indications, CAZ-AVI+/-MTZ treatment group minus comparator treatment group).
[b] Confidence intervals (CIs) for group differences are calculated using the unstratified Miettinen & Nurminen method.
A patient can have more than 1 pathogen. Multiple isolates of the same species in the same patient are counted only once using the isolate with the highest MIC to study drug received.
ME Microbiologically evaluable. TOC Test of cure.
N: Number of patients in treatment group. N1: number of patients with each pathogen
n: number of patients with clinical cure
Clinical cure rates are based on the total number of patients with each pathogen (i.e n/N1).

The CHMP considered that, for the most commonly isolated pathogens in the Bacteraemia subsets for all indications combined, the clinical cure rates by baseline pathogen for CAZ-AVI ± MTZ were supportive of the overall clinical efficacy response. For the Bacteraemia subset, clinical cure rates by baseline pathogen in the CAZ-AVI ± MTZ treatment group were: 100% for E. cloacae (4/4); 81.0% for E. coli (17/21), 100% for K. pneumoniae (7/7); and 72.7% for P. aeruginosa (8/11). The corresponding results in the Overall set were generally comparable with the results seen in the Bacteraemia subset.

Per-patient microbiological response at TOC and at EOT

Table 14. Per-Patient Microbiological Response at EOT and TOC, All Indications: Gram-Negative Extended ME at TOC Population (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

		Number (%) of Patients with Bacteraemia		Comparison between groups	Number (%) of Patients Overall		Comparison between groups
Time point	Per-patient microbiological response	CAZ-AVI+/-MTZ (N=63)	Comparator (N=54)	Difference[a] (%) (95% CI[b])	CAZ-AVI+/-MTZ (N=926)	Comparator (N=984)	Difference[a] (%) (95% CI[b])
End of treatment	Favorable	53 (84.1)	48 (88.9)	-4.8 (-17.55, 8.46)	865 (93.4)	936 (95.1)	-1.7 (-3.86, 0.38)
	Unfavorable	7 (11.1)	5 (9.3)		48 (5.2)	40 (4.1)	
	Indeterminate	3 (4.8)	1 (1.9)		13 (1.4)	8 (0.8)	
Test of cure	Favorable	51 (81.0)	39 (72.2)	8.7 (-6.66, 24.39)	786 (84.9)	805 (81.8)	3.1 (-0.28, 6.41)
	Unfavorable	12 (19.0)	15 (27.8)		140 (15.1)	179 (18.2)	

[a] Difference = Difference in favourable response rates. (For All Indications, CAZ-AVI+/-MTZ treatment group minus comparator treatment group.)
[b] The confidence interval (CI) for the difference is calculated using the unstratified Miettinen & Nurminen method.
EOT End of treatment. TOC Test of cure.
Percentages are based on the total number of patients in the treatment group (N). ME Microbiologically evaluable.

Table 15. Per-Patient Microbiological Response at TOC for Patients in cUTI Studies: Gram-Negative Extended ME at TOC Population (RECAPTURE, REPRISE) - primary endpoint for the cUTI indication

		Number (%) of Patients with Bacteraemia		Comparison between groups	Number (%) of Patients Overall		Comparison between groups
Time point	Per-patient microbiological response	CAZ-AVI (N=28)	Comparator (N=29)	Difference[a] (%) (95% CI[b])	CAZ-AVI (N=423)	Comparator (N=435)	Difference[a] (%) (95% CI[b])
Test of cure	Favorable	26 (92.9)	20 (69.0)	23.9 (3.58, 43.73)	357 (84.4)	320 (73.6)	10.8 (5.41, 16.24)
	Unfavorable	2 (7.1)	9 (31.0)		66 (15.6)	115 (26.4)	

[a] Difference = Difference in favourable response rates. (For cUTI, CAZ-AVI treatment group minus comparator treatment group.)
[b] The confidence interval (CI) for the difference is calculated using the unstratified Miettinen & Nurminen method.
TOC Test of cure.
Percentages are based on the total number of patients in the treatment group (N). ME Microbiologically evaluable.

The CHMP considered that the observed rates of favourable per-patient microbiological response at EOT and TOC for the Bacteraemia subset were similar across treatment groups. For patients in the CAZ-AVI ± MTZ treatment group, the rates between the Bacteraemia subset and the Overall set were largely comparable.

Regarding per-patient microbiological response at TOC (primary endpoint for the cUTI Indication), favourable response rate in the Bacteraemia subset for the cUTI indication was much higher (92.9%, 26/28) in the CAZ-AVI treatment group compared to for the comparator treatment group (69.0%, 20/29). This trend was generally consistent with the results seen in the Overall set.

Per-pathogen microbiological response at TOC

Table 16. Favourable Per-Pathogen Microbiological Response at TOC by Baseline Pathogen for All Indications – Gram negative Extended ME at TOC Population (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Subset/Indication Baseline pathogen	CAZ-AVI ± MTZ			Comparator			Comparison between groups	
	Favorable response rate (%)	Number of favorable responses	n	Favorable response rate (%)	Number of favorable responses	n	Difference[a] (%)	95% CI[b] for % difference
Bacteraemia/ All Indications	**N=54**			**N=47**				
Enterobacteriaceae								
Enterobacter cloacae	100.0	4	4	100.0	1	1	0.0	(-54.55, 82.76)
Escherichia coli	85.7	18	21	100.0	23	23	-14.3	(-34.91, 1.41)
Klebsiella pneumoniae	85.7	6	7	77.8	7	9	7.9	(-35.96, 46.13)
Gram negative pathogens other than *Enterobacteriaceae*								
Pseudomonas aeruginosa	54.5	6	11	50.0	3	6	4.5	(-40.93, 48.75)
Overall/ All Indications	**N=926**			**N=984**				
Enterobacteriaceae								
Enterobacter cloacae	91.7	33	36	82.8	24	29	8.9	(-7.82, 27.70)
Escherichia coli	91.6	282	308	95.7	332	347	-4.1	(-8.18, -0.41)
Klebsiella pneumoniae	89.1	90	101	88.1	104	118	1.0	(-7.98, 9.58)
Gram negative pathogens other than *Enterobacteriaceae*								
Pseudomonas aeruginosa	67.0	59	88	71.8	61	85	-4.7	(-18.32, 9.08)

[a] Difference = Difference in favorable response rates (For All Indications, CAZ-AVI+/-MTZ treatment group minus comparator treatment group).
[b] The confidence interval (CI) for the difference is calculated using the unstratified Miettinen & Nurminen method.
A patient can have more than 1 pathogen. Multiple isolates of the same species from the same patient are counted only once using the isolate with the highest minimum inhibitory concentration (MIC) to study drug received.
N Number of patients in treatment group. ME microbiologically evaluable. TOC test of cure.
Percentages are based on the total number of patients with the pathogen (n).
mMITT Microbiological modified intent-to-treat. TOC Test of cure.
Source: Table 3.18b and Table 3.18d.

The CHMP considered that comparisons of the per-pathogen microbiological favourable response rates in the Bacteraemia subset are limited by small numbers for any given pathogen (apart from E.coli). Notwithstanding this, overall, the results indicated similar favourable response rates across treatment groups, and the response trends for any given pathogen between treatment groups in the Bacteraemia set were largely comparable to the results in the Overall set. The favourable per-pathogen microbiological results were consistent with the corresponding clinical responses by baseline pathogen.

Persistence / presumed persistence / persistence with increasing MICs

The majority of cases with persistence, presumed persistence or persistence with increasing MIC in the Bacteraemia subset were reported from the HAP study. Persistence or presumed persistence at the site of infection and/or blood was observed in 22.2% (12/54) of patients in the CAZ-AVI ± MTZ treatment group and 29.8% (14/47) of patients in the comparator treatment group of the Bacteraemia subset, regardless of indication.

The proportions of patients with persistent bacteraemia were generally low in both treatment groups; all reported cases were presumed persistent based on the clinical response, as no follow-up culture results were available at TOC for any of these cases. A total of 4 (7.4%) patients treated with CAZ-AVI ± MTZ had bacteraemia that was presumed persistent at the TOC visit (3 *E. coli*, and 1 *Salmonella*). In the corresponding comparator groups, 2 patients (4.3%) had bacteraemia that was presumed persistent at the TOC visit (1 *K. pneumoniae* and 1 *P. mirabilis*).

There were no cases of persistent bacteraemia associated with increasing MIC in the CAZ-AVI group.

Per-pathogen microbiological response by MIC category

Per-pathogen microbiological response by MIC category for each indication and for the 3 indications combined, for the Bacteraemia subset were compared to the Overall set. Due to the small numbers of bacteraemia patients in each group, it was, according to the MAH, not possible to identify any trends with respect to response by MIC.

Microbiological response at the TOC visit for patients infected with CAZ-resistant pathogens

Favourable per-patient microbiological response rates for bacteraemic patients infected with CAZ-resistant pathogens were lower than those observed in the Overall set for both treatment groups at TOC. Similar trends were observed for the Bacteraemia subset versus the Overall subset for each indication (cIAI, cUTI, and HAP). However, the small patient numbers (<5 in each treatment group for almost all pathogens) limit interpretation.

Assessment of per-pathogen favourable microbiological response rates for bacteraemic patients infected with CAZ-resistant pathogens was similarly limited by small numbers for any given pathogen.

Emergent infections

Table 17. Emergent Infections for the Bacteraemia Subset – Gram-negative Extended ME at TOC Population (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Indication	Treatment	Patient ID	Infection Type	Pathogen	Date	Culture Source
cUTI	CAZ-AVI	D4280C00004/E7002006	New Infection	*Citrobacter freundii* complex	2013-06-06	Urine
NP	CAZ-AVI	D4281C00001/E1902007	New Infection	*Klebsiella pneumoniae*	2013-11-29	Site of infection
			New Infection	*Staphylococcus aureus*	2013-11-29	Site of infection
		D4281C00001/E1902034	New Infection	Providencia	2015-04-20	Site of infection
	Meropenem	D4281C00001/E1902011	New infection	*Klebsiella pneumoniae*	2014-01-22	Site of infection

2.4.3. Discussion on clinical efficacy

The fact that during the Article 30 procedure of ceftazidime in 2011 (EMEA/H/A-30/001006), treatment of patients with bacteraemia in association with, or suspected to be associated with, the approved adult indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP) was added to the EU SmPC of ceftazidime (brand leader Fortum) is of critical importance for the evaluation of this Type II Variation, is. The additional data submitted for the Fixed Dose Combination Zavicefta, discussed below, are merely supplementary.

Design and conduct of clinical studies

The proposed indication extension for the addition of bacteraemia associated with the currently approved adult indications of cIAI, cUTI and HAP/VAP is mainly based on post-hoc analysis of efficacy and safety data from the sub-group of patients who had bacteraemia at baseline across the previously assessed 5 Phase 3 studies (**RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE**). These studies were conducted to support the currently approved indications of cIAI, cUTI and HAP/VAP. No new documentation to support this indication extension has been submitted.

Main studies: The 5 adult Phase 3 main studies (**RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE**) have been presented, and assessed before, in connection with previous applications for Zavicefta (i.e., EMEA/H/C/004027/0000 – initial MAA and EMEA/H/C/004027II/0002 - Type II variation application to provide the results from the finalized REPROVE study). Therefore, the methods and results for these studies have only been briefly described in this assessment report. The focus has been on the post-hoc analysis of efficacy data from the sub-group of patients who had bacteraemia at baseline across these 5 studies. Of note, randomization was not stratified by bacteraemia status at baseline in any of these studies.

Zavicefta was granted marketing authorisation in adults for the treatment of complicated intra-abdominal and urinary tract infections, hospital-acquired pneumonia (including ventilator-associated pneumonia, VAP) as well as infections due to aerobic Gram-negative organisms where treatment options are limited, primarily based on the outcome of the above mentioned studies.

Study participants included in the pooled analysis, i.e. patients with bacteraemia at baseline: A total of 101 patients in the Bacteraemia subset (54 patients in the CAZ-AVI ± MTZ treatment group and 47 patients in the pooled comparator treatment group) were included in the *Gram-negative extended ME at TOC population*. Within each indication in total 21 patients, 57 patients and 23 patients were included in the following diagnoses categories cIAI, cUTI and HAP/VAP, respectively.

Comparators: The comparators used in the main studies (which also included patients with bacteraemia) have already been considered appropriate by the CHMP in connection with the assessment of the initial MAA for use in the treatment of cIAI, cUTI and HAP (including VAP) as well as infections due to aerobic Gram-negative organisms where treatment options are limited (EMEA/H/C/004027/0000 and EMEA/H/C/004027II/0002). Further, meropenem, the main comparator in the studies concerning cIAI and HAP/VAP, is approved in EU for treatment of bacteraemia in association with these indications. For doripenem, the main comparator in the cUTI studies, no restriction with respect to the use in patients with bacteraemia is included in its EU SmPC.

Demographic and disease characteristics for the Bacteraemia and Overall set: A comparison of demographic and disease characteristics for the Bacteraemia and the Overall set was not provided by the MAH. However, the MAH explained that patients in the Bacteraemia subset were slightly older, had a higher proportion of females and Asian patients and higher mean baseline APACHE II scores compared with the Overall set. The mean creatinine clearance (CrCL) was lower in the Bacteraemia subset than in the Overall set. Although some differences within each indications were observed for the Bacteraemia subset, the distribution of patients according to baseline demographic and disease characteristics were largely similar between treatment groups for the Bacteraemia subset, by indication and across all indications. Considering the small numbers in the Bacteraemia subset for each diagnosis included in these post-hoc analyses, no meaningful conclusions based on these differences can be drawn.

Efficacy data and additional analyses

Comparison and analyses of results across studies - pooled analysis of efficacy

Clinical response at TOC and EOT: For all indications combined, the clinical cure rate at TOC was 87.0% (47/54) for patients in the CAZ-AVI ± MTZ treatment group vs. 83.0% (39/47) in the comparator treatment group. Despite the limited number of patients in each specific diagnosis category (cIAI, cUTI, HAP/VAP), generally the presented results indicate a favourable clinical response at TOC for CAZ-AVI patients with bacteraemia at baseline. Overall, these results were comparable to those seen in the comparator group as well as in the overall population for each of the 3 indications. Although some differences between Clinical response at EOT and TOC were seen, the presented results were largely comparable. However, the small numbers included in these analyses limit the interpretation of the observed differences. In total, there were no substantial differences in the mMITT analysis set (not shown) compared to the Gram-negative extended ME at TOC analysis set.

Per-pathogen clinical response at TOC: For the most commonly isolated pathogens in the Bacteraemia subsets for all indications combined, the clinical cure rates by baseline pathogen for CAZ-AVI ± MTZ were supportive of the overall clinical efficacy response. For the Bacteraemia subset, clinical cure rates by baseline pathogen in the CAZ-AVI ± MTZ treatment group were: 100% for *E. cloacae* (4/4); 81.0% for *E.*

coli (17/21), 100% for *K. pneumoniae* (7/7); and 72.7% for *P. aeruginosa* (8/11). The corresponding results in the Overall set were generally comparable with the results seen in the Bacteraemia subset.

Per-patient microbiological response at TOC and at EOT: The observed rates of favourable per-patient microbiological response at EOT and TOC for the Bacteraemia subset were similar across treatment groups. For patients in the CAZ-AVI ± MTZ treatment group, the rates between the Bacteraemia subset and the Overall set were largely comparable. Regarding per-patient microbiological response at TOC (primary endpoint for the cUTI indication), favourable response rate in the Bacteraemia subset for the cUTI indication was much higher (92.9%, 26/28) in the CAZ-AVI treatment group compared to for the comparator treatment group (69.0%, 20/29). This trend was generally consistent with the results seen in the Overall set. The comparisons of the *per-pathogen* microbiological favourable response rates in the Bacteraemia subset are indeed limited by small numbers for any given pathogen (apart from *E.coli*). Notwithstanding this, overall the results indicated similar favourable response rates across treatment groups, and the response trends for any given pathogen between treatment groups in the Bacteraemia set were largely comparable to the results in the Overall set. The favorable *per-pathogen* microbiological results were consistent with the corresponding clinical responses by baseline pathogen. No trend for outcome by MIC could be discerned.

Discussion

Firstly, during the Article 30 procedure of ceftazidime in 2011 (EMEA/H/A-30/001006), treatment of patients with bacteraemia in association with, or suspected to be associated with, the approved adult indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP) was added to the EU SmPC of ceftazidime (brand leader Fortum).

Additionally, it has previously been demonstrated that ceftazidime and the beta-lactamase inhibitor avibactam penetrate into human epithelial lining fluid (ELF) to the same extent. Overall, it has been concluded that the tissue penetration of avibactam was satisfactory and not poorer compared to ceftazidime alone, thereby ensuring that ceftazidime would be protected from being hydrolyzed by beta-lactamases at various infection sites.

Furthermore, according to the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013) regarding non-pathogen-specific bacteraemia "it may be possible to accumulate sufficient clinical data to support an indication for use of an antibacterial agent in the treatment of bacteraemia that is associated with specific types of infection, with or without restriction to certain pathogens. For example, in the case of agents that have been in use for many years and are indicated for use in a broad range of infections the total evidence may be considered sufficient for an indication that reads *Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above* (i.e. referring to the list of indications approved). If the antibacterial agent has been evaluated in several indications and the total number of bacteraemic patients treated across these indications is deemed sufficient (e.g. ~50 or more) to support a conclusion that efficacy is comparable to that in other patients or, at least, comparable to that of other treatments, then the addition of the sentence could be considered appropriate." The submitted data have shown that the efficacy of Zavicefta in the Bacteraemia subset, comprising 54 patients in the CAS-AVI treatment group, was comparable to the Overall set, and overall the terms as described in the Addendum are fulfilled by Zavicefta.

The additional data provided by the MAH justifies the efficacy of the standard dosing and the adequacy of the treatment duration for the HAP/VAP indication.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

A type II c.I.6a variation application, procedure number EMEA/H/C/004027/II/0015, aiming include a new indication for the use of ceftazidime/avibactam in the treatment of cIAI and cUTI in paediatric patients aged ≥3 months to <18 years, is ongoing at the time of adoption of this assessment report.

2.4.4. Conclusions on the clinical efficacy

Ceftazidime, the antibacterial component of this Fixed Dose Combination is already approved for bacteraemia in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP through an Article 30 procedure in 2011 (EMEA/H/A-30/001006). This was of critical importance to conclude positively on this Type II Variation concerning the applied extension of the indication to include bacteremia for Zavicefta. The data based on the Fixed Dose Combination are considered to be supplementary and most importantly, in that respect, are the similar PK and tissue distribution of ceftazidime and avibactam.

2.5. Clinical safety

Introduction

In seven Phase 2 and Phase 3 clinical trials, 2024 adult patients were treated with Zavicefta. The most common adverse reactions occurring in ≥5% of patients treated with Zavicefta were Coombs direct test positive, nausea, and diarrhoea. Nausea and diarrhoea were usually mild or moderate in intensity.

In the currently approved Summary of Product Characteristics (SmPC) for Zavicefta, there are warnings and precautions regarding hypersensitivity reactions, *Clostridium difficile*-associated diarrhoea, renal impairment, concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products, and direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia.

An overview is given on the important identified and potential risks in adults in the initial RMP submission, which were approved as part of the initial MAA for Zavicefta in 2016, see Table 18.

Table 18 Listing of Important Identified and Potential Risks in the Initial RMP Submission

Important identified risks	*Clostridium difficile*-associated diarrhoea (CDAD) 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

The current Zavicefta European (EU) SmPC is based upon the safety conclusions, submitted in January 2017 as part of variation EMEA/H/C/004027/II/0002, which is referred to as the 2016 Summary of Clinical Safety (SCS) within this document. The 2016 SCS includes the analysis of the overall Phase 2/3 pooled safety analysis population in complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI) and Hospital-acquired pneumonia (HAP) (5 Phase 3 studies listed above plus 2 Phase 2 studies: NXL104/2001 and NXL104/2002, 1 each in cUTI and cIAI respectively).

The MAH is now applying for an extension of the indication by a Type II variation for Zavicefta or ceftazidime-avibactam (CAZ-AVI) to add the indication for the treatment of patients with bacteraemia in association with, or suspected to be associated with, the currently approved adult indications for cIAI, cUTI and HAP, including ventilator-associated pneumonia (HAP/VAP).

A subset of data from patients with bacteraemia at baseline was created from the overall Phase 2/3 pooled safety analysis population in cIAI, cUTI and HAP. However, the patients from the Phase 2 studies were not included because it was not possible to programmatically confirm bacteraemia at baseline due to different methods of data collection. In addition, the dose of CAZ-AVI used in Study NXL104/2001 was lower than the dose used in the Phase 3 studies.

A subset of pooled safety data in patients with bacteraemia at baseline were therefore derived from the five previously performed and assessed Phase 3 adult studies:

- RECLAIM – global, cIAI
- RECLAIM3 – Asia, cIAI
- RECAPTURE – global, cUTI
- REPRISE – global, ceftazidime-resistant pathogens in cIAI & cUTI
- REPROVE – global, HAP/VAP

Bacteraemia was defined as having 1 or more bacteria identified from a blood culture at baseline for all studies, except for RECAPTURE 1 & 2, which also required the same pathogen to be identified in a urine sample. The bacteraemia subset was then assessed against the known safety profile of CAZ-AVI. There were no formal statistical hypotheses for these analyses; all data were summarised descriptively.

The CHMP noted that the clinical development program for ceftazidime/avibactam for this application included patients with bacteraemia in all 5 of the completed Phase 3 clinical trials that were conducted to support the approved indications of cIAI, cUTI and HAP/VAP, referred to as 'Bacteraemia subset'. A post-hoc analysis of efficacy and safety data from this sub-group of patients who had bacteraemia at baseline across these 5 studies was performed.

The Bacteraemia safety subset was assessed against the known safety profile of CAZ-AVI presented in the Summary of Clinical Safety (SCS), submitted in January 2017 as part of variation EMEA/H/C/004027/II/02), referred to as the 2016 SCS. The overall Phase 2/3 pooled safety analysis population, presented within 2016 SCS, is referred to as the 'Overall safety population'.

Patient exposure

- Exposure to Ceftazidime-Avibactam (CAZ-AVI)

The evaluation of safety includes 2 pooled safety datasets according to the International Council for Harmonisation (ICH) M4E guideline (ICH M4E Guideline 2002):

- Overall safety population: 4050 patients in 7 completed Phase 2 (N=338) and Phase 3 (N=3712) CAZ-AVI clinical studies (2016 SCS).
- Bacteraemia subset: 183 patients with bacteraemia at baseline in 5 completed Phase 3 CAZ-AVI clinical studies.

The rationale for selecting the Phase 2/3 pool as the primary dataset for the 2016 SCS was that the patient populations in the included studies were considered representative of the target patient populations (ie, patients with serious Gram-negative infections). The Phase 2/3 pool includes all patients who received at least part of 1 dose of CAZ-AVI and may include patients that have not been included in the safety analysis set for the individual studies.

Additionally, a different Medical Dictionary for Regulatory Activities (MedDRA) version was used for the AE analyses of the Phase 2/3 pool than was used in the analyses for the individual CSRs. Thus, it is not possible to compare individual numbers of AEs noted in CSRs with the numbers reported for the Phase 2/3 pool. For the pooled AE summaries, AEs were coded using MedDRA Version 19.0.

For details of the safety variables collected and methods of evaluation refer to 2016 SCS. Safety data were summarised to the end of treatment (EOT) visit and were also summarised to the end of the reporting period (up to and including the Final Follow-up visit) in each study (up to the "last visit"). Discussions will focus on the last visit (ie, 'any time up to the last visit') summaries.

The CHMP noted that the pooled analysis focused on the Bacteraemia safety subset, which comprised 183 patients, of whom 99 received CAZ-AVI ± MTZ and 84 received comparator treatment (carbapenems). The safety from these patients are compared to the known safety profile of CAZ-AVI based on over 4000 patients in 7 completed Phase 2 (N=338) and Phase 3 (N=3712) CAZ-AVI clinical studies (2016 SCS), of which half of them - 2024 patients - were treated with Zavicefta.

Overall extent of exposure

There was a similar duration of exposure to CAZ-AVI ± MTZ in the Bacteraemia subset, with a mean of 7.7 days of exposure (Table 19) compared to 8.2 days in the Overall safety population (not shown here).

Table 19. Duration of Exposure on Study Drug, for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

		Number (%) of patients							
		cIAI [a]		cUTI [a]		NP [a]		Total	
		CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/-MTZ (N=99)	Comparator (N=84)
Exposure (days) n (%) [b]	1	0 (0.0)	2 (8.3)	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (2.4)
	2 - 4	4 (14.8)	0 (0.0)	2 (4.2)	1 (2.4)	4 (16.7)	2 (11.1)	10 (10.1)	3 (3.6)
	5 - 10	18 (66.7)	15 (62.5)	37 (77.1)	28 (66.7)	11 (45.8)	7 (38.9)	66 (66.7)	50 (59.5)
	11 - 14	5 (18.5)	7 (29.2)	7 (14.6)	12 (28.6)	9 (37.5)	9 (50.0)	21 (21.2)	28 (33.3)
	15 - 21	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
	> 21	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Exposure (days) [b]	n	27	24	48	42	24	18	99	84
	Mean	7.6	8.8	7.0	9.1	9.3	10.2	7.7	9.3
	SD	3.1	4.0	3.0	3.9	4.2	3.8	3.5	3.9
	Median	7.0	9.0	6.0	8.0	8.5	11.0	7.0	8.5
	Minimum	3	1	1	3	2	2	1	1
	Maximum	14	14	14	21	14	14	14	21

[a] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
[b] Duration of exposure is calculated as the difference between the last study therapy date and the first study therapy date converted to days plus 1 day.
Actual calculated duration could be shorter or longer than a full day.
Percentages are based on the total number of patients in the treatment group (N).
n Number of patients included in analysis. SD Standard deviation.
Table created by: /Volumes/app/cdars/prod/prjC359/csr_figaro/Bacteremia_C359/saseng/cdisc3_0/macros/ex200_31_t.sas
PFIZER CONFIDENTIAL Date of SDTM Dataset Creation: Date of Table Generation: 24JUN2019 (14:27)
Table 4.3.2.3 is for Pfizer internal use.

The CHMP considered that the duration of exposure to CAZ-AVI ± MTZ in the Bacteraemia subset varied from mean of 7.0 days in the cUTI indication, 7.6 days in cIAI to 9.3 days in pneumonia (NP/HAP) indications, bearing in mind the limited number of patients with bacteraemia. There was, however, a similar duration of exposure to CAZ-AVI ± MTZ with a mean of 7.7 days in the Bacteraemia subset compared to 8.2 days in the Overall safety population.

Demographics of Study Population

The demographic and baseline characteristics, for the Bacteraemia subset in the safety analysis set are given. Numerical differences in the patient populations which may impact the safety analysis and conclusions are presented below. Demographic and baseline characteristics are further described in the Clinical Efficacy section.

In the Bacteraemia subset, 62% of the patients treated with CAZ-AVI ± MTZ were female, compared with 44% in the Overall safety population treated with CAZ-AVI ± MTZ.

A larger proportion of the Bacteraemia subset treated with CAZ-AVI ± MTZ were 65 years and older compared with the Overall safety population treated with CAZ-AVI ± MTZ:

- Bacteraemia subset: 21.2% were 65 - 74 years; 26.3% were ≥75 - ≤90 years.
- Overall safety population: 17.1% were 65 - 74 years; 15.5% were ≥75 - ≤90 years.
- Bacteraemia subset: mean age was 60.7 years; median 64.0 years.

- Overall safety population: mean age was 53.5 years; median 55.0 years.

Patients were categorised by level of renal function based on their baseline local laboratory CrCl result (calculated using Cockcroft-Gault formula) as follows: CrCl ≥81 mL/min = normal renal function, CrCl 51 to 80 mL/min = mild renal impairment, CrCl 31 to 50 mL/min = moderate renal impairment and CrCl ≤30 mL/min = severe renal impairment

There was a higher proportion of patients with moderate to severe renal insufficiency in the Bacteraemia subset treated with CAZ-AVI ± MTZ compared with the Overall safety population treated with CAZ-AVI ± MTZ:

- Bacteraemia subset: 14.1% moderate; 3.0% severe
- Overall safety population: 8.6% moderate; 1.1% severe
- Mean CrCl in the Bacteraemia subset: 78.2 ml/ min; median 77.0 ml/min
- Mean CrCl in the Overall safety population: 95 ml/min; median 87.5 ml/min

Disease Characteristics

The system "Acute Physiology, Age, Chronic Health Evaluation II" (APACHE II) is a severity-of-disease classification system. The APACHE II scores at baseline were only captured in the study database for patients in the cIAI and NP studies – the APACHE II scores for the Bacteraemia subset are presented in Table 20. The median APACHE II scores for the Bacteraemia subset (12 for both the CAZ-AVI ± MTZ treatment group and the comparator treatment group) were higher than for the Overall safety population (9 for both the CAZ-AVI ± MTZ treatment group and the comparator treatment group).

Table 20. Disease Characteristics (APACHE II score) at Baseline for Patients with Bacteraemia – (Safety Population) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

		Number (%) of Patients with Bacteraemia							
		cIAI		cUTI		NP		All Indications	
		CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/- MTZ (N=99)	Comparator (N=84)
APACHE II score (from eCRF) [a]	n	27	23	0	0	24	18	51	41
	Mean	8.9	10.2	-	-	15.8	16.1	12.1	12.8
	SD	5.69	6.86	-	-	4.39	4.20	6.14	6.49
	Median	9.0	8.0	-	-	15.0	15.5	12.0	12.0
	Minimum	0	3	-	-	10	10	0	3
	Maximum	21	27	-	-	29	24	29	27

In the CAZ-AVI-treatment group, 38 patients were from EU member states. The largest proportion of these patients (18) was recruited in the Czech Republic.

The CHMP considered that there was a higher proportion of patients with moderate to severe renal insufficiency in the Bacteraemia subset treated with CAZ-AVI ± MTZ compared with the Overall safety population (14.1% moderate; 3.0% severe the Bacteraemia subset compared to 8.6% moderate; 1.1% severe Overall). This means that 17 of the 99 patients with bacteraemia dosed with Zavicefta had a moderate/severe renal insufficiency, which then according to the posology recommendation in the SmPC should have received a reduced dose of Zavicefta. However, if the dose reductions are performed as recommended according to renal status, it is not expected that patients with bacteraemia are at greater risk for adverse events than for patients without bacteraemia.

The MAH suggested that the differences between patients included in Bacteremia subset and Overall safety population when evaluating demographic characteristics may be due to small number of patients included in CAZ-AVI ± MTZ group in Bacteremia subset (n=99).

The CHMP took into account that more patients in the CAZ-AVI group were female, older, with more severe renal impairment than in Overall patient pool. The median APACHE II scores for the Bacteraemia subset was also higher than for the Overall safety population, which is not unexpected due to the severity of bacteraemia. In conclusion, the differences observed are compatible with the clinical appearance of the patient with blood stream infection.

Adverse events

AEs with an onset date and time on or after the date and time of the first dose of study drug up to and including the last visit are summarised below.

Analysis of Adverse Events

The incidence of AEs up to last visit in the Bacteraemia subset and the incidence of AEs in the Overall safety population are presented below in Table 21.

A higher rate of AEs and serious adverse events (SAEs) was reported in both treatment arms in the total Bacteraemia subset compared with the Overall safety population and this was also true for the bacteraemic patients with cUTI taking CAZ-AVI compared with the overall cUTI safety population. This may be explained by the difference in the underlying medical condition of the patients in the Bacteraemia subset and may be magnified by the smaller denominators of the Bacteraemia subset as compared to the Overall safety population. This higher rate was not seen with regards to the AEs of severe intensity or AEs with the outcome of death in patients taking CAZ-AVI ± MTZ.

There was a similar rate of severe events in the Bacteraemia subset compared with the Overall safety population. With regards to cUTI, a higher rate of severe events was seen in the Bacteraemia subset compared to the Overall safety population which could reflect that patients with bacteraemia may be more unwell at baseline, however this must be interpreted with caution as the number of patients (2) is very small and it may be caused by the lower denominator.

In the Bacteraemia subset, as the denominators were small in the CAZ-AVI ± MTZ and the comparator arms, and the comparator arm comprises of several different drugs, direct comparison between the two is not appropriate. However, if a difference was seen in the CAZ-AVI ± MTZ arm, the comparator arm was also assessed as to whether the same trend was observed.

Table 21. Adverse Events up to Last Visit in the Bacteraemia Subset Compared to the Overall Safety Population

AE Category	Overall Safety Population n (%) [a]		Bacteraemia Subset n (%) [a]	
	cIAI [b]			
	CAZ-AVI + MTZ (N=857)	Comparator* (N=863)	CAZ-AVI + MTZ (N=27)	Comparator* (N=24)
Any AE	398 (46.4)	381 (44.1)	15 (55.6)	15 (62.5)
Any AE with an outcome of death [c]	11 (1.3)	9 (1.0)	0 (0.0)	0 (0.0)
Any SAE	62 (7.2)	67 (7.8)	2 (7.4)	6 (25.0)
Any AE leading to discontinuation of IP [d]	26 (3.0)	14 (1.6)	2 (7.4)	1 (4.2)
Any AE of severe intensity	41 (4.8)	54 (6.3)	1 (3.7)	4 (16.7)
	cUTI [b]			
	CAZ-AVI (N=731)	Comparator* (N=729)	CAZ-AVI (N=48)	Comparator* (N=42)
Any AE	275 (37.6)	263 (36.1)	35 (72.9)	22 (52.4)
Any AE with an outcome of death [c]	3 (0.4)	4 (0.5)	1 (2.1)	0 (0.0)
Any SAE	35 (4.8)	19 (2.6)	6 (12.5)	0 (0.0)
Any AE leading to discontinuation of IP [d]	10 (1.4)	7 (1.0)	3 (6.3)	0 (0.0)
Any AE of severe intensity	16 (2.2)	18 (2.5)	2 (4.2)	0 (0.0)
	NP# [b]			
	CAZ-AVI (N=436)	Meropenam (N=434)	CAZ-AVI (N=24)	Meropenam (N=18)
Any AE	323 (74.1)	321 (74.0)	19 (79.2)	14 (77.8)
Any AE with an outcome of death [c]	27 (6.2)	24 (5.5)	1 (4.2)	1 (5.6)
Any SAE	79 (18.1)	59 (13.6)	4 (16.7)	2 (11.1)
Any AE leading to discontinuation of IP [d]	16 (3.7)	13 (3.0)	1 (4.2)	2 (11.1)
Any AE of severe intensity	68 (15.6)	55 (12.7)	3 (12.5)	2 (11.1)
	Total#			
	CAZ-AVI ± MTZ (N=2024)	Comparator* (N=2026)	CAZ-AVI ± MTZ (N=99)	Comparator* (N=84)
Any AE	996 (49.2)	965 (47.6)	69 (69.7)	51 (60.7)
Any AE with an outcome of death [c]	41 (2.0)	37 (1.8)	2 (2.0)	1 (1.2)
Any SAE	176 (8.7)	145 (7.2)	12 (12.1)	8 (9.5)
Any AE leading to discontinuation of IP [d]	52 (2.6)	34 (1.7)	6 (6.1)	3 (3.6)
Any AE of severe intensity	125 (6.2)	127 (6.3)	6 (6.1)	6 (7.1)

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 last visit.
*comparator was meropenem in pivotal cIAI; doripenam in pivotal cUTI studies and best supportive care in supportive resistant pathogen study, primarily a carbopenam
#includes HAP MSRIB patients
[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] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers and comparator details.
[c] Deaths due to disease progression are not presented here.
[d] Action taken, investigational product (IP) permanently stopped.

As shown in the table above, the CHMP considered that a higher rate of AEs (69.7% vs. 49.2%) and serious adverse events (SAEs; 12.1% vs.8.7%) was reported in CAZ-AVI treatment arms in the total Bacteraemia subset compared with the Overall safety population. A similar difference was seen for the comparator arm. However, the number of AEs, any SAEs, AEs leading to discontinuation of IP were consistently higher in the CAZ-AVI ± MTZ group, only any AEs of severe intensity was higher (6 vs 7 (6.1% vs 7.1%)) in the comparator group. Thus overall, in the bacteremia subset, the safety was numerically less favourable compared with the comparator. Although this may, as claimed by the MAH, be explained by the difference in the underlying condition of the patients in the Bacteraemia subset and may also be magnified by the smaller denominators, for the CAZ-AVI arm, these differences seem to be driven by the bacteraemic patients with cUTI (both any AEs and SAEs) and NP. The higher rates of AEs in the bacteremia patients treated with CAZ-AVI may also partly be due to the fact that the patients in the Bacteremia subset were older and had more severe renal impairment, compared to the Overall safety population in patients taking CAZ-AVI ± MTZ.

The Committee also noted the very high frequency of SAEs (6 patients, 25%) and AEs with severe intensity (4 patients, 16.7%) in the comparator arm for the pooled cIAI studies, when the corresponding observed frequencies for CAZ-AVI were the same for the total Bacteraemia subset compared with the Overall safety population. However, due to the small number of patients and events, this result should be interpreted with caution. This observation is, however, of no importance for the Zavicefta risk assessment.

Common Adverse Events

The most common adverse events up to the last visit for the Bacteraemia subset are presented below in Table 22.

- The preferred terms (PTs) in the Bacteraemia subset were varied; most PTs only occurred in one patient in either the CAZ-AVI ± MTZ or the comparator group, and no patterns were identified.
- The most frequently occurring PTs in the Bacteraemia subset in the CAZ-AVI ± MTZ-treated group were Diarrhoea and Nausea; these were the same as the most frequently occurring PTs in the Overall safety population and are known common ADRs with CAZ AVI (Zavicefta EU SmPC 2019).

Table 22. Most Common (>=2%) Adverse Events up to Last Visit by Decreasing Order (of the Total) of Incidence for CAZ-AVI +/- MTZ and Preferred Term, for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Number (%) of patients [a]							
	cIAI [b]		cUTI [b]		NP [b]		Total	
Preferred term	CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/-MTZ (N=99)	Comparator (N=84)
Patients with any AE	15 (55.6)	15 (62.5)	35 (72.9)	22 (52.4)	19 (79.2)	14 (77.8)	69 (69.7)	51 (60.7)
Diarrhoea	0 (0.0)	2 (8.3)	3 (6.3)	1 (2.4)	9 (37.5)	1 (5.6)	12 (12.1)	4 (4.8)
Nausea	0 (0.0)	1 (4.2)	5 (10.4)	2 (4.8)	4 (16.7)	2 (11.1)	9 (9.1)	5 (6.0)
Constipation	1 (3.7)	1 (4.2)	5 (10.4)	3 (7.1)	1 (4.2)	1 (5.6)	7 (7.1)	5 (6.0)
Vomiting	2 (7.4)	1 (4.2)	3 (6.3)	0 (0.0)	2 (8.3)	1 (5.6)	7 (7.1)	2 (2.4)
Headache	0 (0.0)	1 (4.2)	4 (8.3)	4 (9.5)	1 (4.2)	2 (11.1)	5 (5.1)	7 (8.3)
Hypertension	2 (7.4)	0 (0.0)	3 (6.3)	2 (4.8)	0 (0.0)	0 (0.0)	5 (5.1)	2 (2.4)
Pyrexia	0 (0.0)	4 (16.7)	5 (10.4)	0 (0.0)	0 (0.0)	1 (5.6)	5 (5.1)	5 (6.0)
Urinary tract infection	1 (3.7)	2 (8.3)	2 (4.2)	0 (0.0)	2 (8.3)	2 (11.1)	5 (5.1)	4 (4.8)
Insomnia	1 (3.7)	0 (0.0)	3 (6.3)	1 (2.4)	0 (0.0)	1 (5.6)	4 (4.0)	2 (2.4)
Nephrolithiasis	0 (0.0)	0 (0.0)	4 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.0)	0 (0.0)
Atrial fibrillation	2 (7.4)	1 (4.2)	0 (0.0)	0 (0.0)	1 (4.2)	2 (11.1)	3 (3.0)	3 (3.6)
Cough	0 (0.0)	0 (0.0)	3 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.0)	0 (0.0)
Hypoalbuminaemia	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (8.3)	0 (0.0)	3 (3.0)	0 (0.0)
Acute kidney injury	1 (3.7)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Back pain	1 (3.7)	0 (0.0)	0 (0.0)	1 (2.4)	1 (4.2)	0 (0.0)	2 (2.0)	1 (1.2)

Preferred term	Number (%) of patients [a]							
	cIAI [b]		cUTI [b]		NP [b]		Total	
	CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/-MTZ (N=99)	Comparator (N=84)
Dizziness	1 (3.7)	0 (0.0)	1 (2.1)	1 (2.4)	0 (0.0)	0 (0.0)	2 (2.0)	1 (1.2)
Flank pain	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	2 (8.3)	0 (0.0)	2 (2.0)	1 (1.2)
Nasopharyngitis	0 (0.0)	0 (0.0)	2 (4.2)	2 (4.8)	0 (0.0)	0 (0.0)	2 (2.0)	2 (2.4)
Pain in extremity	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Pneumonia	2 (7.4)	1 (4.2)	0 (0.0)	1 (2.4)	0 (0.0)	3 (16.7)	2 (2.0)	5 (6.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	2 (8.3)	1 (5.6)	2 (2.0)	2 (2.4)
Wound infection	2 (7.4)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	1 (1.2)
Anaemia	0 (0.0)	2 (8.3)	0 (0.0)	2 (4.8)	1 (4.2)	1 (5.6)	1 (1.0)	5 (6.0)
Asthenia	0 (0.0)	1 (4.2)	1 (2.1)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.0)	2 (2.4)
Cystitis	0 (0.0)	0 (0.0)	1 (2.1)	2 (4.8)	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.4)
Oedema peripheral	1 (3.7)	1 (4.2)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.4)
Candiduria	0 (0.0)	1 (4.2)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (2.4)
Dyspnoea	0 (0.0)	2 (8.3)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.6)
Infusion site phlebitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Restlessness	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	2 (2.4)

[a] Number (%) of patients who reported at least 1 adverse event (AE) for a preferred term, sorted in decreasing order of
frequency in patients treated
with CAZ-AVI+/-MTZ. Includes AEs with an onset date and time on or after the date and time of first dose and up to and
including the last visit.
[b] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
Percentages are based on the total number of patients in the treatment group (N).
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

The CHMP considered that in total 69 of the 99 patients with bacteriaemia treated with CAZ-AVI experienced any AE. There are a number of observed AEs reported in the Bacteraemia subset which are not included in the approved Zavicefta SmPC: constipation (observed in 7 patients, 7.1%), hypertension, pyrexia and UTI (5 patients each, 5.1%), insomnia, nephrolithiasis (4 pts each, 4.0%), atrial fibrillation, cough, hypoalbuminaemia (3 pts each, 3.0%), back pain, flank pain, hypokalaemia, nasopharyngitis, pain in extremity, pneumonia and wound infection (2 pts each, 2.0%). In addition, anaemia, asthenia, and pheripheral oedema were reported in 1 CAZ-AVI treated patient each (1.0%). Most of these are common AEs/symptoms with a high background incidence and study drug relatedness can be difficult to assess (see below for assessment of relationship to study drug).

Incidence of Adverse Events – Maximum Reported Intensity

Up to last visit, in the Bacteraemia subset most patients who had an AE, reported it with a maximum intensity of mild (Table 23).

Table 23. Adverse Events up to Last Visit by Maximum Reported Intensity for Patients with Bacteraemia – (Safety Analysis Set) ((Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Number (%) of Patients [a]							
	cIAI		cUTI		NP		Total	
Maximum Reported Intensity	CAZ-AVI + MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenam (N=18)	CAZ-AVI ± MTZ (N=99)	Comparator (N=84)
Total	15 (55.6)	15 (62.5)	35 (72.9)	22 (52.4)	19 (79.2)	14 (77.8)	69 (69.7)	51 (60.7)
Mild	8 (29.6)	9 (37.5)	23 (47.9)	17 (40.5)	10 (41.7)	4 (22.2)	41 (41.4)	30 (35.7)
Moderate	6 (22.2)	2 (8.3)	10 (20.8)	5 (11.9)	6 (25.0)	8 (44.4)	22 (22.2)	15 (17.9)
Severe	1 (3.7)	4 (16.7)	2 (4.2)	0 (0.0)	3 (12.5)	2 (11.1)	6 (6.1)	6 (7.1)

[a] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
Only terms with at least one record with one intensity will be reported.
Includes AEs with an onset date and time on or after the date and time of first dose and up to and including the last visit.
Percentages are based on the total number of patients in the treatment group (N).
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

There was no individual severe PT reported by >1 patient in the Bacteraemia subset. Six (6) patients who received CAZ-AVI ± MTZ experienced at least 1 severe AE. These were Migraine, Cardiac Arrest, Cardio-respiratory arrest, Cardiac failure congestive, Left ventricular failure, Peripheral artery occlusion, Acute kidney injury and Procedural haemorrhage.

There were no patterns of severe AEs. The AEs with severe intensity tended to be those expected to occur in patients with severe infections and, therefore, reflect the underlying infection or associated surgery.

The CHMP noted that AEs with severe intensity were observed in 6 patients treated with CAZ-AVI in bacteraemia subset. No specific patterns of severe AEs could be seen. The Committee agreed that the observed AEs with severe intensity may reflect the underlying infection or associated surgery.

Incidence of Adverse Events – Relationship to Study Drug

The most common (reported by ≥2 patients in either of the treatment groups) treatment-related adverse events up to last visit for the Bacteraemia subset were Diarrhoea, Headache and Nausea (Table 24) which are known ADRs included in the Zavicefta Investigator's Brochure (IB) Table 7-3 and Zavicefta EU SmPC 2019 Section 4.8. Most AEs in the Bacteraemia subset were assessed as not related to the study drug.

Table 24. Most Common (Reported by ≥2 patients) Related Adverse Events up to Last Visit by Decreasing Order (of the Total) of Incidence for CAZ-AVI + /-MTZ and Preferred Team, for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Number (%) of patients							
	cIAI [a]		cUTI [a]		NP [a]		Total	
Preferred term	CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/-MTZ (N=99)	Comparator (N=84)
Patients with any AE	2 (7.4)	3 (12.5)	8 (16.7)	5 (11.9)	8 (33.3)	1 (5.6)	18 (18.2)	9 (10.7)
Diarrhoea	0 (0.0)	1 (4.2)	1 (2.1)	1 (2.4)	4 (16.7)	0 (0.0)	5 (5.1)	2 (2.4)
Headache	0 (0.0)	0 (0.0)	1 (2.1)	3 (7.1)	0 (0.0)	1 (5.6)	1 (1.0)	4 (4.8)
Nausea	0 (0.0)	0 (0.0)	1 (2.1)	1 (2.4)	0 (0.0)	1 (5.6)	1 (1.0)	2 (2.4)

[a] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
Number (%) of patients who reported at least 1 adverse event related to study drug, sorted in decreasing order of frequency in patients treated with
CAZ-AVI+/-MTZ.
Includes AEs with an onset date and time on or after the date and time of first dose and up to and including the last visit.
Percentages are based on the total number of patients in the treatment group (N).
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

The CHMP noted that most AEs in the Bacteraemia subset were assessed as not related to the study drug. Of the 69 patients with bacteriaemia treated with CAZ-AVI that experienced any AE, there were 18 patients who experienced treatment-related AEs; 2 in cIAI, 8 in cUTI and 8 in NP. No trends regarding AEs related to treatment is apparent and no specific trends are expected, having in mind the low number of patients in this subset; 99 CAZ-AVI treated patients with bacteraemia compared to a total of 2024 patients in the five studies.

The most common treatment-related adverse events up to last visit for the Bacteraemia subset were Diarrhoea (5 pts), Headache and Nausea (1 patient each).

Analysis of Adverse Events by Organ System or Syndrome

Safety topic of interest (STOI) for CAZ-AVI in the Bacteraemia subset is presented here and the corresponding summary of STOI for CAZ-AVI in the Overall safety population is presented in 2016 SCS. The AE PTs and potentially clinically significant (PCS) laboratory results up to the last visit that are relevant to each STOI were assessed for the Bacteraemia subset. The incidence of 5 STOI (liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders and renal disorders) were programmatically assessed based on pre-defined AE PTs (MedDRA Version 19).

Hepatotoxicity and risk of neurological sequelae when the dose is not appropriately reduced in patients with renal impairment are important potential risks in the currently approved Zavicefta EU Risk Management Plan v2.0.

According to the MAH, no new safety findings were identified on review of these events and the majority of the AEs in the STOI were known ADRs. See below for a discussion of the frequency of the AE of diarrhoea.

The CHMP considered that safety topic of interest (STOI) for CAZ-AVI in the Bacteraemia subset was presented in detail in the documentation submitted by the MAH (detailed presentation of the issues and with regard to separate indications and in total for the overall population, is given in 2016 SCS, as stated

above). However, there are few events in these areas: liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders.

Renal disorders were identified as an STOI based on the ceftazidime SmPC in which interstitial nephritis and acute renal failure are recognized ADRs (Fortum SmPC 2016). In the current SmPC for Renal and urinary disorders the following ADRs are listed (frequency uncommon): Blood creatinine increased, Blood urea increased and Acute kidney injury. In addition, Tubulointerstitial nephritis is reported as very rare. In the subset in question, relevant AEs Urinary tract infection is reported in 5 pts, nephrolithiasis in 4 pts, flank pain in 2 pts and acute kidney injury in 2 pts and cystitis in 1 patient treated with CAZ-AVI. As none of these AEs are deemed related to treatment (at least not for 2 or more patients, see comment under "Incidence of Adverse Events – Relationship to Study Drug"), this issue was not discussed any further by the MAH, which was acceptable to the CHMP. The issue of diarrhoea is discussed below.

Adverse Drug Reactions for the Bacteraemia Subset

The frequency of each ADR for the Bacteraemia subset was compared to the frequencies of ADRs for CAZ AVI in the Overall safety population. Important caveats with regard to this assessment are that the bacteraemia pooled data subset has a small denominator which is too small to accurately estimate the true frequency and so any ADR occurring in 1 patient has a frequency of 1/99 (>1.0% = common). The patients who comprise the Bacteraemia subset were included in the original frequency determination for Zavicefta EU SmPC Section 4.8.

ADR frequencies in the Bacteraemia subset were generally in line with the ADR frequencies reported in the Overall safety population and the known safety profile of ceftazidime and no change to the Zavicefta EU SmPC is required.

ADRs observed at a higher frequency in the Bacteraemia subset than in the Overall safety population are presented in Table 25 below.

Diarrhoea is common in the Zavicefta EU SmPC but was very common (12.12%) in the Bacteraemia subset (Table 25). A detailed safety analysis of each individual case was conducted. All the patients in the Bacteraemia subset had non-serious, mild or moderate events of Diarrhoea. Of the 12 patients in the Bacteraemia subset treated with CAZ-AVI ± MTZ who had diarrhoea, 9 were from the REPROVE study with an indication of NP. The frequency of this population was 15.4% in the Overall safety population. The patients with the remaining indications had a frequency of diarrhoea in line with the Overall safety population. There were 7 patients with diarrhoea considered to be unrelated to CAZ-AVI by the investigator and these cases did not have a clear temporal relationship to CAZ-AVI treatment, had prior laxative treatment or resolved even though CAZ-AVI was continued. A slight increase in frequency of diarrhoea (>10%) was seen in the Overall safety population in patients >75 years old, however it was assessed that this was not a significant difference and might have been due to the smaller denominator. As mentioned in section 4.6. Safety in special populations, Bacteraemia subset has a slightly higher age than the Overall safety population. For these reasons, no new safety finding was identified.

This difference in frequency of diarrhoea is not clinically significant and may have been related to the small denominator and the increased age of the patients in the Bacteraemia subset which made the frequency more aligned with that seen in the Overall safety population in patients >75 years old.

Neutropenia, Lymphocytosis, Blood creatinine increased, and Acute kidney injury were expected to be seen in less than 1 in 100 patients (frequency categories of uncommon, rare and frequency unknown as presented in the current Zavicefta EU SmPC), however the denominator of 99 in the Bacteraemia subset automatically makes any reported ADR >1% (i.e. common). There was no evidence of a difference in

safety profile (e.g. severity) on assessment of these ADRs. This difference in frequency is not clinically significant and is related to the small denominator.

Table 25. ADRs Occurring at a Higher Frequency in the Bacteraemia Subset than in the Overall Safety Population

ADR	Zavicefta EU SmPC	Frequency in the Overall Safety Population N=2024 (%)	Frequency in the Bacteraemia Subset N=99 (%)
Neutropenia	Uncommon	16/2024 (0.791)	1/99 (1.010)
Lymphocytosis	Uncommon	6/2024 (0.296)	1/99 (1.010)
Diarrhoea	Common	150/2024 (7.411)	12/99 (12.121)
Blood creatinine increased	Uncommon	16/2024 (0.791)	1/99 (1.010)
Acute kidney injury	Uncommon	12/2024 (0.593)	2/99 (2.020)

Source: Zavicefta EU SmPC.

As mentioned above, the Committee noted that the presentation of the STOI (elsewhere denoted Adverse Events of Special Interest, AEoSI) for CAZ-AVI was minimal. These STOI are, however, previously predefined to be liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders.

It is important to bear in mind that caveats with regard to this assessment are that the bacteraemia pooled data subset has a small denominator which is too small to accurately estimate the true frequency and so any ADR occurring in 1 patient has a frequency of 1/99 (>1.0% = common). It is therefore not expected to observe much differences or new safety issues in this application.

Some ADRs (Neutropenia, Lymphocytosis, Blood creatinine increased, and Acute kidney injury) were observed in higher frequencies than expected from previously reported uncommon frequency (less than 1 in 100 patients). However, in this bacteraemia pooled population these ADRs were observed in frequency common, all represented with only one patient (out of 99), except Acute kidney injury which were experienced by two patients. Diarrhoea was also reported with a higher frequency than previously reported, but within the same frequency category (common). The increase in the reported frequency is explainable by age, indication and small denominator, and is deemed not clinically significant, which is agreed by the Committee.

With regard to the RMP, at the time of adoption of this Assessment Report, a revision of the currently approved RMP v2.0 was under evaluation in the application for paediatric indications (cIAI and cUTI, procedure number EMEA/H/C/004027/II/0015) and hence, amendments are requested within that variation application. Additionally, the RMP was updated as approved in the procedure EMEA/H/C/004027/II/0008 (Opinion April 2018) to remove the important identified risks Anaphylaxis and other severe Hypersensitivity and Clostridium difficile associated diarrhoea (CDAD) from PART II. Module SVII.

Serious adverse event/deaths/other significant events

Deaths

All AEs with a fatal outcome in the Bacteraemia subset were considered unrelated by the Investigator and no new safety findings with regards to CAZ-AVI were observed with regard to the patients who died:

- Six (6) deaths (3 CAZ-AVI ± MTZ; 3 comparator) occurred up to the last visit in patients in the Bacteraemia subset.
- Three (3) patients had death due to disease progression which was not recorded as an AE as the individual studies contained a protocolled exemption of capturing these as AEs because they were part of the study objectives.

- Three (3) patients had an AE with a fatal outcome (Cardiac arrest and Cardio-respiratory arrest in the CAZ-AVI group and Septic shock in the comparator group) all of which were considered by the Investigator to be unrelated to study treatment.
- All patients who died, who had an available score at baseline, had an Acute Physiology and Chronic Health Evaluation (APACHE) II score >10. One (1) patient with cUTI, who did not have an APACHE II score recorded, was over 80 years old and had cardiomyopathy as a secondary cause of death.

The Committee noted that there were 3 deaths reported in patients treated with CAZ-AVI and 3 deaths reported in patients in the comparator treatment arm who were all received meropenem. In the CAZ-AVI group one of these were due to disease progression (PD), the other two cardiac arrest and cardio-respiratory. All AEs with a fatal outcome were considered unrelated to study treatment by the Investigator.

Serious adverse events

A higher rate of SAEs was reported for the Bacteraemia subset compared with the Overall safety population in both treatment groups (Table 21). This may be explained by the difference in the baseline condition of the patients in the Bacteraemia subset, who may be expected to have associated symptoms such as tachycardia, fever or sepsis and may be magnified by the smaller denominator. SAEs up to last visit by decreasing order (of the total) of incidence for CAZ-AVI ± MTZ and by PT, for patients with Bacteremia are presented in Table 27.

Table 26. Serious Adverse Events up to Last Visit by Decreasing Order (of the Total) of Incidence for CAZ-AVI +/- MTZ and by Preferred Term, for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

Preferred term	Number (%) of patients [a]							
	cIAI [b]		cUTI [b]		NP [b]		Total	
	CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/-MTZ (N=99)	Comparator (N=84)
Patients with any SAE	2 (7.4)	6 (25.0)	6 (12.5)	0 (0.0)	4 (16.7)	2 (11.1)	12 (12.1)	8 (9.5)
Nephrolithiasis	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Empyema	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	1 (5.6)	1 (1.0)	1 (1.2)
Chronic hepatitis C	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Hypoalbuminaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Cardiac failure congestive	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Left ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Peripheral artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Hyperventilation	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Localised intraabdominal fluid collection	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Spinal pain	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Acute kidney injury	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Procedural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Gastrointestinal stoma complication	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Systemic candida	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Pneumonia	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.2)
Atrial fibrillation	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Drug eruption	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Pyrexia	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Laceration	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Abdominal wound dehiscence	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Incision site complication	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

[a] Number (%) of patients who reported at least 1 Serious adverse event (AE), sorted in decreasing order of frequency in patients treated with CAZ-AVI+/-MTZ.
[b] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
Includes SAEs with an onset date and time on or after the date and time of first dose and up to and including the last visit.
Percentages are based on the total number of patients in the treatment group (N).
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

The Committee noted that there were 12 patients with bacteraemia treated with CAZ-AVI who experienced a serious adverse event (SAE), it was not stated how many were considered treatment-related.

A higher rate of SAEs was reported for the Bacteraemia subset compared with the Overall safety population in both treatment groups; CAZ-AVI vs. comparator: 12.1% vs. 9.5% compared to 8.7% vs. 7.2% in the Overall safety population. The MAH stated that this higher frequency can be explained by the underlying mores severe disease at baseline. This explanation is reasonable and was accepted by the Committee. There were no new safety findings on review of SAEs.

Laboratory findings

Clinical laboratory evaluations

No trends were identified on assessment of potentially clinically significant (PCS) laboratory evaluations as defined in the 2016 SCS. PCS post-baseline haematology and clinical chemistry values, anytime up to last visit, for the Bacteraemia subset are presented in tables (not shown here). Overall, the CAZ-AVI laboratory results for the Bacteraemia subset were in line with the results seen in the Overall safety population.

Vital signs, physical examination, electrocardiogram, and left ventricular ejection fraction

Electrocardiogram (ECG), vital sign or Physical Examination data were not pooled for the Phase 2 and Phase 3 studies.

Safety in special populations

The intrinsic and extrinsic factors for the Overall safety population are presented in the in the 2016 SCS, and assessed within that procedure.

Effect of Age

A larger proportion of the Bacteraemia subset treated with CAZ-AVI ± MTZ were over 65 years old compared with the Overall safety population treated with CAZ-AVI ± MTZ. The AEs up to last visit in any category by age group, for the Bacteraemia subset are presented below in Table 28.

In the Bacteraemia subset treated with CAZ-AVI ± MTZ, there was a higher incidence of AEs in each age cohort compared to the Overall safety population, in line with what was observed in total. The incidence of AEs also rose with age. In each age cohort, very few patients had AEs with a fatal outcome, SAEs and severe AEs however the incidence tended to rise with increasing age cohort. This was also observed for the comparator group and reflects what was seen in the Overall safety population where the older population has a higher rate of AEs compared with patients <65 years old.

With the caveat that the cohorts were very small to make any firm conclusions, no clinically relevant effect of age on the safety profile in the Bacteraemia subset was identified.

Table 27. Adverse Events up to Last Visit in any Category by Age (Years) Group, for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Total [a] Number (%) of patients [b]							
	CAZ-AVI+/-MTZ				Comparator			
AE category	>=18-45 (N=19)	46-64 (N=33)	65-74 (N=21)	75-90 (N=26)	>=18-45 (N=13)	46-64 (N=28)	65-74 (N=25)	75-90 (N=18)
Any AE	13 (68.4)	20 (60.6)	15 (71.4)	21 (80.8)	8 (61.5)	15 (53.6)	14 (56.0)	14 (77.8)
Any AE with outcome = death [c]	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE	1 (5.3)	3 (9.1)	2 (9.5)	6 (23.1)	4 (30.8)	0 (0.0)	4 (16.0)	0 (0.0)
Any AE leading to discontinuation of IP [d]	1 (5.3)	3 (9.1)	1 (4.8)	1 (3.8)	1 (7.7)	0 (0.0)	2 (8.0)	0 (0.0)
Any AE of severe intensity	1 (5.3)	1 (3.0)	1 (4.8)	3 (11.5)	2 (15.4)	0 (0.0)	4 (16.0)	0 (0.0)

[a] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
[b] Patients with multiple adverse events (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.

[c] Deaths due to disease progression are not presented here.
[d] Action taken, investigational product (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 last visit.
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

Effect of Gender

Most patients (62%) treated with CAZ-AVI ± MTZ were female in the Bacteremia subset, compared to the Overall safety population treated with CAZ-AVI ± MTZ. Nonetheless, there was no clinically meaningful difference in the incidence of AEs in the Bacteraemia subset between genders. Although there was a higher incidence of AEs overall in the Bacteraemia subset compared to the Overall safety population this was also observed for the comparator group and there was no clinically meaningful difference between the Bacteraemia subset and the Overall safety population based on gender.

Effect of Race

AEs were assessed by race and there were no new safety findings. Similar to the Overall safety population, most patients in the Bacteraemia subset were White or Asian. Numbers of patients in all other race categories were too small for meaningful comparisons (<10 patients per treatment group).

The incidence of AEs in the Bacteraemia subset up to the last visit was similar between White and Asian patients and treatment groups. Although there was a higher incidence of AEs overall in the Bacteraemia subset compared to the Overall safety population this was also observed for the comparator group and there was no clinically meaningful difference between the Bacteraemia subset and the Overall safety population based on race.

Effect of Body Mass Index

AEs were assessed by baseline BMI and there were no new safety findings. The incidence of AEs in the Bacteraemia subset up to the last visit was similar across BMI category and treatment groups. There was no clinically meaningful difference between the Bacteraemia subset and the Overall safety population based on baseline BMI.

Effect of Renal Function

As mentioned before, the patients treated with CAZ-AVI ± MTZ had worse renal function in the Bacteremia subset, compared to the Overall safety population treated with CAZ-AVI ± MTZ (mild renal impairment according to mean and median CrCl in the Bacteremia subset and normal renal function in Overall safety population). Most CAZ-AVI ± MTZ-treated and comparator patients in the Bacteraemia subset had normal renal function or mild renal impairment (CrCl ≥51 mL/min) (82.8% and 76.2%, respectively). Numbers of patients in the severe renal impairment subgroup were too small (<5 patients) for meaningful comparison. The number of patients within each CrCl stratum was balanced across treatment groups.

The AEs up to last visit in any category by baseline renal status for the Bacteraemia subset are presented below in Table 29. In the Bacteraemia subset of patients with moderate or severe renal impairment there were no new safety findings. The incidence of AEs in these patients was similar between treatment groups. Although there was a higher incidence of AEs overall in the Bacteraemia subset compared to the Overall safety population, this was also observed for the comparator group and there was no clinically meaningful difference between the Bacteraemia subset and the Overall safety population based on baseline renal status.

Table 28. Adverse Events up to Last Visit in any Category by Baseline Renal Status CrCl (mL/min), for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Total [a] Number (%) of patients [b]							
	CAZ-AVI+/-MTZ				Comparator			
AE category	<= 30 (N=3)	31 - 50 (N=14)	51 - 80 (N=42)	>= 81 (N=40)	<= 30 (N=2)	31 - 50 (N=18)	51 - 80 (N=41)	>= 81 (N=23)
Any AE	2 (66.7)	13 (92.9)	28 (66.7)	26 (65.0)	1 (50.0)	13 (72.2)	22 (53.7)	15 (65.2)
Any AE with outcome = death [c]	0 (0.0)	1 (7.1)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
Any SAE	0 (0.0)	3 (21.4)	6 (14.3)	3 (7.5)	0 (0.0)	2 (11.1)	2 (4.9)	4 (17.4)
Any AE leading to discontinuation of IP [d]	0 (0.0)	2 (14.3)	1 (2.4)	3 (7.5)	0 (0.0)	1 (5.6)	1 (2.4)	1 (4.3)
Any AE of severe intensity	0 (0.0)	2 (14.3)	2 (4.8)	2 (5.0)	0 (0.0)	2 (11.1)	1 (2.4)	3 (13.0)

[a] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
[b] Patients with multiple adverse events (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.
[c] Deaths due to disease progression are not presented here.
[d] Action taken, investigational product (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 last visit.
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.
Percentages are based on the total number of patients in the subgroup and treatment group (N).

Adverse Events by Geographic Region

The number of patients in the Bacteraemia subset that were enrolled by region across treatment groups were balanced and most of the patients in the CAZ-AVI ± MTZ and comparator groups were from Eastern Europe (36.4% and 36.9%, respectively) and Rest of World (44.4% and 42.9%, respectively).

The incidence of AEs in each AE category for CAZ-AVI ± MTZ patients was similar to comparator for each geographic region. There was no clinically meaningful difference between the Bacteraemia subset and the Overall safety population based on region.

The Committee noted that a larger proportion of the Bacteraemia subset treated with CAZ-AVI ± MTZ were over 65 years old compared with the Overall safety population treated with CAZ-AVI ± MTZ. In the Bacteraemia subset treated with CAZ-AVI ± MTZ, there was a higher incidence of AEs in each age cohort compared to the Overall safety population. The incidence of AEs also rose with age. In each age cohort, very few patients had AEs with a fatal outcome, SAEs and severe AEs, however, the incidence tended to rise with increasing age cohort. This was also observed for the comparator group and reflects what was seen in the Overall safety population where the older population has a higher rate of AEs compared with patients <65 years old.

With the caveat that the cohorts were very small to make any firm conclusions, no clinically relevant effect of age on the safety profile in the Bacteraemia subset was identified. In addition, there was apparently no clinically meaningful difference between the Bacteraemia subset and the Overall safety population based on gender, race, baseline BMI, baseline renal status or region which were the other special populations analysed.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

This section describes discontinuations due to AEs in the Bacteraemia subset. According to the MAH, CAZ-AVI was well tolerated in this subset of patients and most events leading to discontinuation were non-serious:

- Six (6) patients in the CAZ-AVI ± MTZ group of the Bacteraemia subset had at least 1 AE leading to discontinuation of study treatment.
- No individual PT was reported in more than 1 patient in the Bacteraemia subset. Two (2) patients in the CAZ-AVI ± MTZ group discontinued due to known ADRs (Vomiting, Drug eruption) (Zavicefta EU SmPC).
- Three (3) AEs in 3 patients that led to discontinuation were SAEs (1 patient in the CAZ-AVI group [Cardio-respiratory arrest] and 2 in the comparator group [Drug eruption, Septic shock])

Adverse events leading to discontinuation of Investigational Product (IP) up to EOT by system organ class (SOC) and PT, for the Bacteraemia subset are presented in Table 30 below.

Table 29. Adverse Events Leading to Discontinuation of IP up to EOT by System Organ Class and Preferred Term, for Patients with Bacteraemia - (Safety Analysis Set) (Studies RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE)

	Number (%) of patients [a]							
	cIAI [b]		cUTI [b]		NP [b]		Total	
System organ class/ Preferred term	CAZ-AVI+MTZ (N=27)	Comparator (N=24)	CAZ-AVI (N=48)	Comparator (N=42)	CAZ-AVI (N=24)	Meropenem (N=18)	CAZ-AVI+/- MTZ (N=99)	Comparator (N=84)
Patients with any AE leading to discontinuation of IP	2 (7.4)	1 (4.2)	3 (6.3)	0 (0.0)	1 (4.2)	2 (11.1)	6 (6.1)	3 (3.6)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.2)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.2)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Hypoproteinaemia	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (3.7)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.2)
Drug eruption	1 (3.7)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.2)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.2)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.2)
General disorders and administration site conditions	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Impaired healing	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

[a] Number (%) of patients who reported at least 1 adverse event leading to discontinuation of IP, sorted by system organ class in international order
and by preferred term in MedDRA hierarchy.
[b] Refer to listing 4.1.1 for indication specific information including abbreviations, study numbers, and comparator details.
Includes adverse events with an onset date on or after the date of first dose.
Percentages are based on the total number of patients in the treatment group (N).
Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.
IP Investigational product.

The Committee noted that, overall, 2.6% and 1.7% of patients in the CAZ-AVI +/− MTZ and comparator treatment groups, respectively, discontinued study drug due to AEs in the Overall safety population (2016 SCS). In the Bacteraemia subset these numbers were higher; 6.1% vs. 3.6%. The 6 patients with bacteraemia who discontinued CAZ-AVI due to AEs were all reported as different PTs. Hence, there were no clustering in events leading to discontinuation.

Post marketing experience

As of 26 April 2019, 46 events in 30 post marketing cases were identified that reported an indication which included at least one PT from the following MedDRA v21.1 Higher Level Terms (HLTs): HLT Sepsis, bacteraemia, viraemia and fungaemia NEC, HLT Endocarditis, HLT Vascular Infections. These were considered to reflect either bacteraemia, sepsis or an intravascular bacterial infection.

The 31 indications in 30 cases identified to be associated with bacteraemia were: Sepsis (12), Bacteraemia (11), Septic shock (3). Abdominal sepsis (2), Endocarditis, Escherichia bacteraemia and Neutropenic sepsis (1 each).

Most cases did not contain sufficient information to fully assess the underlying source of infection:

- Five (5) cases were assessed to be cIAI: Abdominal sepsis (2), Abdominal infection (2), Peritonitis bacterial (1).
- Five (5) cases were assessed to be infections in patients with Gram-negative infections with limited treatment options: Bacteraemia in a patient with refractory B-cell lymphoma, CNS ventriculitis, Endocarditis, Neutropenic sepsis, Osteomyelitis (1 each).
- Nineteen (19) cases did not provide a source or site of infection: Bacteraemia (8), Sepsis (8), Septic shock (3), Bacterial infection, *Enterobacter* infection, *Pseudomonas* infection (1 each).
- One case reported pneumonia but did not confirm if the patient had HAP. With regards to the events reported in the post-marketing cases:
- On assessment, 9 cases do not describe adverse events, but describe the following: Off label use in bacteraemia [PTs Off label use, Product use in unapproved indication], Off label use in Paediatrics [PTs Off label use, Product use issue (5 events)] and prolonged duration of therapy [PT Product use issue (2 events)].
- Seven (7) cases describe progression of the underlying disease or lack of efficacy: PTs Drug ineffective (3), Death (2), Infection and Condition aggravated (1 each).
- Six (6) cases only describe known ADRs without evidence of an increase in severity or frequency: PTs Acute kidney injury (3), Seizure, Toxic encephalopathy, Epilepsy, Encephalopathy, Hypersensitivity (1 each). One (1) of these 6 cases also reports an overdose in a patient with renal impairment (PT Product use issue).
- Three (3) cases did not contain sufficient information to perform a causal assessment: PTs Anaemia, Prothrombin time shortened, Anti factor V antibody positive, Drug interaction (1 each). One (1) of these three cases also reported off label use in paediatrics (Product use issue).
- The remaining 5 cases describe events which were assessed to be due to the patient's underlying medical condition or concomitant treatment: Shock haemorrhagic (2), Metabolic acidosis (2). B-cell lymphoma refractory, Hypernatraemia, Anuria, Jaundice, Hepatitis cholestatic, Renal injury, Thrombocytopenia, Bacterial disease carrier, Hypertension (1 each), Of these 5 cases, 3 also include known ADRs without evidence of an increase in severity or frequency (Platelet count

decreased, Acute kidney injury [2]) and 1 case describes off label use in paediatrics (Product use issue).

No new safety issues have been identified in the population of patients with bacteraemia at baseline or indications indicative of bloodstream infections from post marketing surveillance.

An RMP has not been provided within this application as with regards to this Type II variation there are no changes with respect to the list of safety concerns, no change to the current routine pharmacovigilance activities and routine risk minimisation activities, and no change to the risk-benefit balance of Zavicefta.

The CHMP noted that a search as of 26 April 2019 of AEs in post-marketing cases reporting an indication which was considered to reflect either bacteraemia, sepsis or an intravascular bacterial infection, identified 46 events in 30 post marketing cases. According to the MAH, no new safety issues with Zavicefta treatment were identified from post-marketing surveillance in the population of patients with bacteraemia / bloodstream infections at baseline.

The patients with bacteraemia from the clinical development programme are already included in the current EU-RMP in SIII Clinical trial exposure as this is a subset analysis of the overall safety data set. The MAH did not find any reason for updating the RMP for this Type II variation, which was considered acceptable by the CHMP.

The RMP will anyhow be updated as part of procedure EMEA/H/C/004027/II/0015 (application for extension of indication to include paediatric patients aged 3 months to less than 18 years for Zavicefta for the treatment of cIAI and cUTI), which was ongoing at the time of adoption of this assessment report.

2.5.1. Discussion on clinical safety

With this Type II variation procedure, the MAH is applying for an extension of the indication for ceftazidime-avibactam (CAZ-AVI), to add the treatment of patients with bacteraemia in association with, or suspected to be associated with the currently approved adult indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP).

The clinical development programme for ceftazidime/avibactam included patients with bacteraemia in all 5 of the completed Phase 3 clinical trials that were conducted to support the approved indications of cIAI, cUTI and HAP/VAP. Data was derived from the following clinical studies: RECLAIM (global, cIAI), RECLAIM3 (Asia, cIAI), RECAPTURE (global, cUTI), REPRISE (global, ceftazidime-resistant pathogens in cIAI & cUTI) and REPROVE (global, HAP/VAP). A post-hoc analysis of efficacy and safety data from the sub-group of patients who had bacteraemia at baseline across these 5 studies was performed. The Bacteraemia safety subset was then assessed against the known safety profile of CAZ-AVI presented and submitted in January 2017 as part of variation EMEA/H/C/004027/II/0002). The known safety profile is based on the overall Phase 2/3 pooled safety analysis population (comprising these five studies plus 2 phase 2 studies), and is referred to as the 'Overall safety population'. These comprise 4050 patients, of which 2024 treated with CAZ-AVI.

The Bacteraemia safety subset comprised 183 patients, of whom 99 received CAZ-AVI ± MTZ and 84 received comparator treatment. The differences between patients included in Bacteremia subset and Overall safety population when evaluating demographic characteristics may be due to small number of patients included in CAZ-AVI ± MTZ group in Bacteremia subset (n=99). The duration of exposure to CAZ-AVI ± MTZ in the Bacteraemia subset varied from mean of 7.0 days in the cUTI indication, 7.6 days in cIAI to 9.3 days in pneumonia (NP/HAP) indications. There was, however, a similar duration of exposure to CAZ-AVI ± MTZ with a mean of 7.7 days in the Bacteraemia subset compared to 8.2 days in the Overall safety population.

There was a higher proportion of patients with moderate to severe renal insufficiency in the Bacteraemia subset treated with CAZ-AVI ± MTZ compared with the Overall safety population.

Adverse events:

There were many AEs reported in the bacteraemia safety subset treated with CAZ AVI ± MTZ, both known from the safety profile of Zavicefta, and AEs not known with its use. Most AEs in the Bacteraemia subset were assessed as not related to the study drug. In total 69 of the 99 patients with bacteriaemia treated with CAZ-AVI experienced any AE, and of these 69, there were 18 patients (18%) who experienced treatment-related AEs. The most common AEs in this population were diarrhoea and nausea (12 and 9 patients, respectively), which are known ADRs of CAZ-AVI. The most common treatment-related adverse events up to last visit for the Bacteraemia subset were diarrhoea (5 pts), headache and nausea (1 patient each). There were 12 patients with bacteraemia treated with CAZ-AVI who experienced a serious adverse event (SAE), it is not stated how many were considered treatment-related. A higher rate of AEs (69.7% vs. 49.2%) and serious adverse events (SAEs; 12.1% vs.8.7%) was reported in the CAZ-AVI treatment arm in the total Bacteraemia subset compared with the Overall safety population. A similar difference was seen in the comparator arm. These higher frequencies seem in general to be driven by the cUTI and the NP population. The MAH claimed that these increases in frequencies can be explained by the difference in the underlying condition of the patients in the Bacteraemia subset, who were older and had a higher APACHE score at baseline, who may be expected to have symptoms associated with bacteraemia such as tachycardia, fever or sepsis and may also be magnified by the smaller denominators. This was considered reasonable and accepted by the Committee.

Deaths and serious adverse events:

Deaths:

Six (6) deaths (3 CAZ-AVI ± MTZ; 3 comparator) occurred up to the last visit in patients in the Bacteraemia subset. None of the AEs with a fatal outcome was considered related to study treatment by the Investigator.

Serious adverse events:

The SAEs reported in the Bacteraemia safety subset were in-line with what would be expected for the underlying indications and there were no new safety findings on review of SAEs.

Discontinuation due to AEs:

Overall, 6.1% (6 patients) and 3.6% (4 patients) of patients in the CAZ-AVI +/− MTZ and comparator treatment groups, respectively, discontinued study drug due to AEs in bacteraemia subset. No individual PT was reported in more than 1 patient in the Bacteraemia subset.

Considering all the above, the assessment of the safety from the subset of patients with bacteraemia in the pooled adult safety data did not identify new safety issues in patients with bacteraemia.

Additional expert consultations

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable. Review of a type II c.I.6a variation application (EMEA/H/C/004027/II/0015), aiming to include a new indication for the use of ceftazidime/avibactam in the treatment of cIAI and cUTI in

paediatric patients aged ≥3 months to <18 years, was ongoing at the time of adoption of this assessment report.

2.5.2. Conclusions on clinical safety

The safety of CAZ-AVI ± MTZ was evaluated in a subset of patients with bacteraemia at baseline from the Phase 3 pooled safety population from five Phase 3 adult studies in cIAI, cUTI and HAP: RECLAIM, RECLAIM 3, RECAPTURE, REPROVE and REPRISE. The Bacteraemia safety subset comprised 183 patients, of whom 99 received CAZ-AVI ± MTZ and 84 received comparator treatment, was assessed against the known safety profile of CAZ-AVI.

There were many AEs reported in the bacteraemia safety subset treated with CAZ AVI ± MTZ. The most common AEs in this population were diarrhoea and nausea. Most AEs in the Bacteraemia subset were assessed as not related to the study drug. Six patients of 99 patients with bacteraemia discontinued CAZ-AVI treatment due to AEs. None of the AEs with a fatal outcome were considered related to study treatment by the Investigator. The SAEs reported in the Bacteraemia safety subset were in line with what would be expected for the underlying indications and there were no new safety findings on review of SAEs.

The higher rates of AEs in the bacteremia patients treated with CAZ-AVI may be due to small number of patients included in the Bacteraemia subset compared to Overall safety population, and also due to underlying medical conditions, patients in the Bacteremia subset being older and had more severe renal impairment, compared to the Overall safety population in patients taking CAZ-AVI ± MTZ.

The safety profile of the Bacteraemia safety subset is in line with the expected safety profile for CAZ-AVI in adults and the established safety profile of ceftazidime alone, or the pattern of AEs expected for the patient population. No new safety issues were identified for CAZ AVI, however, acknowledging the limited database of patients with bacteraemia.

Approval to include treatment of patients with bacteraemia in association with the currently approved adult indications for cIAI, cUTI and HAP is recommended from a safety point of view.

2.5.3. PSUR cycle

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

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1 and 4.2 of the SmPC are being updated to reflect the recommendation of approval for including treatment of bacteraemia.

- Section 4.1 (Therapeutic indications):

Zavicefta is indicated for 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)*

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

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.

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1, which includes all agreed changes to the Product Information.

2.6.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed extension of indication for Zavicefta is to include treatment of bacteraemia (in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP in adults.

Bacteraemia due to Gram-negative pathogens is associated with significant morbidity and mortality. Nearly 2 million episodes of bloodstream infection in North America and Europe annually led to ~250,000 deaths and nearly half of community-acquired and one third of healthcare associated cases were caused by Gram-negative bacteria. The aim of the therapy is to cure the infection.

3.1.2. Available therapies and unmet medical need

Infections associated with bacteraemia may be severe, require hospitalisation and have the potential to be life-threatening. Bacteraemia due to resistant pathogens is increasing in frequency and associated with more adverse effects. Prompt administration of effective antibiotics is therefore critical for a favorable outcome. There are no specific treatment guidelines for treatment of bacteraemia as such. The choice of the treatment is dependent of the clinical condition (e.g. site of infection, resistance, pathogens etc.). Relevant treatment options for bacteraemia caused by multi-drug resistant Gram-negative pathogens (e.g. ESBL producing organisms) are carbapenems. Other options that still may be used in the setting of multi-drug resistant Gram-negative bacteraemia (including carbapenem-resistant pathogens), alone or in combination with other agents, include colistin, tigecycline and fosfomycin.

Infections due to multi-drug resistant Gram-negative bacteria are increasingly common. Few antibiotics with activity against ESBL and carbapenemase producing Gram-negative bacteria are currently available. However, alternative treatment options which are efficacious against multi-drug resistant Gram-negative bacteria would be useful.

3.1.3. Main clinical studies

The MAH did not conduct any specific studies to support the proposed indication extension. The main evidence of efficacy and safety is based on post-hoc analysis of efficacy and safety data from the sub-group of patients who had bacteraemia at baseline across the previously assessed 5 Phase 3 studies. These studies (**RECLAIM, RECLAIM3, RECAPTURE, REPRISE, REPROVE**) were conducted to support the currently approved indications of cIAI, cUTI and HAP/VAP in adults. Meropenem was the main comparator in the studies concerning cIAI and HAP/VAP, while doripenem was the main comparator in the cUTI studies.

3.2. Favourable effects

For all indications combined, the clinical cure rate at TOC in the Bacteraemia efficacy subset was 87% (47/54) for patients in the CAZ-AVI ± MTZ treatment group vs. 83% (39/47) in the comparator treatment group. Although some differences between Clinical response at EOT and TOC were seen, the presented results were largely comparable; the clinical cure at EOT in the Bacteraemia set was 92.6% in the CAZ-AVI ± MTZ treatment group compared to 93.6% in the comparator group. The corresponding results in the Overall set were generally comparable with the results seen in the Bacteraemia set.

3.3. Uncertainties and limitations about favourable effects

For all indications combined, the clinical cure rate at TOC in the Bacteraemia efficacy subset was 87% (47/54) for patients in the CAZ-AVI ± MTZ treatment group vs. 83% (39/47) in the comparator treatment group. Although some differences between Clinical response at EOT and TOC were seen, the presented results were largely comparable; the clinical cure at EOT in the Bacteraemia set was 92.6% in the CAZ-AVI ± MTZ treatment group compared to 93.6% in the comparator group. The corresponding results in the Overall set were generally comparable with the results seen in the Bacteraemia set.

3.4. Unfavourable effects

The bacteraemia safety subset comprised 183 patients, of whom 99 received CAZ-AVI ± MTZ and 84 received comparator treatment. In total, 99 CAZ-AVI treated patients with bacteraemia compared to a total of 2024 pts in total in the five studies. The Overall population receiving CAZ-AVI or comparator was 4050 patients.

In total 69 of the 99 patients with bacteriaemia treated with CAZ-AVI experienced any AE, and of these 69, there were 18 patients (18%) who experienced treatment-related AEs. The most common AEs in this population were diarrhoea and nausea (12 and 9 patients, respectively), which are known ADRs of CAZ-AVI. The most common *treatment-related* adverse events up to last visit for the bacteraemia subset were diarrhoea (5 pts), headache and nausea (1 patient each). There were 12 patients with bacteraemia treated with CAZ-AVI who experienced a serious adverse event (SAE), it is not stated how many were considered treatment-related.

A higher rate of AEs (69.7% vs. 49.2%) and serious adverse events (SAEs; 12.1% vs. 8.7%) was reported in the CAZ-AVI treatment arm in the total bacteraemia subset compared with the overall safety population.

Six (6) deaths (3 CAZ-AVI ± MTZ; 3 comparator) occurred up to the last visit in patients in the bacteraemia subset.

Six patients of 99 (6.1%) patients with bacteraemia discontinued CAZ-AVI treatment due to AEs, all different PTs.

3.5. Uncertainties and limitations about unfavourable effects

The bacteraemia safety subset comprised 183 patients, of whom 99 received CAZ-AVI ± MTZ, and hence, the population of patients with bacteriaemia was rather limited. Very few patients had cIAI and NP, the majority of the patients come from the cUTI studies.

There was a higher proportion of patients with moderate to severe renal insufficiency in the Bacteraemia subset treated with CAZ-AVI ± MTZ compared with the Overall safety population.

The observed increases in AEs and SAEs compared to the Overall population represent an uncertainty.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

For ceftazidime, the antibacterial component of this FDC, bacteraemia in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP is already approved through an Article 30 procedure in 2011 (EMEA/H/A-30/001006).

Despite the limitations of data due to the small numbers included in the Bacteraemia subsets, the fact that the randomisation was not stratified by bacteraemia status at baseline in any of the main studies, and that the efficacy analyses were only descriptive; for all indications combined, the clinical cure rate at TOC in the Bacteraemia set was broadly in line with the corresponding results in the Overall set, and the microbiological outcomes were generally in support of the main clinical responses.

Furthermore, the efficacy in the HAP/VAP CAZ-AVI bacteremia subset was comparable to the comparator (i.e., the cure rates at TOC were 66.7% vs. 62.5% in the CAZ-AVI and meropenem groups, respectively). However, the number of patients with bacteraemia included in these HAP/VAP subsets is very limited and hence cure rates should be interpreted with caution. Importantly, a similar shift in the cure rates in HAP/VAP patients from EOT to TOC visit was seen in both the test and comparator groups. Considering the high mortality and serious complications associated with HAP/VAP, this shift could be expected.

For ceftazidime, the antibacterial component of this FDC, bacteraemia in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP is already approved through an Article 30 procedure in 2011 (EMEA/H/A-30/001006). In addition, it has previously been demonstrated that there was no concerns about tissue penetration of the beta-lactamase inhibitor avibactam to the relevant infection sites such as ELF. The pharmacokinetics and the joint target attainment for ceftazidime and avibactam appear similar in patients with and without bacteraemia. This supports that the approved doses for certain site specific infections (including HAP/VAP) are also appropriate for patients with concurrent bacteraemia. Moreover, the formal grounds in terms of being an antibacterial agent used for many years and indicated for use in a broad range of infections as reflected in the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), are fulfilled.

The observed increases in AEs and SAEs can be explained by the difference in the underlying condition of the patients in the Bacteraemia subset, who were older and had a higher APACHE score at baseline. None of the AEs with a fatal outcome was considered related to study treatment by the Investigator.

The higher proportion of patients with moderate to severe renal insufficiency in the Bacteraemia subset treated with CAZ-AVI ± MTZ compared with the Overall safety population might have an impact on the safety profile. However, due to assumed dose reductions according to the recommendations in the SmPC, this unbalance is not considered to induce an additional risk.

The safety profile of the Bacteraemia safety subset is in line with the expected safety profile for CAZ-AVI in adults and the established safety profile of ceftazidime alone, or the pattern of AEs expected for the patient population. In total, acknowledging the limited database of patients with bacteraemia, the assessment of safety from the subset of patients with bacteraemia in the pooled adult safety population did not identify new safety issues in patients with bacteraemia.

3.6.2. Balance of benefits and risks

The overall B/R of Zavicefta for the treatment of patients with bacteraemia in association with the already approved adult indications for cIAI and cUTI is positive. Taking into account the additional data, provided by the MAH, the risk-benefit balance for the bacteraemia indication covering HAP/VAP is also positive. However, the data specific for the FDC Zavicefta are mainly considered to be supplementary. It has to be emphasised that the fact that for ceftazidime, the antibacterial component of this FDC, bacteraemia in association with, or suspected to be associated with, the currently approved indications for cIAI, cUTI and HAP/VAP is already approved through an Article 30 procedure in 2011 (EMEA/H/A-30/001006) was of critical importance for reaching a positive conclusion.

3.6.3. Additional considerations on the benefit-risk balance

None.

3.7. Conclusions

The overall B/R of Zavicefta on the extension of the indications to include bacteraemia in association with the already approved adult indications for cIAI, cUTI and HAP/VAP is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include bacteraemia (in association with, or suspected to be associated with, the currently approved indications for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP)) for Zavicefta; as a consequence, sections 4.1 and 4.2 of the SmPC are updated in order to add this indication and the posology. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The Package Leaflet is updated in accordance.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.