EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2024
EMA/463695/2024
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/0035

Marketing authorisation holder (MAH): Pfizer Ireland Pharmaceuticals

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List of abbreviations

%$fT > C_T$	percentage of time of free drug concentrations > threshold concentration over a dose interval
%$fT > MIC$	percentage of time of free drug concentrations > minimum inhibitory concentration over a dose interval
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AmpC	Ambler Class C
AUC	area under the concentration-time curve
AUC0-t	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC0-8	area under the concentration-time curve from time 0 to 8 hours
AUCinf	area under the concentration-time curve from zero extrapolated to infinity
AUCss,0-24	area under the concentration-time curve over 24 hours at steady state
BSI	Bloodstream infection
CAZ-AVI	ceftazidime-avibactam
CFR	Code of Federal Regulation
cIAI	complicated intra-abdominal infections
Cmax	maximum observed concentration
Cmax,ss	maximum drug concentration at steady state
Cmin,ss	minimum drug concentration at steady state
COVID-19	Corona virus disease - 19
CSR	clinical study report
cUTI	complicated urinary tract infections
DBP	diastolic blood pressure
DCO	data cut-off
DDI	drug-drug interaction
DILI	drug induced liver injury
EBE	empirical Bayes estimates
E-DMC	external data monitoring committee
EFPIA	European Federation of Pharmaceutical Industries and Associations
EOIV	end of intravenous
EOT	end of treatment
ESBL	extended-spectrum β-lactamase
GA	gestational age
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia
HAP	hospital-acquired pneumonia
HTA	Human tissue authority
IAI	Intra-abdominal infection
ICD	informed consent document
IDSA	Infectious disease society of America
ITT	intent-to-treat
IV	intravenous
KPC	Klebsiella pneumoniae carbapenemase
LFU	late follow-up
LTO	limited treatment options
MD	multiple-dose
MDR	multidrug resistant
MedDRA	Medical dictionary for regulatory activities
MIC	minimum inhibitory concentration
MIC50	minimum concentration to inhibit 50% of strains
MIC90	minimum concentration to inhibit 90% of strains
micro-ITT	microbiological intent-to-treat
MITT	modified intent-to-treat
MTZ	metronidazole
N or n	number
NI	non-inferiority
non-BL-BLI	non-β-lactam β-lactamase inhibitor
NONMEM	non-linear fixed effects modelling
NP	nosocomial pneumonia

OPAT	outpatient parenteral antimicrobial therapy
OXA	oxacillinase
PBRER	Periodic benefit-risk evaluation report
PD	pharmacodynamic
PK	pharmacokinetic
PMA	Postmenstrual age (gestational age + postnatal age)
PNA	Postnatal age, i.e. age after birth
PopPK	population pharmacokinetic
PR	pulse rate
PSUR	periodic safety update report
PT	preferred term
PTA	probability of PK/PD target attainment
q8h	every 8 hours
ROW	rest of world
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SBP	systolic blood pressure
SD	single-dose
SmPC	summary of product characteristics
SOC	system organ class
sNDA	supplemental new drug application
spp.	species
SRC	safety review committee
t½	overall terminal elimination half-life
TEAE	treatment-emergent adverse event
Tmax	time of maximum plasma concentration
TOC	test of cure
UTI	urinary tract infection
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 30 November 2023 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 and IIIB

Extension of indication to include treatment of paediatric patients from birth to less than 3-months of age in the following infections: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and in the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options, for ZAVICEFTA, based on final results from study C3591024 and the population PK modelling/simulation analyses. Study C3591024 is a Phase 2a, 2-part, open-label, non-randomized, multicenter, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring intravenous antibiotic treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0551/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0551/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0551/2022.

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: Ingrid Wang Co-Rapporteur: Larisa Gorobets

Timetable	Actual dates
Submission date	30 November 2023
Start of procedure:	27 January 2024
CHMP Rapporteur Assessment Report	27 March 2024
PRAC Rapporteur Assessment Report	3 April 2024
CHMP Co-Rapporteur Assessment	5 April 2024
PRAC members comments	3 April 2024
Updated PRAC Rapporteur Assessment Report	4 April 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 April 2024
Request for supplementary information (RSI)	25 April 2024
PRAC Rapporteur Assessment Report	3 June 2024
PRAC members comments	5 June 2024
Updated PRAC Rapporteur Assessment Report	6 June 2024
CHMP Rapporteur Assessment Report	16 June 2024
PRAC Outcome	13 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	20 June 2024
Request for supplementary information (RSI)	27 June 2024
PRAC Rapporteur Assessment Report	26 August 2024
PRAC members comments	28 August 2024
Updated PRAC Rapporteur Assessment Report	29 August 2024
CHMP Rapporteur Assessment Report	4 September 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

Infections due to resistant Gram-negative bacteria are increasingly common also in paediatric patients. Beta-lactamases are a major cause of resistance to beta-lactam antibacterial agents in infections caused by Gram-negative pathogens. The increasing resistance has significantly limited treatment options in patients with suspected extended-spectrum β-lactamases (ESBL) infections and often only carbapenems have sufficient coverage for empiric use in these cases. Few antibiotics with activity against ESBL and carbapenemase producing Gram-negative bacteria are currently available. Furthermore, only a few antibacterial agents have had their safety and efficacy carefully evaluated in paediatric patients. Hence, there is need for further treatment options for the paediatric patient population.

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.

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.

Ceftazidime is a cephalosporin that has been approved for many years in several member states, also for use in paediatric patients from birth. 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 adult 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.

Zavicefta (CAZ-AVI) is approved for use in Europe for the treatment of adults and paediatric patients aged 3 months and older with complicated intra-abdominal infection (cIAI), complicated intra-abdominal infection (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.

The current submission concerns a variation application to extend the indication to the paediatric population from birth to <3 months of age in the following infections: cIAI, cUTI, including pyelonephritis, HAP, including VAP and in the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options.

The variation application is based on data from paediatric study C3591024 (which included neonates and infants <3 months). Population pharmacokinetic (popPK) models for CAZ and AVI were updated with data from study C3591024 and study C3591025 and used to predict exposures and PK/PD target attainment for recommended doses to support extrapolation of efficacy and safety to neonates and infants from birth to <3 months of age. Supportive safety data is included from previous CAZ-AVI submissions including adult and paediatric subjects aged 3 months and older with cIAI, cUTI, and HAP/VAP.

Studies C3591025 and C3591024 were assessed in the Article 46 procedures EMEA/H/C/004027/P46/004 and EMEA/H/C/4027/P46/005, respectively. However, a detailed critical assessment of the C3591024 study data and a complete assessment of the benefit-risk balance of CAZ-AVI in the age group 0 to 3 months of age was not performed at that time due to the absence of a complete data package, including modelling and simulation (M&S) investigations.

2.1.1. General comments on compliance with GCP

According to the MAH, the CAZ-AVI programme was conducted in conformance with GCP guidelines, ICH guidelines E6 (1996) and E3 (1995), and CFR Title 21 Part 56, and in accordance with the ethical principles as stated in the Declaration of Helsinki. Furthermore, the MAH stated that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

2.2.1. Introduction

At the time of the initial MAA procedure for Zavicefta, the safety and efficacy profile of ceftazidime (CAZ) was already well known from clinical use, including children from 2 months of age. New non-clinical data was therefore only generated and submitted for avibactam (AVI), and to support the combination (CAZ-AVI). The initial MAA dossier included a dose range finding and a definitive juvenile rat toxicity study conducted with the CAZ-AVI (4:1) combination (studies 20040271(3582DR) and 20047213(3694DR), respectively), and two investigative renal studies in neonatal/juvenile rats (studies 3405KR and 200226123(3458KR)). The definitive juvenile rat toxicity study is in compliance with the PIP.

No new non-clinical pharmacology, pharmacokinetic, or toxicology studies have been conducted to support the treatment of paediatric patients from birth with cIAI, cUTI, HAP/VAP and other infections due to aerobic Gram-negative organisms in patients with limited treatment options. An updated ERA has been provided.

2.2.2. Pharmacology

No new pharmacology studies were submitted, which is acceptable.

2.2.3. Pharmacokinetics

No new pharmacokinetic studies were submitted, which is acceptable.

2.2.4. Toxicology

No new studies were submitted. However, the pivotal juvenile toxicity study submitted in connection with the initial MAA are described below.

Juvenile toxicology

14 Day Intravenous Toxicity Study in Neonatal Rats with a 5-Week Recovery Period (Study number 20047213; reference number 3694DR, GLP).

CAZ-AVI was dosed via an IV bolus injection into the tail vein of suckling SD rats (10/sex/group) once daily for 14 days from post-natal Day 7 to post-natal Day 20, using the intended clinical ratio of 4:1 ceftazidime: avibactam (0, 50/13, 150/38, 455/115). An additional 10 rats/sex/group were included in the control and high dose to assess reversibility following a 5-week recovery period and were terminated on PND 56. Additional satellite animals were included for assessment of toxicokinetics on PND 7 and 20.

The following parameters and end points were evaluated in this study: viability, clinical observations, body weights, body weight changes, functional observational battery evaluations, clinical pathology, toxicokinetic evaluation, organ weights (paired kidney, brain and spleen), macroscopic observations, and microscopic examinations.

There were no quantifiable concentrations of ceftazidime or avibactam in the control samples collected from the toxicokinetic satellite animals. All toxicokinetic satellite animals that were dosed with ceftazidime and avibactam showed exposure for both ceftazidime and avibactam that was approximately proportional to dose on both PND 7 and 20, for all doses. Exposure based on AUC(0-t) at PND 20 was less than half the exposure observed at PND 7 for both ceftazidime and avibactam, reflecting an increase in clearance. There was no apparent difference in exposure between males and females.

In general, the exposure to ceftazidime and avibactam in juvenile rats appeared to be higher than in adult rats, when adjusting for administered dose. See Table 1 and Table 2

Table 1. Summary of mean toxicokinetic parameters of ceftazidime in neonatal Sprague Dawley rats (PND 7 and PND 20)

Dose level (mg/kg)	Group 2 50 mg/kg/day		Group 3 150 mg/kg/day		Group 4 455 mg/kg/day	
Day	PND 7	PND 20	PND 7	PND 20	PND 7	PND 20
t_{max} (h)	0.083	0.14	0.083	0.092	0.083	0.083
C_{max} (ng/mL)	127000	149000	320000	478000	1150000	1520000
$AUC_{(0-t)}$ (h*ng/mL)	238000	102000	586000	272000	2100000	785000

n = 36 for males and female groups
t = time after drug administration [time]

Table 2. Summary of mean toxicokinetic parameters of avibactam in neonatal Sprague Dawley rats (PND 7 and PND 20)

Dose level (mg/kg)	Group 2 13 mg/kg/day		Group 3 38 mg/kg/day		Group 4 115 mg/kg/day	
Day	PND 7	PND 20	PND 7	PND 20	PND 7	PND 20
t_{max} (h)	0.083	0.15	0.083	0.092	0.083	0.083
C_{max} (ng/mL)	26000	23900	87600	111000	286000	346000
$AUC_{(0-t)}$ (h*ng/mL)	42400	11600	131000	49600	450000	145000

n = 36 for males and female groups
t = time after drug administration [time]

Renal cortical cysts in all groups, including controls, were observed at necropsy and by histology and were still present at the end of the 5-week recovery phase. The cysts covered a small proportion of the cortex and did not appear to have any significant implications for the animals (no adverse clinical

signs, no effects on body weight gain and no significant changes in clinical pathology or organ weights). Evidence from two additional supportive studies (and the lack of renal cysts in the repeat dose toxicity studies using adult rats of the same species/strain, suggested that the findings were background lesions from one specific breeding facility (3405KR and 200226123(3458KR)).

A minimal to mild, reversible, increase in extramedullary haematopoiesis was observed in the spleen and liver of both sexes at 455/115 mg/kg/day CAZ-AVI. One female at 50/13 mg/kg/day on PND 21 and one female at 455/115 mg/kg/day on PND 56 had unilateral pelvic dilatation in the kidney. The MAH established a NOAEL at 455 /115 mg/kg/day CAZ-AVI. The observation was however consistent with findings from the pre- and postnatal development study, which were associated with administration of avibactam.

2.2.5. Ecotoxicity/environmental risk assessment

Zavicefta is indicated for the treatment of the following infections in adults, infants (aged 3 months and older), children, and adolescents:

- 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.

Zavicefta is also indicated for the treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with cIAI, cUTI, or HAP/VAP.

The active ingredients in Zavicefta are ceftazidime and avibactam.

The recommended dosage of Zavicefta for adult patients with estimated creatinine clearance ≥51 mL/min is one 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.

The recommended dosage of Zavicefta in paediatric patients (aged 3 months to <18 years) is based on the age and weight of the patient, up to a maximum of 1 vial administered by intravenous (IV) infusion over 2 hours, repeated every 8 hours for 5 to 14 days.

The maximum daily dose for infants (aged >28 days to <3 months) patients is 90 mg/kg ceftazidime and 22.5 mg/kg avibactam. For neonatal patients (aged 0 to <28 days) , the maximum dosage will be 60 mg/kg ceftazidime and 15 mg/kg avibactam per day.

Zavicefta was first approved in Europe in 2016, and in 2021 an extension of the indication to include paediatric use for the indications cIAI and cUTI, was approved.

In the current submission, an update of the indication to include neonatal patients (from birth to <3 months with suspected or confirmed bacterial infection with a Gram-negative pathogen is proposed.

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

Avibactam

Table 1. A summary of results for Phase I: avibactam

Substance (INN/Invented Name): Avibactam			
CAS-number (if available): 1192491-61-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- logD_{ow}[a]	OECD107	$LogD_{ow}$ < -1.39 (pH5) $LogD_{ow}$ < -1.36 (pH7) $LogD_{ow}$ < -1.30 (pH9)	Potential PBT **No**
PBT-statement :	**The log D values for avibactam are < 4.5 at all environmentally relevant pHs, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined	0.0063	µg/L	**>0.01 threshold** **N**
Other concerns (e.g. chemical class)	None		
Outcome of Phase I :	**The refined PECsw value is < 0.01 µg/L and therefore no Phase II environmental fate and effect analysis is required.**		

Phase I avibactam

The DOSEai is refined using US hospital data. No data on EU hospitals is available, but there is no indication that patient populations are significantly different.

15% of patients receiving more than one course of treatment within a 12- month period is assumed for the EU. A course of treatment usually lasts from 5 to 14 days, The maximum daily dose was calculated assuming all patients receive the full 14-day course of treatment, resulting in a conservative maximum daily dose, determined as follows:

Avibactam:

$$\text{Refined } DOSEai = \left[\frac{1500\ mg \cdot d^{-1} \times 14\ d}{365\ d}\right] \times 1.15$$

Refined *DOSEai* = 66.2 mg·day^{-1}

The Fpen of avibactam is refined by taking into account the consumption data of avibactam in Croatia in 2020 (16.34kg), and the population in Croatia in 2020 (4,047,680)

$$refined\ Fpen = \frac{16.34x10^6}{66.2\ x\ 4{,}047{,}680\ x\ 365} = 0.00017$$

The PECsw for approved indications and patient populations is:

$$refined\ PECsw = \left(\frac{66.2\ mg\ x\ 0.00017}{200\ L\ x\ 10}\right) = 0.0056\ ug/L$$

Neonatal population

The maximum daily dose for neonatal patients will 22.5 mg/kg avibactam per day for infants < 3 months of age. Based on the 95th percentile weight for 3- month-old boys, as reported by the World Health Organization, of 7.7 kg, the maximum daily dose for neonatal patients may be calculated as follows:

$$Maximum\ daily\ DOSEai = 22.5\ mg \cdot kg^{-1} \times 7.7\ \text{kg}$$

$$Maximum\ daily\ DOSEai = \mathbf{173\ mg}$$

$$\text{Refined } DOSEai = \left[\frac{173\ mg \cdot d^{-1}\ \times\ 14\ d}{365\ d}\right] \times 1.15$$

Refined DOSEai (neonatal pop) = 7.6 mg·day-1

The age demographics in Croatia and Italy over the last several years indicate that approximately 1% of each of these country's populations are 0 years of age. The Fpen values previously determined, based on the highest consumption rates of ceftazidime and avibactam by adult, adolescent, and paediatric patients, will, therefore, represent a highly conservative estimate of the Fpen values for the addition of neonatal patients for the treatment of the approved indications:

$$refined\ PECsw\ (neonatal\ pop) = \left(\frac{7.6\ mg\ x\ 0.00017}{200\ L\ x\ 10}\right) = 0.00065ug/L$$

Total PECsw for avibactam: PECsw (approved patient populations) + PECsw (neonatal population)

0.0056+ 0.00065 = 0,0063 µg/L

$PEC_{surfacewater,\ avibactam}$= = 0.0063 µg/L

$PEC_{surfacewater,\ avibactam}$ is <0.01 µg/L and the ERA stops in phase I

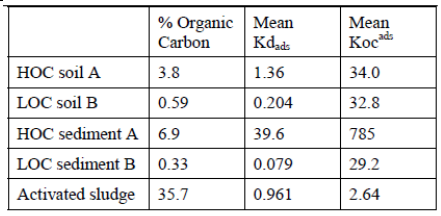
The LOGKow of avibactam is < 4.5 and a PBT assessment is not necessary.

Ceftazidime

Table 2. A summary of results for Phase I, Phase II, Tier A and Tier: ceftazidime

Substance (INN/Invented Name): Ceftazidime			
CAS-number (if available): 78439-06-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- $\log D_{ow}$[a]	OECD107	$LogD_{ow}$ < -2.20 (pH5) $LogD_{ow}$ < -2.21 (pH7) $LogD_{ow}$ < -2.17 (pH9)	Potential PBT **No**
PBT-statement :	**The log D values for ceftazidime are < 4.5 at all environmentally relevant pHs, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.**		
Phase I			

Calculation	Value	Unit	Conclusion
$PEC_{surfacewater}$, refined	**0.112**	µg/L	**>0.01 threshold Y Used for Tier A assessment.**
Other concerns (e.g. chemical	None		
Outcome of Phase I :	**The refined PECsw value is > 0.01 µg/L and therefore a Phase II environmental fate and effect analysis is required. The refined $PEC_{surfacewater}$ value is to be used for Tier A assessment as a probable worst-case.**		

Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	≥1000 mg/L (pH5 and 7) No result (pH9)	Rapid hydrolysis of ceftazidime occurred at pH9 and therefore water solubility at this pH was not determined.
Definitive Hydrolysis	OECD 111	pH 5 half-life: 495 h at 25ºC; 31.4 h at 50ºC; 11.6 h at 60ºC. pH 7 half-life: 433 h at 25ºC; 21.9 h at 50ºC; 7.11 h at 60ºC; pH 9 half-life: 35.4 h at 25ºC; 9.09 h at 50ºC; 3.21 h at 60ºC.	Ceftazidime is hydrolytically unstable at pH 5, 7 and 9. The calculated hydrolysis half lives were 495, 433 and 35.4 hours at pH 5, 7 and 9, respectively.
Ready Biodegradation	OECD 301	<2.1% mineralisation after 28 days	Not readily biodegradable
Inherent Biodegradation	OECD 302B	65% biotic degradation after 14 days 31% abiotic degradation after 14 days	Degradation of Ceftazidime dihydrochloride is, in part, an abiotic process.
Adsorption-Desorption	OECD 106		Ceftazidime is not predicted to adsorb to solids during wastewater treatment. **>3700 L/Kg threshold N**.

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

HOC: High organic carbon
LOC: Low organic carbon

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

Phase II Tier A Effect studies

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} (3h) EC_{20} (3h)	> 1000 320[b]	mg/L mg/L	[b]Used to calculate $PNEC_{microorganisms}$
Algae, Growth Inhibition Test (green algae)	OECD 201	LOEC (72h) NOEC (72h)	>120 120	mg/L mg/L	*Selenastrum capricornutum (aka Pseudokirchneriella subcapitata)*
Algae, Growth Inhibition Test (blue green algae)	OECD 201	LOEC (72h) NOEC (72h)	0.025 0.013[c]	mg/L mg/L	*Anabaena flos-aquae* [c]Used to calculate $PNEC_{surfacewater}$
Daphnia sp. Reproduction Test	OECD 211	LOEC (21d) NOEC (21d)	>9.2 9.2[d]	mg/L mg/L	*Daphnia magna* [d]Used to calculate $PNEC_{groundwater}$
Fish Early-Life Stage Toxicity	OECD 210	LOEC (32d) NOEC (32d)	>8.0 8.0	mg/L mg/L	*Pimephales promelas*
$PEC_{surfacewater}$ $PNEC_{surfacewater}$ **$PEC/PNEC_{surfacewater}$**			0.112 1.3 **0.086**	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

$PEC_{microorganisms}$ $PNEC_{microorganisms}$ **$PEC/PNEC_{microorganisms}$**			1.12 32 000 **3.5×10^{-5}**	µg/L µg/L	Unlikely to represent a risk to wastewater micro-organisms
Phase II Tier B Studies					
Sediment-Water Chironomid Toxicity	OECD 218	Total No. adults emerged Time to emergence. LOEC (28d) NOEC (28d) NOEC (28d) (corrected for organic carbon content)	No effects No effects >100 100 303.03	 mg/kg mg/kg mg/kg	*Chironomus riparius*. PEC/PNEC ratio <1. Ceftazidime unlikely to represent a risk to terrestrial or sediment dwelling organisms
$PEC_{sediment}$ $PNEC_{sediment}$ **$PEC/PNEC_{sedi}$**			1.3 3030 **0.00043**	µg/kg µg/kg	

Phase I ceftazidime

The DOSEai is refined using the same data as for avibactam.

Ceftazidime:

$$\text{Refined } DOSEai = \left[\frac{6000\ mg \cdot d^{-1} \times 14\ d}{365\ d}\right] \times 1.15$$

Refined *DOSEai* = 264.7 mg·day^{-1}

The Fpen (approved indications) of ceftazidime is refined by taken into account the consumption data of ceftazidime in Italy in 2018 (4491 kg), a maximum daily dose of 6000 and a population in Italy in 2016 of 60,421,760:

$$refined\ Fpen = \frac{4491x10^6}{264.7x\ 60{,}421{,}760\ x\ 365} = 0.00077$$

And the refined PECsw (approved populations)

$$refined\ PECsw = \left(\frac{264.7\ mg\ x\ 0.00077}{200\ L\ x\ 10}\right) = 0.1\ ug/L$$

Maximum daily dose calculation - Neonatal Patient Population:

The maximum daily dose for neonatal patients will be 90 mg/kg ceftazidime per day for infants < 3 months of age. Based on the 95th percentile weight for 3- month-old boys, as reported by the World Health Organization, of 7.7 kg, the maximum daily dose for neonatal patients may be calculated as follows:

$$Maximum\ daily\ DOSEai = 90\ mg \cdot kg^{-1} \times 7.7\ \text{kg}$$

$$Maximum\ daily\ DOSEai = \mathbf{693\ mg}$$

$$\text{Refined } DOSEai = \left[\frac{693\ mg \cdot d^{-1}\ \times\ 14\ d}{365\ d}\right] \times 1.15$$

Refined DOSEai = 30.6 mg·day-1

$$refined\ PECsw\ (neonatal\ pop) = \left(\frac{30.6\ mg\ x\ 0.00077}{200\ L\ x\ 10}\right) = 0.012ug/L$$

Total PECsw for ceftazidime: PECsw (approved patient populations) + PECsw (neonatal population)

0.10 + 0.012 = 0.112 µg/L

$PEC_{surfacewater}$, ceftazidime = 0.112 µg/L

$PEC_{surfacewater}$, ceftazidime is >0.01 µg/L and the ERA continues to phase II.

The LOGKow of ceftazidime is < 4.5 and a PBT assessment is not necessary.

Phase II Tier A, ceftazidime

The Phase II Tier A assessment for ceftazidime was assessed during the initial marketing authorisation procedure, and therefore the results of the fate and behaviour and effect studies in table 2 are copied from the previous assessment report. The PEC values are updated to include the neonatal population and new consumption data.

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 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.

$$\frac{PEC_{sediment}}{PNEC_{sediment}} = \frac{1.3\ \mu g \cdot kg^{-1}}{3030\ \mu g \cdot kg^{-1}} = 4.3 \times 10^{-4}$$

No further testing is required and no risk to the environment is expected.

2.2.6. Discussion on non-clinical aspects

No new pharmacology, pharmacokinetic or toxicology data have been submitted in this application, which is considered acceptable. Zavicefta is already approved for use in children from 3 months of age. Notable findings in the already performed 14 Day Intravenous Toxicity Study in Neonatal Rats with a 5-Week Recovery Period are discussed below.

Renal cortical cysts

Non-reversible renal cortical cysts were detected in all groups (including control) of juvenile rats (post-natal day 7-20). This finding was assessed in the MAA procedure and the clinical relevance of renal cortical cysts detected in juvenile rats was discussed in depth. Evidence from two additional supportive studies and the lack of renal cysts in the repeat dose toxicity studies in adult rats of the same species/strain, suggested that the findings were background lesions from one specific breeding facility and therefore unlikely to have any clinical significance. Additional information also suggested that the cysts were substantially distinct from human polycystic renal disease and that since nephrogenesis is still ongoing in juvenile rats, whereas it is complete by 34 weeks gestation in humans, the renal findings observed in the juvenile rats was unlikely to be relevant for humans. Furthermore, based on the nature and very low number of the renal cortical cysts, reflecting an effect on a minimal number of individual nephrons (i.e. each cyst indicating one single nephron), it is considered that should the finding occur in humans it would not have any clinical impact in paediatric patients, including pre-term neonates.

Pelvic dilatation of the kidney

The two cases of unilateral pelvic dilatation in the kidney observed at the end, or during the recovery phase of the definitive juvenile rat study were not discussed in the study report or by the MAH. During the initial MAA procedure, these were however assessed together with the similar observations in the F1 generation in the peri-post natal development (PPND) study in rat. The CHMP did not conclude on the potential risk related to use during pregnancy, or in neonates. Since a human relevance could not be excluded, the findings from the PPND study are reported in section 5.3 of the approved SmPC for Zavicefta. Dilatation of the renal pelvis is a recurring finding in rodents. This change is usually not of pathological or toxicological significance unless accompanied by histological evidence of pathological changes to the renal parenchyma (Histopathology of preclinical toxicity studies, Peter Greaves 3rd Ed.). Pathological changes were indeed not reported in the PPND study or the juvenile toxicity study. Nevertheless, the MAH does not suggest any mechanistic explanations for the dilated pelvis and there are no related reports of urine obstruction. Following receipt of supplementary information, the mechanism leading to an increase of dilated kidney pelvis in both the PPND study and the juvenile rat study, remains unknown. It can however be agreed that factors related to rat specific ontogeny, together with low incidence, indicate spontaneous background findings that does not suggest any specific concern with respect to clinical paediatric use.

Extramedullary haematopoiesis

In the juvenile rat toxicity study, a reversible increase in extramedullary haematopoiesis was observed in the spleen and liver of both sexes at 455/115 mg/kg/day CAZ-AVI. At this dose level, the PND 20 CAZ-AVI AUC0-t was 785/145 µg*h/ml. A similar exposure to CAZ-AVI in children as in adults is expected (same PK/PD target attainment values). The total plasma levels in healthy volunteers given 500 mg avibactam and 2000 mg ceftazidime every 8 hours, 120-minute infusion (D4280C00011) was 935/113 µg*h/ml. This suggests low margins of safety. The increase in extramedullary haematopoiesis was however classified as minimal to mild. Together with the reversible nature and lack of changes in any haematology parameters, this finding is not considered to be of clinical concern. Furthermore, haematological effects have been investigated and reported in the clinical paediatric trials.

Ecotoxicity/environmental risk assessment

An updated environmental risk assessment was submitted that included an updated calculation of the Fpen for avibactam and ceftazidime with reference to the prevalence data for Europe and relevant consumption data for the country with the highest prevalence. The PEC and PNEC calculations were estimated using updated maximum daily dose values including the neonatal patient population.

The vP properties of ceftazidime transformation products are now mentioned in the scientific overview.

2.2.7. Conclusion on the non-clinical aspects

According to the EPAR, nephrogenesis is still ongoing in juvenile rats, whereas it is complete by 34 weeks gestation in humans. The renal findings observed in the juvenile rats are therefore considered to be unlikely to be relevant for humans. Together with the clinical safety data, the existing non-clinical data supports the safe use of Zavicefta for the treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and in the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options in paediatric patients from birth to less than 18 years of age.

An updated environmental risk assessment was submitted showing that the inclusion of paediatric patients from birth is not considered to result in an increased risk to the environment, however two of the metabolites were shown to be very persistent in LOC water/sediment systems.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 3. Listing of all studies (based on M5.2 Tabular listing of clinical studies)

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment/ follow-up	Dates/Status
C3591024 (Estonia, Greece, Hungary, India, Italy, Philippines, Slovakia, Taiwan, and USA).	Phase 2a, 2-part, open-label, non-randomized, multicenter, single and multiple dose trial to evaluate PK, safety and tolerability of CAZ and AVI in neonates and infants from Birth to <3 months of age with suspected or confirmed infections due to Gram-negative pathogens requiring IV antibiotic treatment.	Cohort 1 (>28 days[a] to <3 months old): 30 mg/kg CAZ + 7.5 mg/kg AVI Cohort 2 (GA ≥37 weeks and ≤28 days old): 20 mg/kg CAZ + 5.0 mg/kg AVI Cohort 3 (GA ≥26 weeks to <37 weeks and ≤28 days old): 20 mg/kg CAZ + 5.0 mg/kg AVI. Max infusion volume 2 mL/kg/dose. Infusion duration was 120 min. Infusion frequency was q8h (Part B only).	Randomized: 48, 27 in Part A and 21 in Part B. Part A Treated: 25 Completed follow-up phase: 23. Part B Treated: 21 Completed treatment phase: 18 Completed follow-up phase: 20.	Part A Sex: Mean Age (± SD): Race (W/B/O): 18/2/5. Part B Sex: Mean Age (± SD): Race (W/B/O): 18/2/1.	Part A: Single dose. Follow-ups at 24 and 48 hours. LFU = 28 to 35 days. Part B: Multiple doses from Days 1 to 14. LFU = 28 to 35 days.	14 Jan 2020 (FPFV)/ 30 Dec 2022/ Completed (terminated early).
C3591025 (China, Estonia, Greece, India, Italy, Phillipines, Slovakia, Taiwan, UK, and USA).	Phase 1, open-label, single-dose study to assess the PK, safety and tolerability of CAZ-AVI in children from 3 Months to <18 years of age who are hospitalized and receiving systemic antibiotic therapy for suspected or confirmed NP, including VAP.	**Cohort 1 (12 years to <18 years):** ≥40 kg *CrCL ≥50 mL/min/1.73 m²*: 2000 mg CAZ 500 mg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 1000 mg CAZ 250 mg AVI <40 kg *CrCL ≥50 mL/min/1.73 m²*: 50 mg/kg CAZ 12.5 mg/kg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 25 mg/kg CAZ 6.25 mg/kg AVI **Cohort 2 (6 years to <12 years):** ≥40 kg *CrCL ≥50 mL/min/1.73 m²*: 2000 mg CAZ 500 mg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 1000 mg CAZ	No participants were randomized to Cohort 1. One patient per cohort 2, 3, 4a and 4c randomised, treated, completed (N=4 patients)	**Cohort 2** Sex: Age: Race: W/B/O: 0/0/1. **Cohort 3** Sex: Age: Race: W/B/O: 0/0/1. **Cohort 4a** Sex: Age: Race: W/B/O: 0/0/1. **Cohort 4b** Sex: Age: Race: W/B/O: 0/0/1	Single dose. Follow-ups at 24 and 48 hours. LFU = 28 to 35 days.	15 Jun 2020 (FPFV)/07 May 2021/ Completed (terminated early).

		250 mg AVI <40 kg *CrCL ≥50 mL/min/1.73 m²*: 50 mg/kg CAZ 12.5 mg/kg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 25 mg/kg CAZ 6.25 mg/kg AVI **Cohort 3 (2 years to <6 years):** *CrCL ≥50 mL/min/1.73 m²*: 50 mg/kg CAZ 12.5 mg/kg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 25 mg/kg CAZ 6.25 mg/kg AVI **Cohort 4 (3 months to <2 years [born ≥37 weeks GA]):** **Cohort 4a (1 year to <2 years):** *CrCL ≥50 mL/min/1.73 m²*: 50 mg/kg CAZ 12.5 mg/kg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 25 mg/kg CAZ 6.25 mg/kg AVI **Cohort 4b (3 months to <6 months):** *CrCL ≥50 mL/min/1.73 m²*: 40 mg/kg CAZ 10.0 mg/kg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 20 mg/kg CAZ 5.0 mg/kg AVI **Cohort 4b (6 months to <1 year):** *CrCL ≥50 mL/min/1.73 m²*: 50 mg/kg CAZ 12.5 mg/kg AVI *CrCL ≥30 to <50 mL/min/1.73 m²*: 25 mg/kg CAZ 6.25 mg/kg AVI				

Abbreviations: AVI = avibactam; B = black; CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam; CrCL = creatinine clearance; F = female; FPFV = first participant first visit; GA = gestational age; IV = intravenous(ly); LFU = late follow-up; M = male; max = maximum; min = minimum; No = number; NP = nosocomial pneumonia; O = other; PK = pharmacokinetic; q8h = every 8 hours; SD = standard deviation; UK = United Kingdom; USA = United States of America; VAP = ventilator associated pneumonia; W = white.

[a]: Includes term infants (GA ≥37 weeks) >28 days of age and pre-term infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age.[1] Corrected age was used only for determining eligibility of pre-term infants in Cohort 1. Actual age (chronological age) was used for determining eligibility of pre-term neonates in Cohort 3.

2.3.2. Pharmacokinetics

Refer to the MAA (EMEA/H/C/4027) and previous extension of indication variations (EMEA/H/C/004027/II/0002 and EMEA/H/C/004027/II/0015) for details on the pharmacokinetics of ceftazidime (CAZ) and avibactam (AVI).

There are no expected differences in the mechanism of action of CAZ-AVI based on age as both CAZ and AVI exert their effects by acting on the causative pathogen, and the Gram-negative causative pathogens are similar in adults and children, and the same joint PK/PD targets would be relevant to dose setting in paediatric patients. Thus, the aim of the dose selection was to achieve comparable exposures to those calculated for the Phase III studies in adult patients with cIAI, cUTI and HAP/VAP. The concept of extrapolation of clinical efficacy and safety from adults to paediatric subjects is in accordance with ICH E11(R1) and has been previously applied to older paediatric age groups (3 months to <18 years) for CAZ-AVI indications (cIAI, cUTI, HAP/VAP, and the treatment of infections due to aerobic gram-negative organisms in adults and paediatric patients with limited treatment options).

The proposed CAZ-AVI dose in full term and preterm infants and neonates with serum creatinine (SCR) at or below the upper limit of normal (ULN) for age is shown in Table 4. The proposed paediatric doses were used in the clinical phase II study C3591024 (except for patients 26 to <31 weeks PMA which are based on PK modelling only). In Part A, subjects received a single IV infusion of CAZ-AVI. In Part B, subjects received CAZ-AVI IV treatment for 2 to up to 14 days (8h dosing interval). The formulation used is identical to the final drug product for commercial use.

Table 4. Proposed dose recommendation in neonates and infants <3 months (response to 2nd RSI)

Age group		Dose of **ceftazidime**/avibactam	Frequency	Infusion time
Full term neonates and infants	> 28 days to < 3 months	**30 mg/kg**/7.5 mg/kg	Every 8 hours	2 hours
	Birth to ≤ 28 days	**20 mg/kg**/5 mg/kg		
Preterm[1] neonates and infants	> 44 weeks to < 53 weeks PMA	**30 mg/kg**/7.5 mg/kg	Every 8 hours	
	31 to ≤ 44 weeks PMA	**20 mg/kg**/5 mg/kg		
	26 to < 31 weeks PMA	**20 mg/kg/5 mg/kg**	Every 12 hours	

[1]Preterm defined as <37 weeks gestation

Methods

Bioanalytical methods

The validated bioanalytical methods used in the clinical development programmes were precise and accurate, and the assay validation characteristics were acceptable for all applications. There is no new biopharmaceutical information in this submission, and no new bioanalytical methods were used for the analysis of samples from the paediatric study C3591024.

Pharmacokinetic data analysis

Descriptive statistics are used to summarise PK characteristics. Population pharmacokinetic (popPK) modelling was performed using nonlinear mixed effects modelling (NONMEM Vs. 7.5.0).

Evaluation and qualification of models

Data from study C3591024 (CAZ-AVI single and multiple doses in patients from birth to <3 months of age) were used to update popPK and PD analyses used to support the extension of indication to paediatric patients from birth to <3 months. The popPK models have also previously been updated with PK data from four patients in study C3591025.

PopPK model report PMAR-EQDD-C359m-sNDA-1155

Methods

Prior modelling

Table 5. Prior CAZ and AVI popPK modelling

Prior popPK modelling	Purpose/objectives	Dataset	Comments
CAZ-MS-06 (2015)	Inform development and support dose selection, and dose adjustments in renal impairment, in adult patients	Phase I studies CXL-PK-01, -03, -04, -06; NXL104-1001 and -1002; NXL104/1003 and -/1004; D4280C00010, - 011, -020. Phase II studies NXL104/2001 and -/2002 Phase III Studies D4280C00001/5, D4280C00006	Main CAZ and AVI models submitted in support of the original MAA (EMA). Adult healthy subjects and patients (cIAI, cUTI)
CAZ-MS-PED-01 (2015)	Inform development and support paediatric dose selection for phase II studies C3591004 and C3591005	Additional phase I paediatric study D4280C00014	Based on CAZ-MS-06. Includes paediatric data (patients with suspected/confirmed infection).
CAZ-MS-09 (2016)	Inform development and support dose selection and dose adjustments in renal impairment in adult patients for the cIAI, cUTI and HAP/VAP indications	Additional phase III studies: D4280C00002/4, D4280C00006 (final data), D4280C00018, D4281C00001	Based on CAZ-MS-06. Assessed in EMEA/H/C/4027/II/2. Adult healthy subjects and patients (cIAI, cUTI, HAP/VAP) and adult Asian cIAI patients.
CAZ-MS-PED-02 (PMAR-EQDD-C359a_Other-762, 2018)	Inform development and confirm dose selection, and dose adjustments in renal impairment, in paediatric patients for the cIAI and cUTI indications	Additional phase I and II studies: D4280C00014, C3591004, C3591005	Based on CAZ-MS-09. Includes paediatric cIAI and cUTI patients. Assessed in EMEA/H/C/4027/II/15 (EoI ≥3 months).
PMAR-EQDD-C3591-Other-1320 (2022)	Updated popPK and target attainment simulations for recommendation of doses in paediatric patients ≥3 months to < 18 years with HAP/VAP	Additional phase I study C3591025	Based on CAZ-MS-PED-02. Includes additional four paediatric patients (HAP/VAP).
PMAR-EQDD-C359m-sNDA-1155 (2023) **Current, main model**	Perform updated PopPK and target attainment simulations for recommendation of doses in paediatric patients from birth to < 3 months of age with gram-negative infection	Additional phase II study C3591024	Based on PMAR-EQDD-C3591-Other-1320. Includes additional 44 paediatric patients (neonatal sepsis)

Objectives

- To update the previously developed PopPK models for AVI and CAZ (PMAR-1320) with plasma concentration data from neonates and infants from birth to <3 months of age (study C3591024).

- To describe the PK of AVI and CAZ in neonates and infants from birth to <3 months of age by the estimation of secondary PK parameters for the subjects in study C3591024.
- To assess, through PopPK simulations, the proposed paediatric dosing regimen for neonates and infants from birth to <3 months old.

Estimation method

Plasma concentration-time data were analysed using a nonlinear mixed-effects modelling approach using NONMEM vs.7.5.0 and the estimation algorithm FOCE-I.

Database

Separate PopPK analysis datasets for AVI and CAZ popPK analysis were created by combining the final datasets from previous popPK analyses reported in PMAR-1320 (Table 6) and PK data from study C3591024 (see section on Special populations).

A total of 2452 subjects were initially included in the AVI popPK analysis and 2179 subjects in the CAZ popPK analysis. A total of 203 paediatric subjects were included in the current popPK analysis (202 for AVI analysis). There are only 6 and 3 paediatric subjects corresponding to the populations of cIAI and NP respectively, in the younger age groups of 3 months to <6 years old. The majority of the subjects in this age range correspond to subjects with cUTI.

There was PK data available from a total of 45 subjects from the Study C3591024 for a total of 134 PK samples for each drug substance. Three PK samples were obtained from each subject following a single dose in part A and after at least three consecutive doses in part B. The samples were collected at the following time points: 1) anytime within 15 minutes after stopping infusion, 2) anytime between 30 minutes and 90 minutes after stopping infusion, and 3) anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping infusion.

Covariates

Demographic characteristics for study C3591024 by cohort and study part are shown in Table 15 (Special populations). There were in total 17 subjects in Cohort 1 (term or pre-term infants), 12 subjects in Cohorts 2 (term neonates) and 16 subjects in Cohort 3 (pre-term neonates). Age from birth ranged from 0.3 to 12.7 weeks and gestational age from 31 to 40.7 weeks, sex was evenly distributed with 24 females and 21 males and most of the subjects were white (n = 35) with only 4 black and 5 Asian. There were no subjects with ESRD or on dialysis and it was assumed there was no presence of ventilator for any of these subjects. The subjects from C3591024 were not assigned to any of the population types (cUTI, cIAI or NP) considered as covariates in both AVI and CAZ popPK models.

Demographic characteristics for the adult and paediatric subjects >3 months in the data set are described in prior popPK model reports (Table 6).

Data handling (BLQs, missing data, outliers)

Exclusions from the previous studies have been described in CAZ-MS-PED-02. There were no data exclusions from Study C3591025.

Data from one subject (part A cohort 1) in study C3591024 was excluded from the popPK analysis as the CAZ and AVI concentrations was ~3.5-5 times higher compared to the highest concentration observed for remaining subjects. For this patient, there was a deviation in the procedure for dilution of the stock volume of the study intervention and it is presumed an unknown and undocumented error occurred in the dose administered as a result of the documented procedural deviation based on the participant's plasma CAZ and AVI concentrations being markedly higher than expected. No BLQs were reported.

Methodology

Base models were the previously used to describe CAZ and AVI PK in adults and children ≥3 months (*i.e.* final models in CAZ-MS-PED-02 and PMAR-1320). Some of these covariates (Table 7 and Table 8) are not relevant for neonates or infants <3 months old, but are kept in the model, as the model aimed to describe the PK from birth to adulthood.

For the CAZ popPK model, no subject was considered to have a presence of ventilator and the population type for C3591024 was not any of the three populations studied (cUTI, cIAI or NP). For the AVI popPK model, no subject was considered to have ESRD or to be on dialysis and the population type for C3591024 was not any of the three populations studied (cUTI, cIAI or NP). In the CAZ and AVI datasets it was classified as population 6 (sepsis or infection in neonates and subjects <3 months old), study C3591024 was the only study with this population type.

Table 6. Summary of AVI popPK model covariates (PMAR-EQDD-C359m-sNDA-1155, Table 4)

Covariate	Vc	Vp	CL	Q
Body Weight	Allom (1)	Allom (1)	Allom (0.67)	Allom (0.67)
PMA	-	-	≤ 2 years	-
nCrCL	-	-	> 2 years	-
ESRD	-	-	ESRD	-
Dialysis	-	-	Dialysis	-
Population	cUTI or cIAI adult Ph2 or cIAI/NP/cIAI(ped)	-	cIAI adult Ph2	-
Ventilator	Present	-	-	-
APACHE II	-	-	Score >10	-

Vc = Central volume of distribution, Vp = Peripheral volume of distribution, CL = clearance, Q = intercompartmental clearance, Allom = allometric scaling power model with fixed exponents of 1 or 0.67 and reference weight of 70 kg, PMA = Post-menstrual age, nCrCL = creatinine clearance normalized to 1.73 m^2 body surface area, ESRD = End Stage Renal Disease, cUTI = complicated urinary tract infection, cIAI = complicated intra-abdominal infection, NP = nosocomial pneumonia, APACHE II = Acute Physiology and Chronic Health Evaluation

Table 7. Summary of CAZ popPK model covariates (PMAR-EQDD-C359m-sNDA-1155, Table 5)

Covariate	Vc	Vp	CL	Q
Body Weight	Allom (1)	Allom (1)	Emax[a]	Allom (0.67)
PMA	-	-	≤2 years	-
nCrCL	-	-	> 2 years	-
Population	cUTI or cIAI/NP	-	cIAI or NP	-
Ventilator	Present	-	-	-
Race	Asian/Chinese/Japanese	-	Asian or Chinese	-

[a]Corresponds to a simple E_{max} model where a maximum covariate effect for weight in CL and a half-maximal effect of on CL were estimated Vc = central volume of distribution, Vp = peripheral volume of distribution, CL = clearance, Q = intercompartmental clearance, Allom = allometric scaling power model with fixed exponents of 1 or 0.67 and reference weight of 70 kg, PMA = Post-menstrual age, nCrCL = creatinine clearance normalized to 1.73 m^2 body surface area, cUTI = complicated urinary tract infection, cIAI = complicated intra-abdominal infection, NP = nosocomial pneumonia

It was assessed if the models were adequate to describe the PK of neonates and infants <3 months old by the inspection of GOF plots and VPC for the paediatric subjects on Study C3591024, stratified by age cohort.

Results

The concentration time profiles for subjects in study C3591024 stratified by cohort are shown in Figure 1 (one subject is excluded). Drug elimination is occurring slower in Cohort 3 (pre-term patients) mainly in comparison to Cohort 1. The AVI concentration profiles seem to be more variable than CAZ profiles, mainly in Cohort 2. From the three cohorts, Cohort 3 is the most variable. One subject in Cohort 3 showed very low concentrations at the 3 sample windows, with none of these concentrations being above the CAZ minimum inhibitory concentration (MIC) or AVI concentration threshold at any time point.

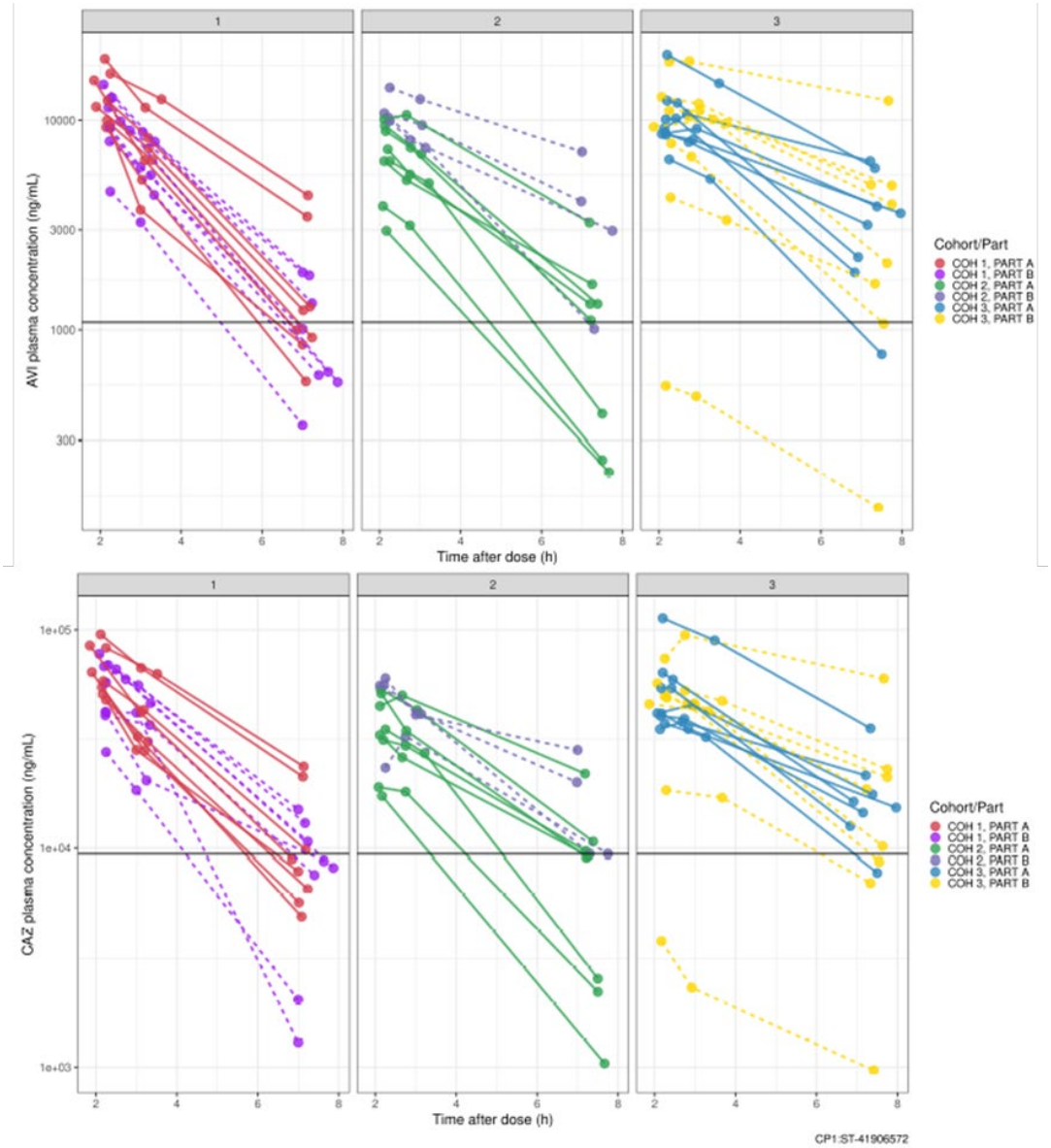


Figure 1. Study C3591024 concentration-time profiles (n = 44) for AVI (top) and CAZ (bottom) in log-scale. Black horizontal line corresponds to 1000 ng/mL threshold free concentration (AVI) or 8000 ng/mL MIC (CAZ). (Source: PMAR-EQDD-C359m-sNDA-1155 Figure 3)

In the Vc-ETA vs covariate (WT and age) plots for the AVI and CAZ base models it was seen that younger subjects, including subjects from C3591024, mostly had ETA values above 0. Also, in GOF plots based on data from study C3591024 only, a trend in CWRES vs PRED plot (where at lower PRED values, higher CWRES values were seen and at higher PRED values, lower CWRES values were seen)

and CWRES vs time after dose (TAD) plot (where at higher TAD values, higher CWRES values were seen and at lower TADs lower CWRES values are present) was detected. The modelling results indicated that the Vcs estimated for this age group just based on the allometric function and race were not as high as what these subjects should have to describe the data. A modified popPK model, adding a categorical covariate effect for the age group <3 months (corresponding to subjects in Study C3591024) on Vc, was tested for both AVI and CAZ. A decrease in the objective function value (OFV) was obtained when using these models and there was improvement in GOF plots. Therefore, the models in Step 40 (Table 7) and Step 7 (Table 8) were considered the final AVI and CAZ popPK models, respectively. For the CAZ model, the OFV increased when trying to describe the body weight effect on CL with the more commonly used power function with a fixed exponent of 0.67 (Step 13), therefore the Emax function was kept.

Table 8. AVI PopPK Model Development (Source: PMAR-EQDD-C359m-sNDA-1155, Table 8)

Model	Description	OFV	Δ OFV
Step 2 (CP1:ST-41529240)	Final model from PED-02 [2] (n = 2452)	226719.784	-
Step 38 (CP1:ST-42671629)	Base Model: Same as Step 2 but ID[redacted] excluded[a] (n = 2451)	226651.349	-
Step 40 (CP1:ST-42672236)	Final Model: Categorical age (<3m old) effect in Vc (n = 2451)	226618.359	-30.99

[a]Subject [redacted] (Part A, Cohort 1) was considered to have outlier concentrations and reported to have a medication error [4]. OFV: Objective Function Value, Δ OFV: Change in OFV from previous model, n: number of subjects in analysis, m: months, Vc: Central volume of distribution, WT: body weight

Table 9. CAZ PopPK Model Development (Source: PMAR-EQDD-C359m-sNDA-1155, Table 10)

Model	Description	OFV	Δ OFV
Step 2 (CP1:ST-41661977)	Final model from PED-02 [2] (n = 2179)	192968.251	-
Step 10 (CP1:ST-41835883)	Base Model: Same as Step 2 but ID[redacted] excluded[a] (n = 2178)	192850.711	-
Step 7 (CP1:ST-41726361)	Final model: Categorical age (<3m old) effect in Vc (n = 2178)	192831.572	-19.139
Step 13 (CP1:ST-41974612)	Test allometric function instead of Emax model to describe WT effect on CL (n = 2178)	193049.215	217.643

[a]Subject [redacted] (Part A, Cohort 1) was considered to have outlier concentrations and reported to have a medication error [4]. OFV: Objective Function Value, Δ OFV: Change in OFV from previous model, n: number of subjects in analysis, m: months, Vc: Central volume of distribution, WT: body weight, CL: Clearance

The final model parameters for ceftazidime and avibactam are given below in Table 11 and Table 12.

Table 10. Parameter estimates for the final AVI popPK model (M2.7.2, Table 5)

Parameter	Estimate	% RSE	IIV (%)
θ_1: CL (L/h)	11.7	1.57	57.9
θ_2: V_c (L)	13.5	8.63	81.2
θ_3: V_p (L)	8.13	7.72	110
θ_4: Q (L/h)	7.69	21.5	205
θ_5: Relative CL estimate for patients with ESRD, CL × θ_5	0.0652	20.5	-
θ_6: CL estimate for dialysis patients (L/h)	23.2	6.98	-
θ_7: Power nCrCL on CL	1.02	4.36	-
θ_8: Linear nCrCL on CL	0.00335	11.5	-
θ_9: Population effect on V_c (cIAI) adult Phase 2, V_c × (1 + θ_9)	2.04	36.9	-
θ_{10}: Population effect on CL (cIAI) adult, Phase 2, CL × (1 + θ_{10})	0.442	38.5	-
θ_{11}: Population effect on V_c (cUTI), V_c × (1 + θ_{11})	0.536	22.2	-
θ_{12}: Population effect on V_c (cIAI adult Phase 3, NP, paediatric cIAI), V_c × (1 + θ_{12})	0.349	28.0	-
θ_{15}: APACHE on CL	-0.178	13.3	-
θ_{28}: Presence of ventilator on V_c, V_c × (1 + θ_{28})	0.241	38.9	-
θ_{38}: Neonatal and infants <3 m on V_c, V_c × (1 + θ_{38})	0.772	26.6	-
OMEGA Values			**Shrinkage (%) or correlation[a]**
ω^2CL	0.335	8.19	4.68
ω V_c-CL	0.152	17.1	r = 0.323[a]
ω^2V_c	0.660	29.6	27.6
ω V_p-CL	0.573	28.9	r = 0.900[a]
ω V_p-V_c	-0.0702	102	r = -0.0785[a]
ω^2V_p	1.21	29.6	10.7
ω Q-CL	1.04	15.0	r = 0.879[a]
ω Q-V_c	-0.198	135	r = -0.119[a]
ω Q-V_p	2.24	28.8	r = 0.996[a]
ω^2Q	4.18	28.9	11.3
Residual Error			
θ_{17}: Proportional variability, Phase 1	0.175	8.02	-
θ_{18}: Additive variability, Phase 1 (ng/mL)	44.7	22.9	-
θ_{19}: Proportional variability, Phase 2	0.519	4.98	-
θ_{20}: Proportional variability, Phase 3	0.389	4.49	-

ω = inter-individual variance; θ = typical value of pharmacokinetic parameter; RSE = relative standard error; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; ESRD = end-stage renal disease; IIV = inter-individual variability; NCrCL = body surface area normalised creatinine clearance; Q = intercompartmental flow rate; V_c = central volume of distribution; V_p = peripheral volume of distribution

a. Correlation coefficient (r) between random effects.

Note: IIV coefficient of variation (CV)% expressed as a variance.

Cross reference: PMAR-EQDD-C359m-sNDA-1155 Table 9

Table 11. Parameter estimates for the final CAZ popPK model (M2.7.2, Table 4)

Parameter	Estimate	% RSE	IIV (%)
nCrCL Effect on CL			
Slope 1: nCrCL < 100 mL/min, Slope 1 × nCrCL	0.01030360 (Fixed)	-	-
Slope 2: nCrCL ≥ 100 mL/min, Slope 1 × 100 + Slope 2 × (nCrCL - 100)	0.00125182 (Fixed)	-	-
NONMEM Fixed Effects			
θ_1: CL (L/h)	7.75	31.8	39.3
θ_2: V_c (L)	11.2	3.52	32.9
θ_3: Q (L/h)	5.27	6.55	45.8
θ_4: V_p (L)	6.52	3.08	15.4
θ_{13}: Maximum covariate effect for WT on CL as an E_{max} function	1.64	32.0	-
θ_{15}: WT at half-maximal effect of WT on CL as part of an E_{max} function	44.8	8.05	-
θ_{16}: Population effect on CL for patients with cIAI, CL × θ_{16}	1.32	2.37	-
θ_{17}: Population effect on CL for patients with NP, CL × θ_{17}	1.10	2.93	-
θ_{18}: Race effect on CL for ASN, CL ´ (1 + θ_{18})	-0.141	19.2	-
θ_{19}: Race effect on CL for CHN, CL ´ (1 + θ_{19})	-0.0930	26.0	-
θ_{20}: Population effect on V_c for patients with cUTI, V_c × θ_{20}	1.50	4.57	-
θ_{21}: Population effect on V_c for patients with cIAI or NP, V_c × θ_{21}	1.83	3.96	-
θ_{22}: Population effect on V_c for presence of ventilator, V_c × (1 + θ_{22})	0.201	33.5	-
θ_{23}: Race effect on V_c for ASN, CHN, and JPN, V_c × (1 + θ_{23})	-0.138	22.3	-
θ_{24}: Neonates and infants <3 m on V_c, V_c × θ_{24}	1.68	9.29	-
OMEGA Values			**Shrinkage**
ω^2CL	0.154	5.13	10.4
ω^2V_c	0.108	22.4	49.8
ω^2Q	0.210	37.4	79.5
ω^2V_p	0.0236	41.8	83.2
Residual Error			
Proportional variability, Phase 1	0.172	10.4	-
Additive variability, Phase 1 (ng/mL)	125	16.2	-
Proportional variability, Phase 2 or 3	0.371	2.19	-

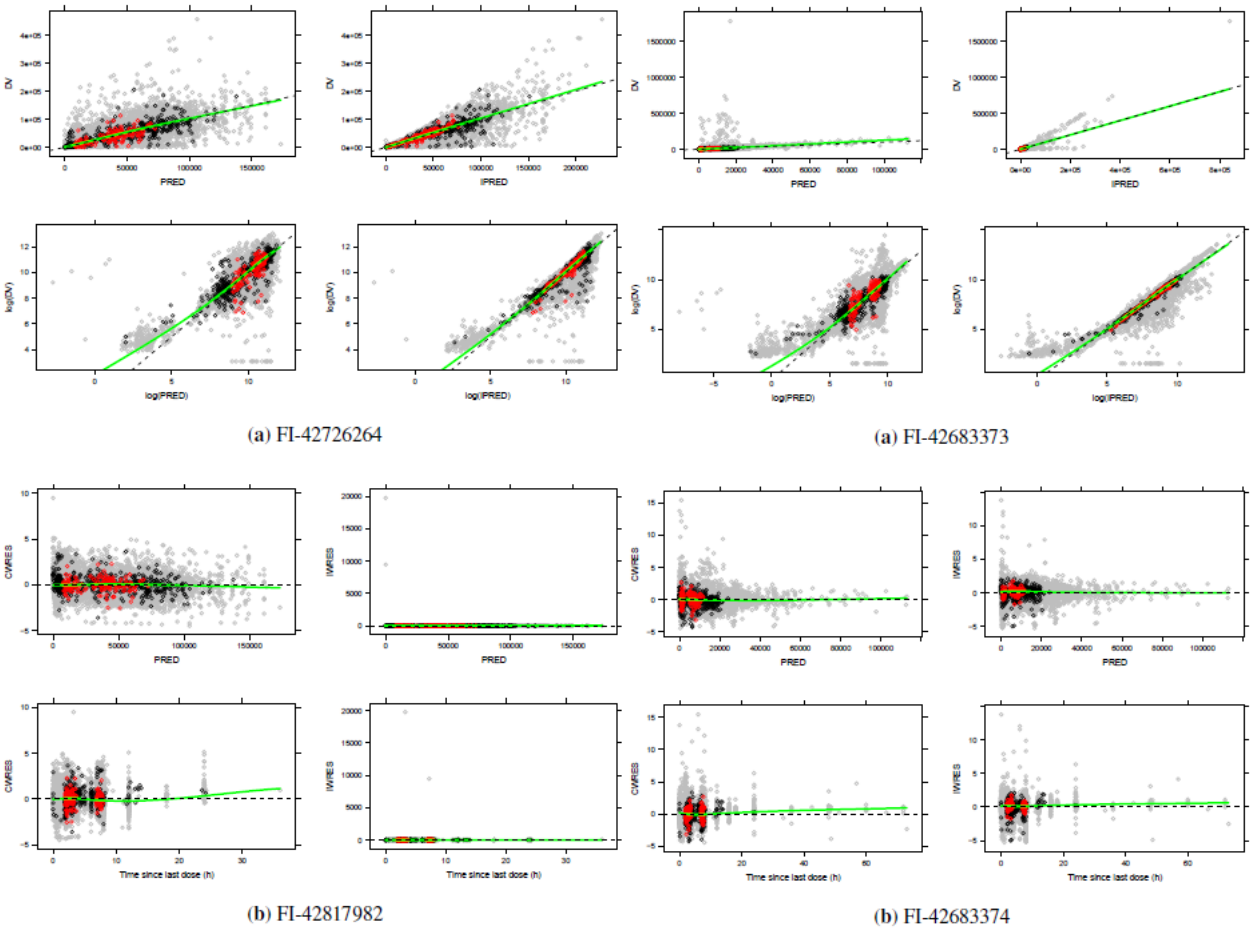
ω = inter-individual variance; θ = typical value of pharmacokinetic parameter; ASN = Asian; CHN = Chinese; JPN = Japanese; NP = nosocomial pneumonia; nCrCL = body surface area normalised creatinine clearance; PopPK = population pharmacokinetic; IIV = inter-individual variability; E_{max} = maximum effect; RSE = relative standard error; WT = weight
Cross reference: PMAR-EQDD-C359m-sNDA-1155 Table 11

distribution, WT = Body weight, cIAI = complicated intra-abdominal infection , cUTI = complicated urinary tract infection, NP = nosocomial pneumonia, ASN = Asian, CHN = Chinese, JPN = Japanese.

Parameter uncertainty were evaluated by sampling importance resampling (SIR), based on 1000 samples and 3 iterations with resampling size of 200, 400 and 500 (results not shown).

Model evaluation

Diagnostic GoF plots for both CAZ and AVI final popPK models are shown below. Posterior predictive checks (PPC), based on 1000 simulations for each age cohort with body weights generated based on the Olsen et al. 2010 (pre-term subjects) or CDC (term subjects) growth charts, were also provided (not shown).

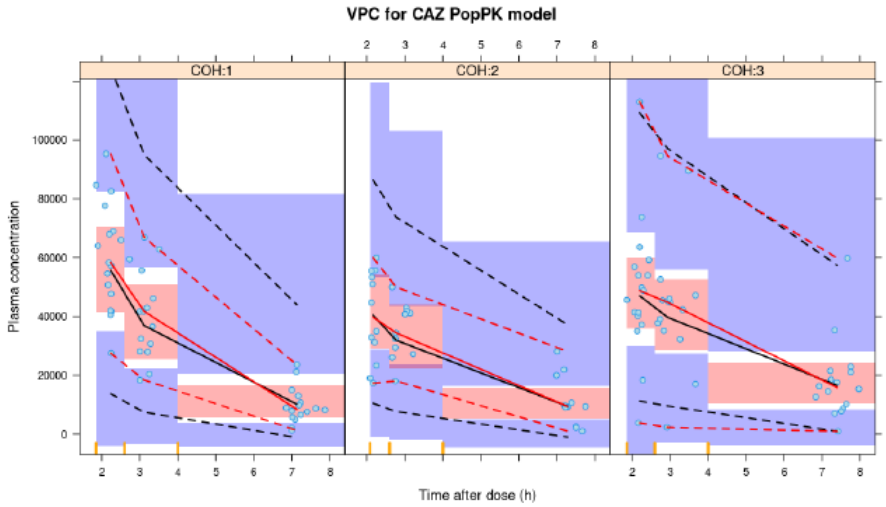


(a) FI-42726264 (a) FI-42683373

(b) FI-42817982 (b) FI-42683374

Repository artifact IDs are shown in subfigure labels.
Each symbol represents an individual PK prediction (PRED, IPRED, CWRES, IWRES) and observation (DV). Gray circles represent adult patients/subjects while black circles represent pediatric patients, red circles represent pediatric patients from Study C3591024. The solid green line is a loess to the data and the dashed line is the zero horizontal line (a) or the identity line (b).
Abbreviations: CWRES = conditional weighted residual, DV = dependent variable, IPRED = individual predictions, PK = pharmacokinetic, PRED = population predictions.

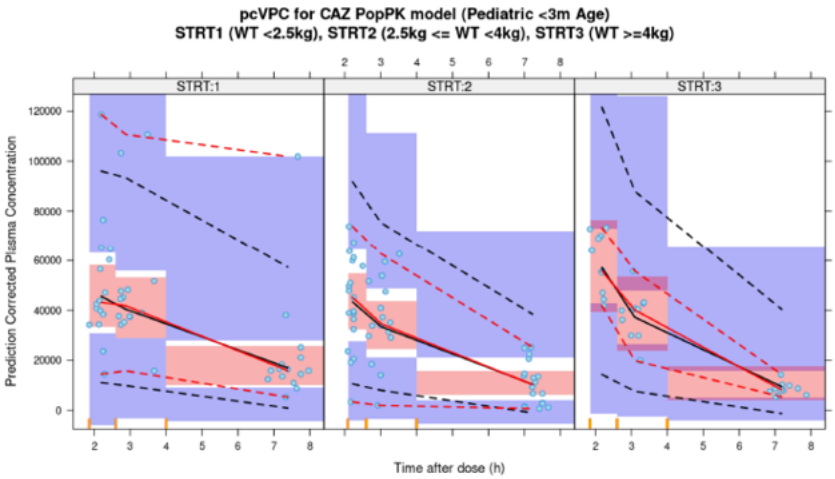
Figure 2. GOF Plots for the final CAZ (left) and final AVI (right PK models (Outlier excluded) (PMAR-EQDD-C359m-sNDA-1155, Figures A5.6 and A5.18)



Repository artifact ID FI-41770394.

Abbreviations: CAZ = Ceftazidime, PK = pharmacokinetics, VPC = visual predictive check. Each symbol represents an individual PK observation. The solid red line connects the median observed concentrations while the solid black line is the simulated median. The shaded region represents the 5th to 95th prediction interval for the median, 5th and 95th percentile based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.

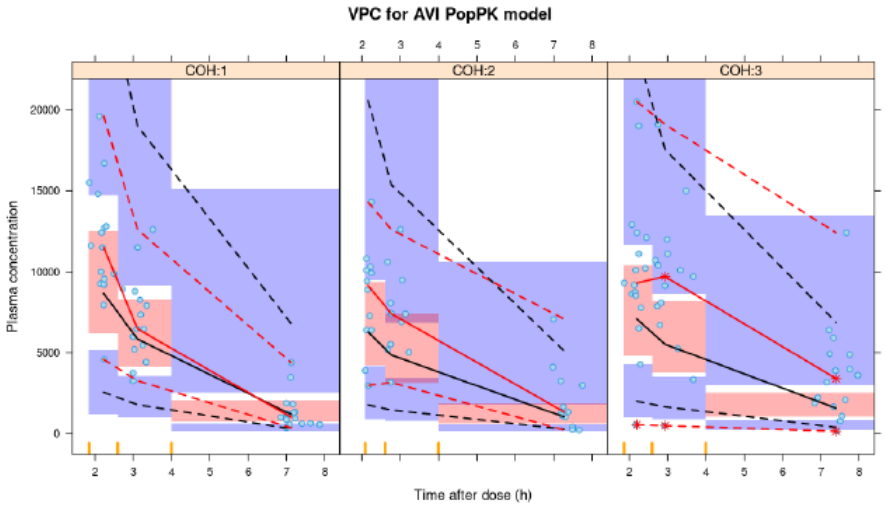
Figure 3. Predictive check (VPC) for CAZ final popPK model by study cohort (PMAR-EQDD-C359m-sNDA-1155, Figure A5.22)



Repository artifact ID FI-56724618.

Red and black lines are the 5th, 50th (solid) and 95th percentile of observed and simulated data, respectively. Shadow areas are 95% CI for the 5th, 50th (red) and 95th percentile prediction intervals based on simulated data, blue dots correspond to prediction-corrected observations.

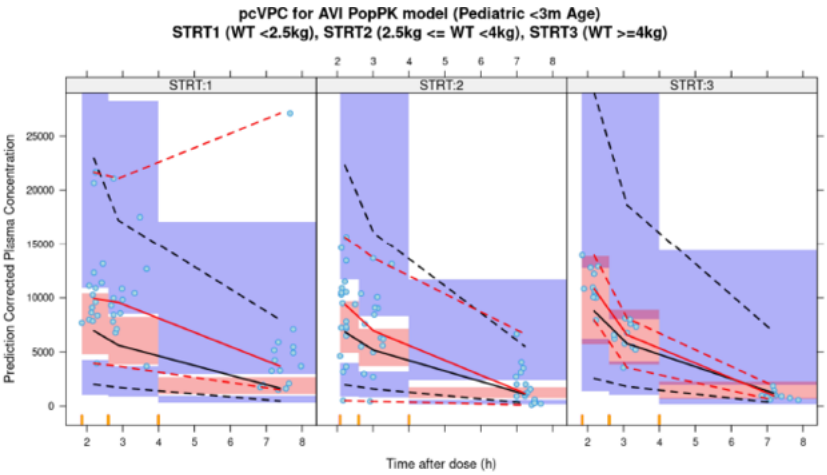
Figure 4. Predictive check (VPC) for CAZ final popPK model stratified by body weight (Response to 1st RSI, Figure 11)



Repository artifact ID FI-43304587.

Abbreviations: AVI = Avibactam, PopPK = population pharmacokinetics, Each symbol represents an individual PK observation. The solid red line connects the median observed concentrations while the solid black line is the simulated median. The shaded region represents the 5th to 95th prediction interval for the median, 5th and 95th percentile based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.

Figure 5. Predictive check (VPC) for AVI final popPK model by study cohort (PMAR-EQDD-C359m-sNDA-1155, Figure A5.10)



Repository artifact ID FI-56743260.

Red and black lines are the 5th, 50th (solid) and 95th percentile of observed and simulated data, respectively. Shadow areas are 95% CI for the 5th, 50th (red) and 95th percentile prediction intervals based on simulated data, blue dots correspond to prediction-corrected observations.

Figure 6. Predictive check (VPC) for AVI final popPK model stratified by body weight (Response to 1st RSI, Figure 5)

Model application

Individual predictions in study C3591024

Model-based individual predictions were used to estimate exposure parameters and the joint PTA for the subjects in study C3591024. For results, see section on Special populations.

Simulated drug exposure and joint PTA for neonates and infants <3 months with cUTI, cIAI or NP

Simulation scenarios for indications cUTI, cIAI and NP for which CAZ-AVI is approved in adults and paediatric patients >3 months old, were evaluated for each age group studied in Study C3591024. The indication-specific effect used in the simulations for subjects <3 months old was estimated based on subjects older than 3 months. It was assumed these effects can be extrapolated to the younger subjects. These indication effects were included in the simulations in addition to all other covariates effects present in the model for this specific age group (<3 months), under the assumption that the indication effect, is compatible with these covariate effects. It was further assumed that the demographic covariates of the overall population with these diseases was adequately represented by the virtual populations, and that the effect of WT in CL or Vc is adequately described by the equations used on the models.

CAZ-AVI concentrations versus time profiles after a 2-hour IV infusion, were simulated for each indication (cIAI, cUTI, HAP/VAP) using the final CAZ and AVI popPK models and the approved or proposed dose regimens for relevant age cohorts (Table 13). The simulations used a virtual population of 1000 subjects (whites, with normal renal clearance) for each age group and indication (cUTI, cIAI and NP).

Demographic covariates used included body weight, age, PMA (for subjects <2 years old), and nCrCL (for subjects ≥2 years old, nCrCL 80-150 mL/min/1.73m^2). Other popPK model covariates (ESRD, dialysis, presence of ventilator, and APACHE score) were not used in the simulations. An overview of simulations, including source of covariates, are given in Table 13.

For each age cohort, simulations were conducted with IIV (but not parameter uncertainty or residual variability). IIV was obtained non-parametrically through re-sampling of individual eta (η) estimates from those obtained for the subjects used in the final AVI and CAZ models for each relevant parameter. For each virtual subject, the etas for the AVI model parameters and for the CAZ model parameters were obtained from the same subject *(i.e.* eta-pairs). Thus, only etas from subjects present in both AVI and CAZ analyses were used, which preserved the inherent correlations between random effects for AVI and CAZ. Virtual subjects that had demographics coming from the ceftaroline dataset were assigned eta-pairs by sampling with replacement from the paediatric eta-pairs available from the subjects analysed in both CAZ and AVI popPK analyses. The same set of 1000 eta-pairs was used for the virtual population <2 years. These were obtained from sampling with replacement from the paediatric CAZ-AVI dataset, that included etas from all paediatric subjects present in both CAZ and AVI analysis and that had nCRCl>80 mL/kg/1.73m^2.

Shrinkage of the random effects has the potential to underestimate IIV. To mitigate this, the same approach used in previous analyses (CAZ-MS-PED-02) was used: The post-hoc random effect estimates (etas) were re-inflated before the simulation step was performed by dividing the post-hoc nonlinear mixed effects modelling (NONMEM) estimated η by 1 - (shrinkage/100).

Results from these simulations were compared to the results obtained for these same indications from simulations for adults and older children. Results are presented in section 5.3.4.

Table 12. Simulation scenarios by age group (PMAR-EQDD-C359m-sNDA-1155, Table 6)

Age [a]	C3591024 Age Cohort	CAZ:AVI Dose (mg/kg) [b]	Covariate Source	IIV source
26 - <37 w	3	20:5	Olsen	CAZ-AVI ped dataset[e]
0 - ≤ 4 w	2	20:5	CDC	CAZ-AVI ped dataset[e]
>4 w - <3 m	1	30:7.5	CDC	CAZ-AVI ped dataset[e]
3 - <6 m	NA	40:10	CDC	CAZ-AVI ped dataset[e]
6 - <12 m	NA	50:12.5	CDC	CAZ-AVI ped dataset[e]
12 - <24 m	NA	50:12.5	CDC	CAZ-AVI ped dataset[e]
2 - <6 y	NA	50:12.5	Internal Combined Dataset[c]	CAZ-AVI 2 - <6y and sampled from CAZ-AVI ped dataset[g] for Ceftaroline demograp
6 - <12 y	NA	50:12.5	Internal Combined Dataset [c]	CAZ-AVI 6 - <12y and sampled from CAZ-AVI ped dataset [g] for Ceftaroline demograp
12 - <18 y	NA	50:12.5	Internal Combined Dataset [c]	CAZ-AVI 12 - <18y and sampled from CAZ-AVI ped dataset [g] for Ceftaroline demograp
Adults	NA	2000:500[d]	Adult CAZ-AVI dataset (cUTI, cIAI, NP)[f]	Adult CAZ-AVI dataset (cUTI, cIAI, NP)[f]

[a]Age corresponds to gestational age for ages from 26 to <37 weeks (Cohort 3 in C3591024).
[b]Dose did not exceeded adult dose of 2000:500 mg.
[c]Internal Combined Dataset includes demographics from Internal Pfizer CAZ-AVI and Ceftaroline studies (total number of subjects with nCrCL ≥ 80 mL/min/1.73 m^2 = 294).
[d]Dose in mg for Adults
[e]1000 η-pairs from pediatric dataset <18 years old and nCrCL ≥ 80 mL/min/1.73 m^2 (eta.ped.master in R script)
[f]Adults with nCrCL ≥ 80 mL/min/1.73 m^2
[g]η-pairs from pediatric dataset <18 years old and nCrCL ≥ 80 mL/min/1.73 m^2

Abbreviations: AVI = Avibactam, CAZ = Ceftazidime, CDC = Centers for Disease Control and Prevention, w = weeks, m = months, y = years, h = hours.
For every simulation scenario infusion duration was 2 hours and dosing interval was every 8 hours.

Special populations

Children

Clinical study reports for PIP studies C3591024 and C3591025 have been provided. The former is relevant for the currently sought indication and is presented below.

Study C3591024

Title: A Phase 2a, 2 Part, Open label, non-randomised, multi-centre, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to gram negative pathogens requiring intravenous antibiotic treatment.

Objectives:

Part A: The primary objective was to characterise the PK of a single IV dose of CAZ-AVI in hospitalised neonates and infants from birth to <3 months. Secondary objectives included safety and tolerability.

Part B: Secondary objectives included evaluation of multiple IV dose PK of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.

Methodology:

An overview of the study design is given below and is further detailed in section 5.4. Blood samples for PK assessments (max 3 samples per patient and 0.3 mL/sample) were collected at 0-15 minutes after EoI, 30-90 min after EoI and 300-360 min after EoI on study day 1 (part A) or study day 2-14 (part B).

Table 13. Study C3591024 design (PMAR-EQDD-C359m-sNDA-1155, Table 1)

Cohort	Description	GA (w)	Age	CAZ:AVI Dose (mg/kg)	Part A	Part B
1	Term Infants[a]	>= 37	>28 days - < 3 m	30:7.5	n = 8	n = 8
2	Term Neonates	>= 37	birth - <= 28 days	20:5	n = 8	n = 8
3	Pre-term Neonates	26 - < 37	birth - <= 28 days	20:5	n = 8	n = 8

[a]Or pre-term infants with corrected age > 28 days to <3 months (limited to 3 in each part). Corrected age is the age of the infant from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age.

GA = Gestational Age (time elapsed between the first day of the last menstrual period and birth), w = weeks, m = months, n = number of subjects. Source: C3591024 CSR [4]

Part A. single dose. Part B: multiple doses (every 8h). Doses were infused over 120 minutes, and maximum total volume allowed was 2 mL/kg/dose.

Results:

Overall, 45 participants were included in the PK data analysis set (Table 15). Almost all patients provided PK data at all three scheduled sampling points (134 samples). The 30-90 min EoI sampling was not collected for one patient in part A cohort 2. For details on demographics etc, see section 5.4 (including Table 30).

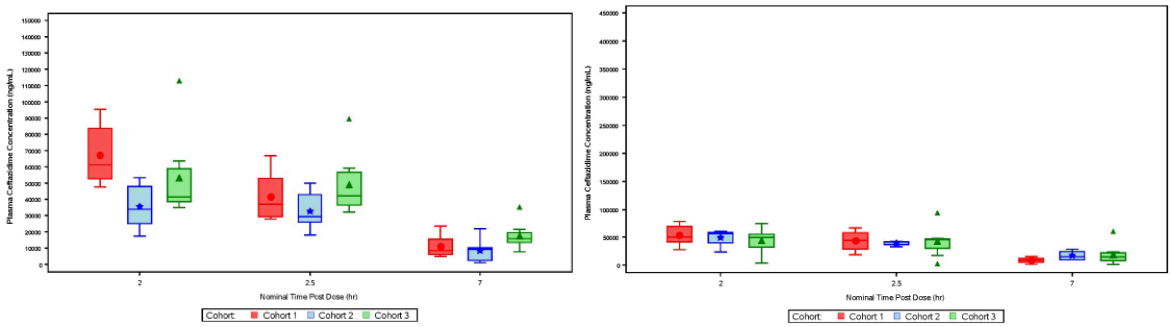
Table 14. Demographic characteristics for subjects in study C3591024 (PMAR-EQDD-C359m-sNDA-1155, Table 7)

Cohort	Part	Number subjects	Weight (kg)	Age from birth (weeks)	Gestational Age (weeks)	Sex		Race			
						Female	Male	White	Black	Asian	Other
1	A	9	4.9 (3.3-6.3)	8.7 (5-12.7)	39.1 (35.3-40.7)	5	4	6	1	2	0
1	B	8	4.3 (2.9-6)	6 (5-12.3)	38.7 (37.9-41)	3	5	5	2	1	0
2	A	8	3.5 (3-4)	3.2 (0.7-4)	39.2 (37.3-41.3)	4	4	5	1	2	0
2	B	4	2.7 (2.2-3.1)	1.9 (0.9-3.3)	37.7 (37-39.1)	0	4	4	0	0	0
3	A	8	1.7 (1.3-2.6)	2.4 (0.3-3.1)	31.1 (31-34.6)	6	2	7	0	0	1
3	B	8	1.8 (1.5-2.5)	2.3 (1.3-5.3)	33.6 (31.9-35.4)	6	2	8	0	0	0
All	All	45	3.1 (1.3-6.3)	3.3 (0.3-12.7)	37.9 (31-41.3)	24	21	35	4	5	1

Repository artifact ID FI-41900510. Line 1 substituted.

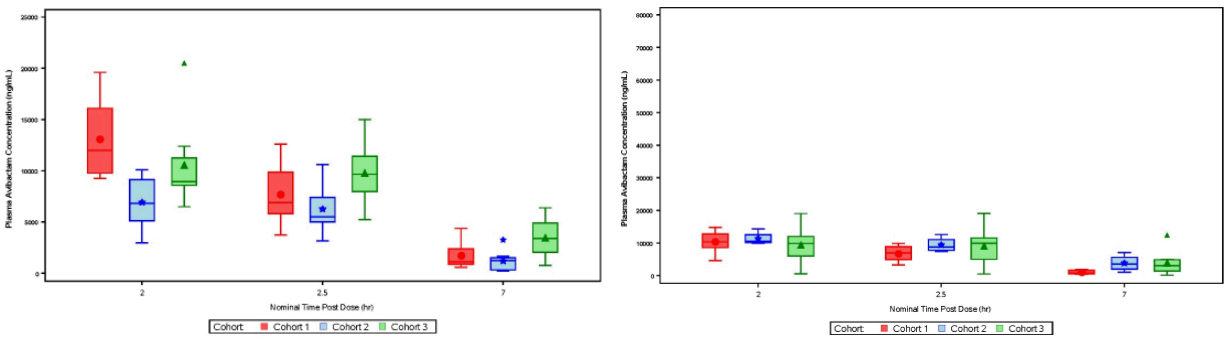
Median and range shown

Median plasma concentrations of CAZ and AVI were generally similar across part A and B and cohorts 1-3 (Figure 7 and Figure 8) although concentrations were slightly lower in Cohort 2 compared to Cohorts 1 and 3 (Part A). Inter-patient variability is explained by the wide window of PK sampling and by one medication error in part A cohort 1.



Part A cohort 1: deviation in the procedure for dilution of the stock volume. Patient excluded from plot.
Part B cohort 2: 105 minutes infusion rate instead of 120 min. Patient included in plot.

Figure 7. Box and whisker plots of plasma ceftazidime concentration versus nominal time post dose by cohort excluding patient with medication error (Part A left, Part B right) - PK Analysis Set (C3591024 CSR, Figures 9 and 16)



Part A cohort 1: deviation in the procedure for dilution of the stock volume. Patient excluded from plot.
Part B cohort 2: 105 minutes infusion rate instead of 120 min. Patient included in plot.

Figure 8. Box and whisker plots of plasma avibactam concentration versus nominal time post dose by cohort (Part A left, Part B right) - PK Analysis Set (C3591024 CSR, Figures 15 and 17)

Table 15. Summary of plasma concentrations (ng/mL) of ceftazidime by nominal time post dose – pharmacokinetic analysis set (Study C3591024 CSR, Table 28)

		Part A				Part B			
Time Point	Statistics	Cohort 1 (N=9)	Cohort 2 (N=8)	Cohort 3 (N=8)	Total (N=25)	Cohort 1 (N=8)	Cohort 2 (N=4)	Cohort 3 (N=8)	Total (N=20)
2H	n	9	8	8	25	8	4	8	20
	Mean (SD)	104544.4 (113161.34)	35537.5 (13473.88)	53212.5 (25972.32)	66036.0 (73750.58)	52950.0 (17565.47)	48625.0 (17010.46)	43711.3 (22229.93)	48389.5 (18958.08)
	Median (Min, Max)	64000.0 (47700, 403000)	33900.0 (17300, 53300)	41350.0 (35000, 113000)	50700.0 (17300, 403000)	49650.0 (27500, 77600)	55600.0 (23300, 60000)	49300.0 (3790, 73800)	51200.0 (3790, 77600)
	(Q1, Q3)	(54600, 84700)	(25100, 47850)	(38700, 58800)	(37200, 63600)	(41100, 68500)	(39400, 57850)	(32000, 54750)	(41100, 58650)
	CV(%)	108.24	37.91	48.81	111.68	33.17	34.98	50.86	39.18
	Geo. Mean	79877.7	33071.0	49270.8	51609.0	50256.6	45594.6	33808.7	42060.2
2H 30 MIN	n	9	7	8	24	8	4	8	20
	Mean (SD)	76822.2 (106423.76)	32571.4 (10842.00)	49012.5 (18832.45)	54645.8 (66557.27)	43037.5 (17433.21)	39000.0 (4415.88)	42465.0 (26800.19)	42001.0 (19547.53)
	Median (Min, Max)	41700.0 (27900, 358000)	29400.0 (18100, 50000)	42150.0 (32200, 89500)	38450.0 (18100, 358000)	43900.0 (18400, 66000)	40950.0 (32400, 41700)	45150.0 (2320, 94600)	42000.0 (2320, 94600)
	(Q1, Q3)	(30700, 62800)	(26000, 42900)	(36450, 56600)	(30050, 52000)	(28500, 57550)	(36600, 41400)	(29650, 46600)	(34500, 46650)
	CV(%)	138.53	33.29	38.42	121.80	40.51	11.32	63.11	46.54
	Geo. Mean	50399.8	31041.0	46431.6	42575.8	39365.8	38796.8	30235.7	35319.5
7H	n	9	8	8	25	8	4	8	20
	Mean (SD)	15635.6 (15243.22)	8305.0 (6728.50)	17608.8 (8165.42)	13921.2 (11236.18)	8323.8 (4805.65)	16735.0 (9070.87)	18658.4 (18268.92)	14139.9 (12989.20)
	Median (Min, Max)	8960.0 (4910, 52100)	9170.0 (1040, 21900)	15800.0 (7770, 35300)	9810.0 (1040, 52100)	8480.0 (1300, 15000)	14710.0 (9420, 28100)	14400.0 (967, 59800)	9810.0 (967, 59800)
	(Q1, Q3)	(6550, 21200)	(2385, 10195)	(13550, 19550)	(7770, 17600)	(4815, 11850)	(9420, 24050)	(7850, 22000)	(7890, 19300)
	CV(%)	97.49	81.02	46.37	80.71	57.73	54.20	97.91	91.86
	Geo. Mean	11423.9	5706.2	16193.7	10229.1	6455.6	14943.7	11576.9	9645.0

Part A: After a single dose of CAZ-AVI infusion on Day 1, Part B: After at least 3 consecutive doses of CAZ-AVI infusion from Day 2 to Day 14, Q8H.
Cohort 1 (30 mg/kg CAZ/7.5 mg/kg AVI): > 28 days to < 3 months; Cohort 2 (20 mg/kg CAZ/5.0 mg/kg AVI): Full Term to <= 28 days; Cohort 3 (20 mg/kg CAZ/5.0 mg/kg AVI): Premature to <= 28 days.
2H: Within 15 minutes after stopping CAZ-AVI infusion.
2H30Min: Between 30 minutes and 90 minutes after stopping CAZ-AVI infusion.
7H: Between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.
N = Number of participants in each cohort group. n = Number of observations (non-missing PK concentrations).
PFIZER CONFIDENTIAL SDTM Creation: 24MAR2023 (01:10) Source Data: adpc Table Generation: 06APR2023 (08:11)
(Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_CSR/adpc_s101
Table 14.4.4.1 Ceftazidime-Avibactam is for Pfizer internal use.

When excluding the patient with medication error, the geometric mean (CV%) concentrations (2H, 2H30min, 7H) in part A cohort 1 were 65247.7 ng/mL (26.57%), 39445.4 ng/mL (37.00%) and 9450.1 ng/mL (65.01%), respectively.

Table 16. Summary of Plasma Concentrations (ng/mL) of Avibactam by Nominal Time Post Dose – Pharmacokinetic Analysis Set (Study C3591024 CSR, Table 29

		Part A				Part B			
Time Point	Statistics	Cohort 1 (N=9)	Cohort 2 (N=8)	Cohort 3 (N=8)	Total (N=25)	Cohort 1 (N=8)	Cohort 2 (N=4)	Cohort 3 (N=8)	Total (N=20)
2H	n	9	8	8	25	8	4	8	20
	Mean (SD)	19210.0 (18747.86)	6910.0 (2553.50)	10570.0 (4342.69)	12509.2 (12373.55)	10340.0 (3262.63)	11330.0 (2012.53)	9410.1 (5551.00)	10166.1 (4056.13)
	Median (Min, Max)	12400.0 (9250, 68300)	6825.0 (2970, 10100)	8955.0 (6500, 20500)	9410.0 (2970, 68300)	10360.0 (4570, 14800)	10550.0 (9920, 14300)	9850.0 (541, 19000)	10350.0 (541, 19000)
	(Q1, Q3)	(9990, 16700)	(5135, 9145)	(8575, 11250)	(8530, 12400)	(8565, 12750)	(10110, 12550)	(6020, 12000)	(8565, 12750)
	CV(%)	97.59	36.95	41.09	98.92	31.55	17.76	58.99	39.90
	Geo. Mean	15226.2	6419.9	9979.1	10089.1	9799.6	11208.0	6828.7	8712.1
2H 30 MIN	n	9	7	8	24	8	4	8	20
	Mean (SD)	13250.0 (16906.67)	6251.4 (2363.99)	9788.8 (2956.39)	10055.0 (10581.17)	6825.0 (2386.26)	9380.0 (2317.14)	9064.0 (5694.05)	8231.6 (4036.47)
	Median (Min, Max)	7350.0 (3740, 57700)	5510.0 (3150, 10600)	9660.0 (5250, 15000)	7640.0 (3150, 57700)	6940.0 (3260, 9870)	8765.0 (7390, 12600)	9895.0 (482, 19100)	8420.0 (482, 19100)
	(Q1, Q3)	(6450, 11500)	(5010, 7410)	(7970, 11400)	(5380, 10650)	(4935, 8860)	(7720, 11040)	(5020, 11550)	(5725, 9985)
	CV(%)	127.60	37.82	30.20	105.23	34.96	24.70	62.82	49.04
	Geo. Mean	9058.8	5883.8	9386.1	8082.5	6416.1	9181.3	6362.6	6869.7
7H	n	9	8	8	25	8	4	8	20
	Mean (SD)	2058.2 (1670.32)	1190.4 (998.69)	3475.6 (1931.10)	2234.1 (1788.04)	1025.3 (592.83)	3787.5 (2533.46)	3890.5 (3867.47)	2723.8 (2946.12)
	Median (Min, Max)	1240.0 (568, 4810)	1220.0 (212, 3250)	3385.0 (765, 6380)	1330.0 (212, 6380)	820.0 (351, 1880)	3535.0 (1010, 7070)	3025.0 (144, 12400)	1740.0 (144, 12400)
	(Q1, Q3)	(920, 3470)	(321, 1490)	(2050, 4895)	(920, 3470)	(586, 1580)	(1990, 5585)	(1365, 4900)	(820, 4035)
	CV(%)	81.15	83.90	55.56	80.03	57.82	66.89	99.41	108.16
	Geo. Mean	1550.3	825.4	2923.1	1552.3	877.2	3053.7	2237.8	1637.3

Part A: After a single dose of CAZ-AVI infusion on Day 1, Part B: After at least 3 consecutive doses of CAZ-AVI infusion from Day 2 to Day 14, Q8H.
Cohort 1 (30 mg/kg CAZ/7.5 mg/kg AVI): > 28 days to < 3 months; Cohort 2 (20 mg/kg CAZ/5.0 mg/kg AVI): Full Term to <= 28 days; Cohort 3 (20 mg/kg CAZ/5.0 mg/kg AVI): Premature to <= 28 days.
2H: Within 15 minutes after stopping CAZ-AVI infusion.
2H30Min: Between 30 minutes and 90 minutes after stopping CAZ-AVI infusion.
7H: Between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.
N = Number of participants in each cohort group. n = Number of observations (non-missing PK concentrations).
PFIZER CONFIDENTIAL SDTM Creation: 24MAR2023 (01:10) Source Data: adpc Table Generation: 06APR2023 (08:11)
(Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_CSR/adpc_s101a
Table 14.4.4.2 Ceftazidime-Avibactam is for Pfizer internal use.

When excluding the patient with medication error, the geometric mean (CV%) concentrations (2H, 2H30min, 7H) in part A cohort 1 were 12621.5 ng/mL (29.03%). 7187.2 ng/mL (39.27%) and 1345.7 ng/mL (81.91%), respectively.

PopPK

Individual model-predicted exposures for the 44 paediatric subjects in Study C3591024 were calculated in the present analysis using the EBEs reported by NONMEM (PMAR-EQDD-C359m-sNDA-1155), see the Table below.

Table 17. Geometric mean (CV%) CAZ-AVI PK parameters – study C3591024 (M2.7.2, Table 2)

Parameter	Cohort 1	Cohort 2	Cohort 3
N	16	12	16
Avibactam			
$AUCss_{0-24}$ (ug/mL•hr)	115 (35.8)	94.1 (62)	119 (99.6)
$C_{min,ss}$ (ug/mL)	0.75 (77.4)	1.05 (138)	2.07 (142)
$C_{max,ss}$ (ug/mL)	12.1 (29.8)	8.4 (48)	9.18 (95.7)
Ceftazidime			
$AUCss_{0-24}$ (ug/mL•hr)	626 (23.8)	505 (30)	653 (35.7)
$C_{min,ss}$ (ug/mL)	5.65 (74.8)	6.78 (73.4)	11.6 (83.7)
$C_{max,ss}$ (ug/mL)	61.4 (14)	43.6 (18)	50.4 (22.1)
Ceftazidime/Avibactam			
jPTA at T4 (%)	100	100	94

Abbreviations: AVI = Avibactam; CAZ = Ceftazidime; $AUCss_{0-24}$ = area under the plasma concentration-time curve over 24 hours at steady state; $C_{min,ss}$ = minimum concentration at steady state; $C_{max,ss}$ = maximum concentration at steady state; jPTA = joint probability of target attainment; MIC = minimum inhibitory concentration; T4 = 50% $fT > MIC$ at MIC 8 mg/L for CAZ and 50% $fT > 1$ mg/L for AVI
One participant from Part A, Cohort 1 was excluded due to medication error.
Repository artifact ID FI-41843685. Line 1 substituted.
Note: Values are the geometric mean (% CV); $AUCss_{0-24}$ is obtained by multiplying $AUCss_{0-8}$ by 3. C_{maxss} is obtained at the end of infusion. $Cmin_{ss}$ is obtained 8 hours after the start of infusion.
Cross reference: PMAR-EQDD-C359m-sNDA-1155 Table 12

Based on the model simulated exposures in Table 20, Table 21 and Table 22, the following relative exposures are predicted in paediatric patients <3 months of age compared to adults:

Table 18. Simulated geometric mean exposure metrics in (pre)term neonates and infants <3 months with the proposed posology as percent of corresponding adult simulated exposure metrics following 2/0.5g CAZ-AVI for the indications cUTI, cIAI and HAP/VAP (based on PMAR-EQDD-C359m-sNDA-1155, Tables 13-15, and Tables 1-3 in the response to 2nd RSI)

Age groups	Dose (interval)	Ceftazidime (% of adult values)			Avibactam (% of adult values)		
		Cmax,ss	Cmin,ss	AUCss,0-24	Cmax,ss	Cmin,ss	AUCss,0-24
cIAI							
- 26-<31w GA	20/5 (q12h)	75	259	108	67	166	84
- 26-<31w GA	20/5 q8h	94	504	162	80	379	126
- 31-<37w GA	20/5 (q8h)	70	268	106	68	247	98
- 0-≤4w	20/5 (q8h)	57	151	76	60	160	78
- >4w-<3m	30/7.5 (q8h)	73	128	87	80	156	96
cUTI							
- 26-<31w GA	20/5 (q12h)	74	222	104	65	136	78
- 26-<31w GA	20/5 (q8h)	94	420	157	79	299	118
- 31-<37w GA	20/5 (q8h)	70	229	103	67	198	92
- 0-≤4w	20/5 (q8h)	57	133	74	58	131	73
- >4w-<3m	30/7.5 (q8h)	72	117	85	78	132	90
NP (HAP/VAP)							
- 26-<31w GA	20/5 (q12h)	76	250	112	70	131	81
- 26-<31w GA	20/5 (q8h)	99	465	169	81	334	121
- 31-<37w GA	20/5 (q8h)	73	258	111	70	208	94
- 0-≤4w	20/5 (q8h)	58	153	79	61	128	75
- >4w-<3m	30/7.5 q8h	74	137	91	83	118	93

cIAI=complicated intra-abdominal infections, cUTI=complicated urinary tract infections, NP=nosocomial pneumonia.

2.3.3. Pharmacodynamics

Susceptibility of Paediatric Isolates to CAZ-AVI

Details regarding the activity of CAZ-AVI against isolates from IAI and UTI collected from children in the ATLAS 2022 European Report have been previously presented (paediatric cIAI and cUTI MAA submission). Isolates collected during 2019 from hospitalised patients with pneumonia (children <18 years) were presented in a previous report (ATLAS 2022 European Report) and in the paediatric HAP/VAP Type II variation submission (EMEA/H/C/004027/II/0015).

As part of the ATLAS surveillance program, isolates collected during 2021 from hospitalised paediatric patients ≤1 year old with BSI, pneumonia, UTI, and IAI were compared to isolates from paediatric patients >1 year old for their susceptibility to CAZ-AVI. The clinical isolates were collected from medical centres geographically distributed across Europe and were submitted to a central laboratory (IHMA, Schaumburg, IL USA) for identification confirmation and susceptibility testing in accordance with Clinical Laboratory Standards Institute Guidelines.

Analysis of surveillance isolates from children ≤1 year old hospitalised with BSI, pneumonia, UTI, or IAI showed a similar prevalence of causative organisms when compared with isolates from patients >1 year old. Among the Enterobacterales, E. coli was the most prevalent pathogen accounting for 31.27% of pathogens from children ≤1 year-old and 29.3% from patients >1 year old. The second most prevalent pathogen was K. pneumoniae among patients <1 year old at 24.4% and 29.0% from the >1 year old cohort. Of the total 3621 P. aeruginosa isolates, 77 (2.13%) were from children ≤1 year-old while 3544 isolates (97.87%) were among patients >1 year old. Furthermore, the minimum concentrations to inhibit 90% of strain (MIC50/90s) were the same for organisms from children ≤1 year old 0.12 - 0.5 mg/L for Enterobacterales. For P. aeruginosa, the MIC50/90s for organisms from patients <1 year old was 2 and 128 mg/L respectively while the MIC50/90 was 2 and 8 mg/L for organisms from patients >1 year old.

In summary, surveillance data has shown that contemporary isolates of gram-negative bacteria from paediatric patients ≤1 year old exhibit similar susceptibility rates to CAZ-AVI when compared with isolates obtained from patients >1 year old. The PK/PD target attainment analyses for paediatric patients ≤1 year old therefore focused on the same MIC as in those >1 year old (8 mg/L) for assessing the adequacy of dose regimens.

Clinical Studies in paediatric patients with cIAI, cUTI and HAP/VAP

Clinical and microbiological outcomes in paediatric patients with cIAI (study C3591004) and paediatric patients with cUTI (study C3591005) have been summarised in previous submissions. Paediatric patients with HAP/VAP have not been evaluated because Study C3591025 was a single-dose, PK study. A meaningful interpretation of the clinical and microbiological response in study C3591024 was difficult due to the low number of participants, especially those with microbiologically confirmed infection.

2.3.4. PK/PD modelling

The aim of the dose selection would be to achieve comparable exposures to those calculated for the studies in adult patients with HAP/VAP, cUTI, and cIAI. The relevant PK/PD indices for CAZ and AVI, and the magnitudes of these indices related to the efficacy of CAZ-AVI, were described in the original MAA. Because there are no expected differences in the mechanism of action of CAZ-AVI based on age as both CAZ and AVI exert their effects by acting on the causative pathogen, and the gram-negative

causative pathogens are similar in adults and children, the same joint PK/PD targets would be relevant to dose setting in paediatric patients.

As explained above (section 5.3.2), the final PopPK models for CAZ and AVI were used to conduct simulations to support paediatric dose recommendations in patients from birth to <3 months old with cIAI, NP and cUTI using the dose regimens administered in study C3591024 and using neonates/infants covariate on Vc with normal renal function and indication-specific effects from older populations. Simulations were also conducted for adult and paediatric patients for the approved CAZ-AVI doses for comparison with predicted exposures in neonates and infants.

PTA was determined as the percent of 1000 patients meeting PK/PD targets for both ceftazidime and avibactam. The target corresponds to the target T4, (previously defined in CAZ-MS-PED-02 report) of ≥50% fT > MIC of 8 mg/L for CAZ (in the presence of AVI) and a ≥50% fT > CT of 1.0 mg/L for AVI. Free plasma concentration of CAZ and AVI were calculated using unbound percentages of 85% and 92%, respectively.

Dose for paediatric patients with normal (for age) renal function

Predicted exposures (Cmax,ss, Cmin,ss and AUCss,0-24) for CAZ and AVI, as well as joint PTA, in adult and paediatric patients, including those from birth to < 3 months of age, from the simulations are shown in the Tables below.

For CAZ, geom. mean Cmax,ss, Cmin,ss and AUCss,0-24 in paediatric patients <3 months old were 57%-99%, 117%-504%, and from 74%-169%, respectively, of corresponding adult values. For AVI, geom. mean Cmax,ss, Cmin,ss and AUCss,0-24 were 58%-83%, 118%-379%, and 73%-126%, respectively, of adult values (Table 19). Overall, the predicted CAZ and AVI exposures in paediatric patients <3 months old demonstrate that the administered dose regimens for each age group result in exposures that are similar to those in adult patients. Therefore, the large safety database for CAZ-AVI in adults and paediatric patients from completed studies in the CAZAVI paediatric development program can be extrapolated to paediatric patients from birth to <3 months old. The predicted exposures in paediatric patients < 3 months old in the present analysis (PMAR-EQDD-C359m-sNDA-1155) were similar to those in paediatric patients with cUTI, cIAI, and HAP/VAP in the previous analysis which was used to support dose selection for Study C3591024 (CAZ-MS-PED-02).

The proposed doses in paediatric patients (birth to <3 months of age) are predicted to result in >90% PTA for all age cohorts and infections at an MIC of 8 mg/L based on the model simulations. For these age groups, the PTA was slightly lower with cIAI indication, which also was the case for the older age groups. The simulation results indicated that cIAI was the indication associated with lower CAZ exposure in general. CAZ exposure and PTA were slightly lower in the current model compared to CAZ-MS-PED-02 in older paediatric groups, mainly 1 to 6 years of age, due to the change in the Emax function parameter estimates describing the weight effect on CL (PMAR-EQDD-C359m-sNDA-1155).

Table 19. Geometric mean ceftazidime and avibactam Cmax,ss, Cmin,ss and AUCss,0-24, and joint PTA in 1000 simulated patients with normal renal function with cUTI (based on Table 1 in the response to 2nd RSI)

Age Group[b]	Dose[c] (CAZ-AVI)	Freq[d]	CAZ $C_{max,ss}$ [mg/L]	CAZ $C_{min,ss}$ [mg/L]	CAZ $AUC_{ss,0-24}$ [mg.h/L]	AVI $C_{max,ss}$ [mg/L]	AVI $C_{min,ss}$ [mg/L]	AVI $AUC_{ss,0-24}$ [mg.h/L]	jPTA [%]
26 - <31 weeks	20/5	12 hours	55 (25.8)	20.5 (70.5)	860 (39)	6.55 (52.5)	1.5 (88)	87.8 (48.8)	98.8
26 - <31 weeks	20/5	8 hours	70.6 (29.6)	38.7 (55.8)	1290 (39)	8.02 (49.9)	3.29 (64.1)	132 (48.8)	99.1
31 - <37 weeks	20/5	8 hours	52.3 (26)	21.1 (63.2)	847 (37.3)	6.8 (50.6)	2.18 (70.9)	103 (48.5)	99
0 - ≤4 weeks	20/5	8 hours	42.1 (20.9)	12.3 (65.7)	609 (31.6)	5.9 (50.9)	1.44 (78.7)	82.1 (47.1)	98.5
>4weeks - <3 months	30/7.5	8 hours	53.9 (20.3)	10.8 (82.5)	696 (31.8)	7.88 (51.4)	1.45 (92.8)	101 (46.9)	98.6
3 - <6 months	40/10	8 hours	76.1 (20.4)	4.37 (149)	736 (32.2)	11.6 (52.5)	0.649 (141)	114 (47)	95.2
6 - <12 months	50/12.5	8 hours	85.6 (20.5)	3.05 (172)	763 (31.4)	13.4 (52.1)	0.527 (160)	124 (46.6)	93.2
1 - <2 years	50/12.5	8 hours	81.3 (20.6)	2.28 (185)	697 (31.2)	13 (51.8)	0.444 (168)	118 (46.3)	89.3
2 - <6 years	50/12.5	8 hours	83.5 (22.3)	2.41 (189)	714 (32.5)	12.9 (52.5)	0.4 (169)	114 (46.2)	88.8
6 - <12 years	50/12.5	8 hours	91.6 (20.5)	5.02 (143)	862 (32.3)	13.8 (44.3)	0.752 (128)	133 (39.7)	96.2
12 - <18 years	50/12.5	8 hours	79.6 (24.2)	6.78 (103)	804 (33.2)	11.3 (68.5)	0.871 (90.1)	115 (53.9)	98.5
Adults	2000/500	8 hours	74.4 (30.9)	9.22 (139)	823 (48)	10.1 (60)	1.1 (150)	112 (65.6)	96.9

a. Target T4 was defined to be 50 % of time of a dosing interval with a free drug concentration above the minimum inhibitory concentration (%fT > MIC) of 8 mg/L for CAZ and 50 % of time of a dosing interval with a free drug concentration above concentration threshold (%fT > CT) of 1 mg/L for AVI
b. Age group corresponds to post-natal age, except for 26 - <31 weeks and 31 - <37 weeks where it corresponds to GA.
c. Dose corresponds to mg/kg, except for the adults where dose corresponds to a fixed dose in mg, infused over 2 hours. Pediatric maximum doses did not exceed adult dose.
d. Freq corresponds to the dosing interval, either every 12 hours or every 8 hours.

Table 20. Geometric mean ceftazidime and avibactam Cmax,ss, Cmin,ss and AUCss,0-24, and Joint PTA in 1000 simulated patients with normal renal function with cIAI (based on Table 2 in the response to 2nd RSI)

Age Group[b]	Dose[c] (CAZ-AVI)	Freq[d]	CAZ $C_{max,ss}$ [mg/L]	CAZ $C_{min,ss}$ [mg/L]	CAZ $AUC_{ss,0-24}$ [mg.h/L]	AVI $C_{max,ss}$ [mg/L]	AVI $C_{min,ss}$ [mg/L]	AVI $AUC_{ss,0-24}$ [mg.h/L]	jPTA [%]
26 - <31 weeks	20/5	12 hours	43.3 (25.1)	14.4 (76.2)	649 (39)	6.86 (53.1)	1.36 (93.2)	87.8 (48.8)	98
26 - <31 weeks	20/5	8 hours	54.8 (28.9)	28 (58.5)	974 (39)	8.27 (50.3)	3.1 (65.8)	132 (48.8)	99.1
31 - <37 weeks	20/5	8 hours	40.9 (25.4)	14.9 (67.7)	640 (37.3)	7.05 (51.1)	2.02 (73.6)	103 (48.5)	98.6
0 - ≤4 weeks	20/5	8 hours	33.2 (20.7)	8.38 (72.1)	459 (31.6)	6.14 (51.4)	1.31 (82.4)	82.1 (47.1)	95.2
>4w - <3 months	30/7.5	8 hours	42.6 (20.3)	7.1 (92.7)	525 (31.8)	8.23 (51.8)	1.28 (98.1)	101 (46.9)	96.4
3 - <6 months	40/10	8 hours	60.7 (20.8)	2.41 (181)	556 (32.2)	12.1 (52.5)	0.543 (145)	114 (47)	87.3
6 - <12 months	50/12.5	8 hours	68.1 (21)	1.59 (211)	576 (31.4)	13.9 (52.1)	0.432 (163)	124 (46.6)	81.9
1 - <2 years	50/12.5	8 hours	64.5 (21.2)	1.17 (228)	526 (31.2)	13.5 (51.7)	0.363 (170)	118 (46.3)	72.6
2 - <6 years	50/12.5	8 hours	66.2 (22.8)	1.24 (233)	539 (32.5)	13.4 (52.2)	0.326 (171)	114 (46.2)	73.3
6 - <12 years	50/12.5	8 hours	72.7 (20.8)	2.82 (170)	651 (32.3)	14.4 (44.1)	0.635 (131)	133 (39.7)	89.8
12 - <18 years	50/12.5	8 hours	63.3 (24.3)	4.02 (119)	607 (33.2)	11.7 (68.6)	0.764 (89.5)	115 (53.9)	95.3
Adults	2000/500	8 hours	58.1 (31.2)	5.56 (116)	601 (42.7)	10.3 (65.1)	0.818 (110)	105 (61.1)	94.8

a. Target T4 was defined to be 50%fT > MIC of 8 mg/L for CAZ and 50%fT > CT of 1 mg/L for AVI
b. Age group corresponds to post-natal age, except for 26 - <31 weeks and 31 - <37 weeks where it corresponds to GA.
c. Dose corresponds to mg/kg, except for the adults where dose corresponds to a fixed dose in mg, infused over 2 hours. Pediatric maximum doses did not exceed adult dose.
d. Freq corresponds to the dosing interval, either every 12 hours or every 8 hours.

Table 21. Geometric mean ceftazidime and avibactam Cmax,ss, Cmin,ss and AUCss,0-24, and joint PTA in 1000 simulated patients with normal renal function with NP (based on Table 2 in the response to 2nd RSI)

Age Group[b]	Dose[c] (CAZ-AVI)	Freq[d]	CAZ $C_{max,ss}$ [mg/L]	CAZ $C_{min,ss}$ [mg/L]	CAZ $AUC_{ss,0-24}$ [mg.h/L]	AVI $C_{max,ss}$ [mg/L]	AVI $C_{min,ss}$ [mg/L]	AVI $AUC_{ss,0-24}$ [mg.h/L]	jPTA [%]
26 - <31 weeks	20/5	12 hours	48.8 (26.4)	19.5 (67.7)	784 (39)	7.66 (54.4)	1.05 (106)	87.8 (48.8)	98.1
26 - <31 weeks	20/5	8 hours	63.2 (30.1)	36.2 (54.4)	1180 (39)	8.94 (51.3)	2.67 (70)	132 (48.8)	99.1
31 - <37 weeks	20/5	8 hours	46.5 (26.4)	20.1 (61)	773 (37.3)	7.7 (52)	1.66 (79.9)	103 (48.5)	98.9
0 - ≤4 weeks	20/5	8 hours	37.3 (21.2)	11.9 (62.8)	555 (31.6)	6.76 (52.3)	1.02 (90.7)	82.1 (47.1)	97.8
>4w - <3 months	30/7.5	8 hours	47.5 (20.5)	10.7 (78.2)	635 (31.8)	9.1 (52.5)	0.946 (110)	101 (46.9)	98.6
3 - <6 months	40/10	8 hours	67.6 (20.4)	4.4 (144)	672 (32.2)	13.2 (52.5)	0.353 (147)	114 (47)	94.7
6 - <12 months	50/12.5	8 hours	76.1 (20.5)	3.09 (168)	696 (31.4)	15.1 (52)	0.27 (162)	124 (46.6)	92.8
1 - <2 years	50/12.5	8 hours	72.4 (20.5)	2.31 (182)	636 (31.2)	14.6 (51.5)	0.226 (167)	118 (46.3)	88
2 - <6 years	50/12.5	8 hours	74.3 (22.2)	2.43 (183)	652 (32.5)	14.5 (51.7)	0.202 (169)	114 (46.2)	87
6 - <12 years	50/12.5	8 hours	81.2 (20.7)	5.01 (140)	787 (32.3)	15.7 (43.5)	0.426 (133)	133 (39.7)	96
12 - <18 years	50/12.5	8 hours	70.4 (24.3)	6.68 (101)	733 (33.2)	12.7 (68.4)	0.563 (84.5)	115 (53.9)	98
Adults	2000/500	8 hours	63.8 (27.4)	7.79 (96.7)	699 (37.9)	11 (76.4)	0.8 (97.6)	109 (68.9)	96.3

a. Target T4 was defined to be 50% $fT > MIC$ of 8 mg/L for CAZ and 50% $fT > CT$ of 1 mg/L for AVI
b. Age group corresponds to post-natal age, except for 26 - <31 weeks and 31 - <37 weeks where it corresponds to GA.
c. Dose corresponds to mg/kg, except for the adults where dose corresponds to a fixed dose in mg, infused over 2 hours. Pediatric maximum doses did not exceed adult dose.
d. Freq corresponds to the dosing interval, either every 12 hours or every 8 hours.

Proposed posology in paediatric patients <3 months of age

Based on results from the updated population PK/PD target attainment analysis, the following dose regimens are recommended for patients from birth to <3 months old with cIAI, cUTI, HAP/VAP, or infections due to aerobic Gram-negative organisms in patients with limited treatment options, and with normal renal function:

- Preterm (<37 weeks GA) neonates 26-<31 weeks PMA: 20 mg/kg ceftazidime and 5 mg/kg avibactam q12h as a 2-hour infusion
- Preterm neonates ≥31 to ≤44 weeks PMA and full term neonates ≤28 days: 20 mg/kg ceftazidime and 5 mg/kg avibactam q8h as a 2-hour infusion
- Term infants >28 days to <3 months and preterm infants (>44 weeks PMA to <53 weeks PMA): 30 mg/kg ceftazidime and 7.5 mg/kg avibactam q8h as a 2-hour infusion

The age cut offs for the posology recommendations reflect the cohorts 1-3 in study C3591024.

Though preterm infants from 26 weeks gestation were eligible for enrolment in Study C3591024, the earliest gestation neonates enrolled in the study were 31 weeks. Per the protocol, Study C3591024 allowed preterm infants with a corrected age[1] >28 days (>44 weeks PMA) and <3 months (<53 weeks PMA) to be enrolled along with their full-term counterparts. The simulation results for full term infants older than 28 days of age could be applied to preterm infants with equivalent corrected age or postmenstrual age. The proposed posology recommendation is presented in Table 4.

[1] *Corrected age is the age of the infant from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age (weeks) = chronological age in weeks – (40 – gestational age in weeks).

2.3.5. Discussion on clinical pharmacology

With this application, the MAH is extending all four indications (cUTI, cIAI, NP (HAP/VAP) and aerobic Gram-negative infections with limited treatment options) in adults and children ≥3 months, to preterm and term neonates and children <3 months of age.

A phase I study C3591024 investigating ceftazidime (CAZ) and avibactam (AVI) PK in 45 paediatric patients <3 months with suspected or confirmed infection, population pharmacokinetic (popPK) models incorporating all available paediatric PK data, as well as PKPD target attainment analyses have been submitted to support the proposed posology recommendations.

In accordance with relevant guidance (EMA/CHMP/187859/2017), the assessment of this extension of indication application is based on extrapolation with a supportive PK bridge under the assumption that the pharmacokinetics are similar across the currently sought indications and the studied infections in the paediatric population <3 months. Extrapolation of efficacy in adults to the paediatric population could be made provided similar exposures to those in adults, and provided that there are no additional safety concerns in the new population (see section 4.5. Clinical safety). Thus, the aim of the dose selection was to achieve comparable exposures to those calculated for the Phase III studies in adult patients with cIAI, cUTI and HAP/VAP. The PK bridge is informed by observed CAZ and AVI concentration data from study C3591024, and PKPD modelling and simulation exercises.

Bioanalytical methods

The pre-study and in-run validation of the analytical method employed in study C3591024 is satisfactory, and in accordance with the EMA Guideline on bioanalytical method validation. Failed analytical runs and some events of carry-over have been commented on. The MAH's position that these events do not compromise the results and the conclusion of the study is endorsed.

Evaluation and qualification of popPK models

The CAZ and AVI popPK and PKPD (joint target attainment) models support the proposed dose regimens in paediatric patients from birth to 3 months of age and are of high regulatory impact. In this section, an assessment of the popPK model evaluation and qualification is given.

In the current application, the previous CAZ and AVI popPK models (CAZ-MS-PED-02) have been updated with paediatric PK data from the phase II study C3591024 which included (pre)term neonates and infants <3 months of age. The dataset was also updated with four patients from study C3591025 (HAP/VAP in patients ≥3 months to <18 years). The latter study was early terminated due to slow enrolment.

A significant number of subjects have been included in each age cohort in the pivotal PK study C3591024 in view of the recognised complexity of investigating medicinal products in the neonatal population, which is acknowledged. Also, it appears that three PK samples were obtained as planned in all but one subject. The age and weight range across cohorts appear relevant for the target population and for the objectives of the popPK analysis. There were no subjects with ESRD or on dialysis. Moderate or severe renal impairment defined as serum creatinine ≥2 times the upper limit of normal (ULN) for age OR urine output <0.5 mL/kg/h (measured over at least 8 hours) OR requirement for dialysis, was an exclusion criterion in study C3591024. None of the included paediatric patients had confirmed infections relevant for the sought indications.

The parameters in the final AVI and CAZ popPK models were overall similar to the those previously reported (CAZ-MS-PED-02), but some differences were noted. The only modification made to the structural models following inclusion of PK data from studies C3591024 and C3591025 is the categorical covariate (neonates/infants <3months) on Vc. As discussed by the MAH, this effect could

represent physiological differences in early stages of life, or weight effects not adequately described with the current functions in the model.

Patient population (cIAI/±NP and cUTI) was identified in previous modelling investigations as a significant covariate impacting CL and/or Vc of CAZ and AVI. Allometric scaling of PK parameters (AVI CL, CAZ-AVI V and Q) and a renal maturation function on CL in subjects <2 years (Rhodin et al. 2009) have been used, which is supported. An Emax model was used to describe impact of body weight on CAZ CL. Although fixed theoretical allometric exponents would have been preferred, the data are reasonable well described across the studied body weight range and based on sensitivity analyses jPTA is not expected to differ significantly.

PMA is used to account for renal function on CL in children <2 years, and the current models are thus not able to account for changes in CrCL beyond what is expected based on PMA. The influence of CrCL on CAZ and AVI CL is ignored for patients <2 years old. According to the MAH, no improvement of the models in terms of OFV were observed when CrCL was incorporated as a covariate on CL in addition to the maturation function based on PMA.

For the final AVI model, the typical value of CL and Vc increased from 10.7 to 11.7 L/hr and 11.5 to 13.5 L, respectively. The population effects on cUTI (θ11) and cIAI/NP (θ12) on Vc increased in magnitude. The predicted Vc in paediatric patients <3 months was 77.2% higher than in a typical subject (healthy, 70 kg, nCrCL of 80 mL/min/1.73m2). The unexplained IIV in Vc was reduced in the updated model (omega values of 0.660 vs 1.139). Of note, a different estimation algorithm (SAEM/IMP) was used for the AVI model in the previously submitted popPK analysis (CAZ-MS-PED-02).

For the final CAZ model, the typical parameter estimates for CL decreased from 9.13 to 7.75 L/h, Emax increased from 1.5 to 1.64, and weight at half of the Emax effect decreased from 53.4 to 44.8 kg. This translates into a more pronounced effect of weight in lighter subjects for the current model. The predicted Vc in paediatric patients <3 months was 68% higher than in a typical subject (healthy, non-Asian, 70kg, nCrCL of 100 mL/min/1.73m2).

Fixed effects parameters were estimated with acceptable precision (RSE 5.3-20.5%). Parameter uncertainty was evaluated using sampling importance resampling (SIR). Parameter estimates were generally similar to the SIR generated statistics, and zero (additive effects) or one (proportional effects) was not included in the 95 inter-percentile range for covariate effects.

VPCs vs time after dose stratified by cohorts (and thus dose groups) have been presented. The CAZ model fits the observed data well. Both central tendency and variability (95th percentile) is adequately captured for cohort 3 (preterm neonates), but the 5th percentile is slightly overestimated. The variability is overestimated in cohort 1 and 2, but the 5th and 95th percentiles of observed data are contained within the prediction interval. A somewhat poorer, but still reasonable fit to data is shown also for the AVI model, but there are differences between cohorts. In cohort 1 and 2, central tendency and variability is reasonably well captured, although there is a tendency for underprediction of the median and overprediction of the variability. For cohort 3, there is underprediction of both central tendency and variability. The median and 5th percentile of observed data mostly fall outside the prediction interval (shown in the plot by asterisks). Additional pcVPCs stratified by body weight (2.5 kg, ≤2.5 kg to <4 kg, ≥4 kg) and renal function in terms of nCrCL (≤50 mL/min/1.73 m2 or >50 mL/min/1.73 m2, presumably calculated using the bedside Schwartz equation), were provided with the response confirming acceptable ability of the CAZ and AVI models to capture the observed PK data. It is noted that the AVI model underestimates the median concentration over time in subjects in the lower body weight and renal function strata. Underprediction of exposure levels could yield conservative PTA estimates, which is reassuring from an efficacy perspective. However, this should be

kept in mind when evaluating safety margins for the AVI component. The pcVPCs demonstrate a reasonable fit to the observed data for the adult population across indications.

Model application

The MAH has presented model-simulated exposures across age groups with associated joint PKPD target attainment. The results are addressed further below.

In general, the methodology used for PKPD simulations i.e. bootstrapping of post-hoc random effect estimates from the final models and using published virtual populations as a covariate source, is similar to previous investigations (EMEA/H/C/4027/II/15). The indication-specific effect used in the simulations for subjects <3 months old was estimated based on subjects older than 3 months, and it was thus assumed that these effects can be extrapolated to the younger subjects.

It is noted that the simulated AVI AUC (mean and CV) for each paediatric age group are identical across indication specific simulations, indicating that the same virtual age-specific dataset were used for all simulations. This appears to deviate from the conduct of simulations as described by the MAH, stating that a virtual population of 1000 subjects for each age group and indication (cUTI, cIAI and NP) were used.

Although shrinkage for CL is acceptable (5-10%), relatively high shrinkages were reported for CAZ and AVI central (49.8%/27.6%) and the CAZ peripheral (79.5%) volumes of distribution. As the volume of distribution in children, in particular in the youngest, is different than that of adults and as limited PK data in children are available compared to adults, the high shrinkages confer uncertainty on the parameter and variability estimates and consequently to the results of the PTA analysis in the paediatric population. As for previous PTA investigations (CAZ-MS-PED-02), the popPK post-hoc random effect estimates were re-inflated to mitigate underestimation of IIV and give a conservative estimate of PTA. The shrinkage and required shrinkage adjustment was assumed to be similar in adults and children. This is questioned as PK sampling was generally more sparse in children, which in turn would lead to higher shrinkage in children and a need for more extensive shrinkage adjustment. The MAH has investigated the sensitivity of the PTA simulations towards the inflation of variability, comparing the original analysis (inflations as previously used in EMEA/H/C/4027/II/15) with no inflation and "higher" inflation. Joint PTA values decreased with increasing inflation but were at least 94% across indications and age groups for paediatric patients <3 months.

Simulated scenarios included relevant covariates which were supported by the available data (body weight, white), and only normal renal function (80-150 mL/min/1.73m2/with upper limit for CrCL) was considered (see below). Also, ESRD, dialysis, presence of ventilator, and APACHE score were not considered in the simulations. The lowest age group in the PTA analyses was GA 26-<31 weeks. The youngest subjects in the popPK data set were 31 weeks gestation, and the predictive performance of the popPK models has not been established for preterm neonates born before 31 weeks. The proposed dose recommendations for preterm neonates born before 31 weeks PMA is discussed below.

Simulation scenarios that informed the PTA calculations were based on growth charts/curves (CDC and Olsen et al.2010) specific to the U.S. population. Simulations for subjects <3 months old using virtual populations relevant for the EU paediatric population (Sumpter and Holford 2011), have also been submitted and demonstrate acceptable jPTAs of >94% across age groups and indications.

CAZ and AVI exposure in (pre)term neonates and infants <3 months

The aim of the dose selection in paediatric patients <3 months was to achieve comparable exposures to that of adult patients with cIAI, cUTI or NP (HAP/VAP) for whom efficacy have been established. The proposed paediatric age- and body-weight tiered doses was administered to 45 patients in the phase II study C3591024. The formulation used is identical to the final drug product for commercial use. Sparse

PK sampling was performed (as described above), and comparisons thus rely on model predicted exposures. No pre-specified acceptance limits for similarity of exposure have been presented and no tabulated comparison of observed and/or individually predicted exposures in paediatric subjects <3 months and older children/adults have been presented. Model-simulated exposures across all age groups have been presented together with associated joint PTA values, see the discussion further below.

The exclusion of one patient (Part A cohort 1) with a documented dosing error (leading to very high exposures 3.5-5 times that of the highest exposures in remaining subjects within the cohort) from PK summary statistics and the popPK dataset, is endorsed. However, based on provided plots it is noted that another patient (part B, cohort 3) achieved very low CAZ and AVI exposures following administration of 50/12.5°mg CAZ/AVI (20/5°mg/kg). The reason for the low exposures are not known. No dosing errors are reported for this subject and the patient was evaluated as clinical cure. A second medication error is noted for another patient (part B, cohort 2), where the infusion rate was shortened from 120 minutes to 105 minutes. The actual infusion time is used in the popPK analysis.

Model-simulated exposures across all age groups are shown for PTA analyses (section 1.3.4). A lower Cmax (CAZ: 57-99%, AVI: 58-83%), with higher Cmin (CAZ: 117-504%, AVI: 118-379%) and comparable AUC (CAZ: 74-169%, AVI: 73-126%) are simulated in (pre)term neonates and infants <3 months compared to adults.

Plots of simulated and observed CAZ and AVI exposures versus body weight and age compared to a simulated adult reference exposure range have been presented. For preterm neonates ≥31 weeks GA, term neonates and infants <3 months, maximum and total exposures of CAZ and AVI are similar or somewhat lower compared with adults. For preterm neonates with GA 26 to <31 weeks (with the initially proposed posology of 20/5 mg q8h), the predicted range of AVI maximum and total exposures are similar as in adults. As demonstrated by popPK model performance plots/pcVPCs, the AVI concentrations may be somewhat underestimated. For CAZ, maximum exposures are similar as in adults, while the range of predicted total exposures is in the higher end of, and even exceeds, predicted adult total exposures.

PKPD (target attainment) analyses

There are no expected differences in the mechanism of action of CAZ-AVI based on age as both CAZ and AVI exert their effects by acting on the causative pathogen, and the gram-negative causative pathogens are similar in adults and children. Thus, the same joint PKPD targets are considered relevant to dose setting in paediatric patients. The jPTA target used in the current application (T4, i.e. ≥50% fT > MIC of 8 mg/L for CAZ in the presence of AVI, and ≥50% fT >CT of 1.0 mg/L for AVI) has been used in previous Zavicefta MAH and EoI procedures.

For all paediatric subgroups relevant for the current application (age groups <3 months and cIAI, cUTI, NP indications), acceptable PTAs of >95% are demonstrated at the proposed dosing recommendations using this conservative joint PKPD target.

The current models' predictive ability and PKPD target attainment in patients ≥3 months to <18 years have not been specifically assessed in this AR. Please refer to previous assessment (EMEA/H/C/4027/II/15).

Adequacy of the proposed dose regimens in patients with normal (for age) renal function

Dose recommendations in paediatric patients ≥31 weeks PMA to <3 months have been adequately justified based on exposure matching in accordance with current guidance (EMA/CHMP/187859/2017, ICH E11). The MAH also presented dose recommendations for preterm neonates <31 weeks PMA. The

currently proposed dose recommendations in patients 26 weeks to <31 weeks PMA, however, are supported by modelling exercises only.

Overlapping, but higher exposures are predicted in the age cohort 26-<31 weeks GA compared with preterm neonates born ≥31 weeks with the initially proposed dose regimen (q8h), as expected due to organ immaturity. The PK-PD analyses show jPTA >99%, and efficacy in this youngest group is therefore expected to be adequate. However, as predicted total CAZ (but not maximum) exposures are in the upper end, and also exceeding, those in adults, there could be a concern with respect to safety. It is also noted that the AVI popPK model tends to underpredict exposures. There are no PK data available in patients 26 to <31 weeks (study C3591024), and limited literature on clinical use is available. There are, however, published case reports and (retrospective) studies on use of CAZ and CAZ/AVI in preterm infants with similar or higher doses than those proposed in the current application, which report no major safety concerns. Furthermore, CAZ is a well-known active substance, for which there is extensive clinical experience, and CAZ monotherapy is used in comparable doses in neonates as proposed for CAZ/AVI. The seriousness of the clinical indications in this vulnerable population, the short treatment duration and the potential for curative therapy must also be taken into consideration. Expecting further paediatric PK data in this population is not realistic, and there is a high clinical need for dose recommendations also in this lower age group. Reassuringly, the safety profile of CAZ-AVI in paediatric patients from birth (≥31 weeks GA) to <3 months seem to be in line with findings in adults and previous paediatric studies in patients from 3 months of age and older. The potential of CAZ and AVI over-exposure in preterm neonates <31 weeks GA, even with a certain potential margin of error, is thus not considered to preclude a conclusion of a positive-benefit risk balance in these patients.

As a response to the safety concerns in patients 26 to <31 weeks described above, the MAH has proposed to increase the dose interval from 8qh to 12 hourly dosing in this population thus reducing the daily mg/kg dose by one third. Simulated median (and interquartile range) steady state maximum and total exposures for both CAZ and AVI with this new posology in subjects 26-<31 weeks GA are well within the adult 5th to 95th percentile reference range across the sought indications. Also, the exposures are comparable with the exposures simulated in preterm neonates receiving 20/5 mg/kg q8h CAZ-AVI, which is reassuring from a safety perspective. The high joint target attainment is maintained with the new posology with PTAs of ≥98%, and the extended dose interval in this age group is thus not expected to impact on efficacy.

The totality of data supports the currently proposed dose recommendations from 26 weeks PMA (with an extended dose interval). Considering the risk of extrapolation beyond the PK data which have been used to build the popPK models, this uncertainty should be communicated clearly in the SmPC. A statement has been included in section 4.2 that dose recommendations in patients <31 weeks PMA are informed by popPK simulations only, which is endorsed.

Reflecting that there is no well established and validated method for estimating GFR and categorise renal function in the paediatric population <3 months of age, a cut-off for dosing recommendations in patients with renal function normal for age are proposed based on SCR values (≤ULN) instead of nCrCL which appear reasonable. The chosen cut-off differs from the exclusion criteria in the paediatric study C3591024; "moderate or severe renal impairment defined as SCR ≥2 times the ULN for age or urine output <0.5 mL/kg/hour (measured over at least 8 hours) or requirement for dialysis". However, very few subjects enrolled had baseline SCR >ULN for age (N=2). It is agreed that the available data should inform the posology recommendations, and the currently proposed SCR cut off (i.e. SCR ≤ULN for age) for dosing recommendations in patients <3 months of age is endorsed.

The use of CAZ-AVI for the indication Gram negative infections in paediatric patients <3 months with limited treatment options has not been specifically addressed by the MAH. The use of CAZ-AVI in this indication in adults and paediatric patients ≥3 months is based on experience with ceftazidime alone

and on analyses of PKPD relationship in adults and children (initial MAA, EMEA/H/C/4027/II/15). The same dose is approved for this indication as for site-specific indications in patients ≥3 months of age (based on exposure-mathing). Considering the unmet medical need for further treatment options against infections due to resistant Gram-negative bacteria, the extrapolation of this indication to paediatric patients <3 months is supported provided similar exposures to those of adults with the proposed posology.

Dosing recommendations in children with renal impairment

As preexisting renal impairment could be expected also in the sought paediatric population, dosing recommendations also in this subgroup are desirable. However, it is acknowledged that it is challenging to disentangle the effects of pathological renal impairment from renal immaturity and that renal impairment categories based on nCrCL are not suitable in the current context (see discussion above).

2.3.6. Conclusions on clinical pharmacology

In conclusion, the currently applied extension of approved adult indications cIAI, cUTI, HAP/VAP and Gram negative infections with limited treatment options to paediatric patients from birth to less than 3-months of age (with dose recommendations ≥26 weeks PMA) is acceptable based on exposure-matching. The uncertainty regarding the extrapolation beyond the PK data which have been used to build the popPK models is clearly communicated in the SmPC.

2.4. Clinical efficacy

Dose response studies

Not applicable

Main study

Study C3591024

Title of study: A Phase 2a, 2-part, open-label, non-randomised, multicenter, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to Gram-negative pathogens requiring intravenous antibiotic treatment

Methods

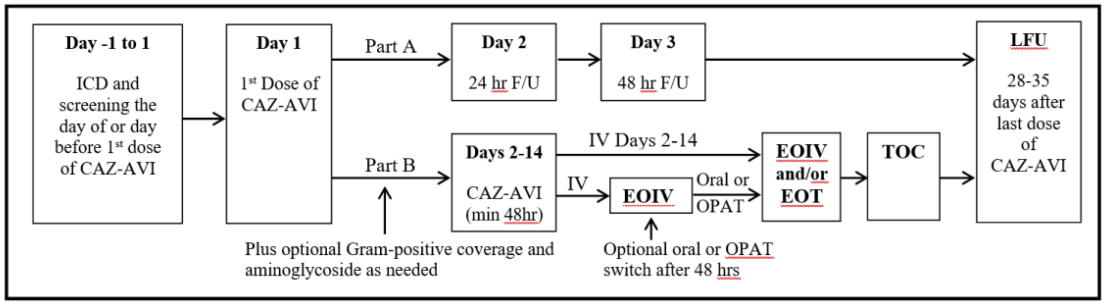
Study C3591024 was conducted in 2 parts, Part A and Part B. Part A was a non-randomised, open-label and single-dose study with PK as primary endpoint. Part B was a non-randomised, open-label, multi-dose and single treatment arm study with safety as primary endpoint. Efficacy was assessed as a secondary objective in Part B.

Parts A and B were divided in 3 age cohorts:

- Cohort 1: *Full term infants* (gestational age ≥37 weeks) with chronological age >28 days to <3 months (<89 days) or *pre-term infants* with corrected age >28 days to <3 months (<89 days)
- Cohort 2: *Full term neonates* (gestational age ≥37 weeks) from birth to ≤28 days

- Cohort 3: *Pre-term neonates* (gestational age ≥26 to <37 weeks) from birth to ≤28 days

The study outline and sequence of cohort startup are provided in Figure 9 and Figure 10, respectively.



EOIV = End of IV; EOT = End of Treatment; F/U = Follow-Up; hr(s) = hour(s); ICD = Informed Consent Document; IV = Intravenous; LFU = Late Follow-Up; OPAT = outpatient parenteral antimicrobial therapy; TOC = Test of Cure.
Figure 9. Study outline. Source: Appendix 16.1.1

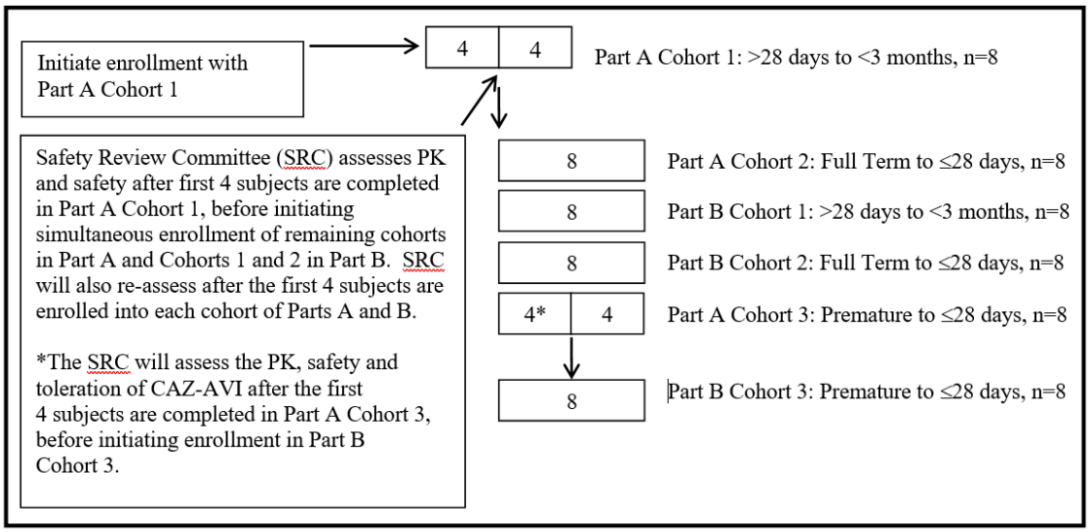


Figure 10. Cohort startup. Source: Appendix 16.1.1

Study participants

Main inclusion criteria

All subjects

1. Male or female neonates and infants with age at screening:

   a. Cohort 1: Full term infants (gestational age ≥37 weeks) with chronological age >28 days to <3 months (<89 days) or pre-term infants with corrected age*>28 days to <3 months (<89 days). A maximum of 3 pre-term corrected age infants may be enrolled in each part (A and B) of Cohort 1.

   b. Cohort 2: Full term neonates (gestational age ≥37 weeks) from birth to ≤28 days.

   c. Cohort 3: Pre-term neonates (gestational age ≥26 to <37 weeks) from birth to ≤28 days. Gestational age is the time elapsed between the first day of the last menstrual period and birth

*Corrected age is the age of the infant from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age (Engle, 2004). Corrected age (in weeks) = chronological age in weeks – (40 – gestational age in weeks).

Part A subjects only

Hospitalised and receiving intravenous antibacterial therapy for the treatment of a suspected or confirmed bacterial infection.

Part B subjects only

1. Hospitalised with suspected or confirmed aerobic Gram-negative bacterial infection requiring intravenous antibacterial therapy.
2. Subjects must meet at least 1 clinical and 1 laboratory criterion or meet at least 2 of the clinical criteria:

Clinical criteria:

a. Hypothermia (<36ºC) OR fever (>38.5ºC);
b. Bradycardia OR tachycardia OR rhythm instability;
c. Urine output 0.5 to 1 mL/kg/h OR hypotension OR mottled skin OR impaired peripheral perfusion;
d. Petechial rash OR sclerema neonatorum;
e. New onset or worsening of apnoea episodes OR tachypnoea episodes OR increased oxygen requirements OR requirement for ventilation support;
f. Feeding intolerance OR poor suckling OR abdominal distension;
g. Irritability;
h. Lethargy;
i. Hypotonia.

Laboratory criteria:

a. White blood cell count $\leq 4.0 \times 10^9$/L OR $\geq 20.0 \times 10^9$/L;
b. Immature to total neutrophil ratio >0.2;
c. Platelet count $\leq 100 \times 10^9$/L;
d. C-reactive protein (CRP) >15 mg/L OR procalcitonin ≥2 ng/mL;
e. Hyperglycaemia OR hypoglycaemia;
f. Metabolic acidosis.

Main exclusion criteria

All subjects:

1. Use of potent inhibitors of organic anion transporters OAT1 and/or OAT3 (e.g., probenecid, p-aminohippuric acid (PAH), or teriflunomide) are prohibited. This prohibition of OAT1 and/or OAT3 inhibitors also applies to the mothers of any neonates or infants who are breast feeding during the trial.
2. Documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic.
3. Refractory septic shock within 24 hours before screening that does not resolve after 60 minutes of vasopressor therapy.
4. Moderate or severe renal impairment defined as serum creatinine ≥2 times the upper limit of normal (ULN) for age OR urine output <0.5 mL/kg/h (measured over at least 8 hours) OR requirement for dialysis. Deterioration of renal function after enrolment during Part B of the study will be handled on a case-by-case basis in discussion with the Medical Monitor.
5. Documented history of seizure.
6. Active acute viral hepatitis or acute hepatic failure.
7. Known *Clostridium difficile* associated diarrhoea.

8. Requiring or currently taking antiretroviral therapy for human immunodeficiency virus (HIV) or known HIV positive mother.
9. Treatment with ceftazidime within 12 hours of CAZ-AVI administration.

Part A subjects only

1. Subject received a blood or a blood component transfusion within 24 hours of the start of CAZ-AVI infusion.
2. Subject is expected to be discharged less than 24 hours after the start of CAZ-AVI infusion.

Part B subjects only

1. At study entry, subject has confirmed or strongly suspected infection with a pathogen known to be resistant to CAZ-AVI or only a Gram-positive pathogen or viral, fungal, or parasitic pathogens as the sole cause of infection.
2. Confirmed or suspected central nervous system (CNS) infection (e.g., meningitis, brain abscess, subdural abscess).
3. Anticipated need for antibacterial therapy longer than 14 days (e.g., osteomyelitis, endocarditis). This applies to both study treatment with CAZ-AVI as well as adjunctive IV antibacterial treatment for suspected co-infection with Gram-positive organisms or multi-drug resistant Gram-negative organisms.
4. Receipt of more than 24 hours of non-study systemic antibacterial treatment for Gram-negative organisms after culture and before administration of study doses of CAZ-AVI. Empiric coverage with an aminoglycoside for suspected multidrug resistant organisms is permitted, provided CAZ-AVI is initiated within 24 hours after culture.
5. IV treatment with chloramphenicol within 24 hours of administration of study doses of CAZ-AVI.

Treatments

Part A

On Day 1 participants in Part A received a single IV infusion of CAZ-AVI over a 2-hour (±10 min) period according to their cohort as indicated in the table below. The infusion was administered any time during the participant's course of treatment with the other IV antibiotic, with the exception that no doses of ceftazidime were permitted within 12 hours of CAZ-AVI infusion. The CAZ-AVI infusion was to be timed to not interfere with dosing of the other antibiotic.

Part B

On Day 1, participants in Part B began receiving IV CAZ-AVI over a 2-hour (±10 min) period every 8 hours (±1 hour) according to their cohort as indicated in the table below. Treatment was to continue for 2 to 14 days (with an optional switch to alternative oral therapy or outpatient parenteral antimicrobial therapy [OPAT] with another IV antibiotic after at least 48 hours of IV CAZ-AVI). The dose was to remain the same throughout the dosing period unless local standard practice was to reassess weight changes regularly (e.g. weekly) and make dose adjustments.

Table 22. CAZ-AVI weight-based doses for each cohort

Cohort	Age	CAZ-AVI weight-based dose	Infusion		
			Volume	Duration	Frequency
1	>28 days[a] to <3 months old	30 mg/kg CAZ 7.5 mg/kg AVI	Varies, will not exceed 2 mL/kg/dose	120 min	q8h (Part B Only)
2	GA ≥37 weeks and ≤28 days old	20 mg/kg CAZ 5.0 mg/kg AVI			
3	GA ≥26 weeks to <37 weeks and ≤28 days old	20 mg/kg CAZ 5.0 mg/kg AVI			

[a] Includes term infants (gestational age [GA] ≥37 weeks) >28 days of age and pre-term infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age was used only for determining eligibility of pre-term infants in Cohort 1. Actual age (chronological age) was used for determining eligibility of pre-term neonates in Cohort 3. Source: Appendix 16.1.1, Protocol Table 2

Concomitant treatment: Adjunctive IV antibacterial treatment for suspected co-infection with Gram-positive organisms was allowed to be given per standard of care, with preference for ampicillin or vancomycin. Metronidazole could be added to CAZ-AVI to provide coverage for anaerobic organisms. Adjunctive coverage for aerobic Gram-negative organisms was discouraged, but if additional coverage against multi-drug resistant Gram-negative organisms was empirically indicated to ensure adequate therapy while awaiting baseline culture and susceptibility results, additional Gram-negative coverage with aminoglycosides gentamicin or amikacin was allowed to be added per standard of care.

Objectives

Table 23. Study objectives and endpoints - Part A

Type	Objective	Endpoint
Primary		
PK	To characterise the PK of a single intravenous dose of CAZ-AVI in hospitalised neonates and infants from birth to < 3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
Secondary		
Safety	To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in hospitalised neonates and infants from birth to < 3 months.	Safety and tolerability endpoints included AEs, SAEs, deaths, discontinuations due to AEs, and laboratory abnormalities.

Source: Module 5.3.3.3 Study C3591024 Appendix 16.1.1 Protocol Section 2

Table 24. Study objectives and endpoints - Part B

Type	Objective	Endpoint
Primary		
Safety	To evaluate the safety and tolerability of CAZ-AVI for the treatment of aerobic gram-negative infection in neonates and infants from birth to < 3 months.	Safety and tolerability endpoints included AEs, SAEs, deaths, discontinuations due to AEs, and laboratory abnormalities.
Secondary		
PK	To evaluate the pharmacokinetic profile of multiple intravenous doses of CAZ-AVI in hospitalised neonates and infants from birth to < 3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
Efficacy	To evaluate the efficacy of CAZ-AVI for the treatment of aerobic gram-negative infection in neonates and infants from birth to < 3 months.	Efficacy outcome measures included: All-cause mortality. Clinical outcome at EOIV, EOT, TOC, and LFU. Cure defined as clinical improvement and no need for further antibacterial treatment, 7 to 14 days after EOT. Microbiological eradication 7 to 14 days after EOT (micro-ITT analysis set). Emergent infections.

Source: Module 5.3.3.3 Study C3591024 Appendix 16.1.1 Protocol Section 2

Outcomes/endpoints

See information under "Objectives" above.

Efficacy response definitions

Table 25. Definition of clinical response categories at the EOIV, EOT, TOC and LFU

Clinical Response	Definition
Clinical Cure	Resolution of all acute signs and symptoms of infection or improvement to such an extent that no further antibacterial therapy is required.
Clinical Improvement[a]	Subjects who switch to oral therapy and meet all of the following criteria at EOIV: • Afebrile (temperature ≤38.0°C) for at least 24 hours. • Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none.
Clinical Failure[b]	Subjects who received ≥48 hours of study treatment and meet any of the following: • Discontinuation of study therapy due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, worsening in signs and symptoms of infection, or isolation of a resistant pathogen that requires alternative nonstudy antibacterial therapy. • Discontinuation of study therapy due to a study therapy related AE and requirement for alternative nonstudy antibacterial therapy for infection. • Death in which infection is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which infection is clearly noncontributory. • Lost to follow up. • Extenuating circumstances precluding classification as a cure or failure. • Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC at any time after enrollment. • Received <48 hours of study therapy.

Abbreviations: AE=adverse event; CNS=central nervous system; NEC=necrotising enterocolitis. [a]Clinical improvement is only applicable at EOIV for subjects who are being switched to oral therapy after less than 14 days of IV CAZ-AVI. [b]A clinical failure at EOIV will be carried forward to EOT, TOC and LFU

End of intravenous treatment (EOIV)= ≤ 24 hr after last IV infusion; End of treatment (EOT)= ≤ 48 hr after last drug dose; Test of cure (TOC)= 7-14 days after last drug dose; Late follow up (LFU)= 28-35 days after last CAZ-AVI infusion.

Emergent infections

An emergent infection was defined as follows:

- Superinfection: A culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy requiring alternative antimicrobial therapy.
- New infection: A culture identified pathogen other than a baseline pathogen at any time after study treatment has finished requiring alternative antimicrobial therapy.

Microbiological response definitions

Table 26. Per-pathogen microbiological outcomes categories at TOC

Microbiological Response[a]	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Presumed eradication	Source specimen was not available to culture and the subject was assessed as a clinical cure
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Presumed persistence	Source specimen was not available to culture and the subject was assessed as a clinical failure
Indeterminate	Source specimen was not available to culture and the subject's clinical outcome was assessed as indeterminate

Abbreviations: TOC=Test of Cure

a. For subjects who are clinical failures before TOC, the microbiological outcome will be carried forward to TOC and will be determined based on the cultures and/or clinical outcome at the time of the early clinical failure determination.

Per-subject microbiological response at TOC was determined programmatically based on individual outcomes for each baseline pathogen, as per the table below.

Table 27. Per-subject microbiological response

Number of pathogens at baseline	Pathogen 1 Outcome at TOC	Pathogen 2 Outcome at TOC	Per-subject microbiological response at TOC
1 pathogen	Favorable		Favorable
	Unfavorable		Unfavorable
	Indeterminate		Indeterminate
2 pathogens	Favorable	Favorable	Favorable
		Unfavorable	Unfavorable
		Indeterminate	Indeterminate
	Unfavorable	Any result	Unfavorable
	Indeterminate	Favorable	Indeterminate
		Unfavorable	Unfavorable
		Indeterminate	Indeterminate

Sample size

The planned total sample size (48 subjects; 3 cohorts of 16 subjects, Part A + Part B) was considered adequate to evaluate the pharmacokinetics of CAZ-AVI in neonates and infants and to provide critical insight into safety and toleration in this population. Similarly, the planned sample size in Part B (24 subjects, 3 cohorts of 8 subjects) was considered adequate to provide insight into efficacy in this suspected or confirmed aerobic Gram-negative bacterial infection population. Considerations of the sample size were not based on any statistical hypotheses.

Randomisation and blinding (masking)

The study was not randomised. All enrolled subjects received CAZ-AVI either as a single dose in Part A or multiple doses in Part B. The study was open label.

Statistical methods

The study was not powered for inferential statistical analysis. Descriptive methods were used to summarise all data. Descriptive methods for binary data included counts and percentages, and 95% CI for proportions when applicable.

All-cause mortality was summarised with counts and proportions of deaths and 95% confidence intervals when applicable, for the ITT analysis set.

In general, descriptive statistics for continuous data were to include mean, standard deviation, median, minimum and maximum observed values. For each Part, A and B and each Cohort 1, 2, and 3, the plasma concentration was to be summarised by nominal sampling time using appropriate descriptive statistics (e.g., number, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and coefficient of variation).

Analysis sets

The analysis of efficacy was performed using the Intent-to-Treat (ITT), Modified-ITT (MITT) and Microbiological (Micro)-ITT Analysis Sets:

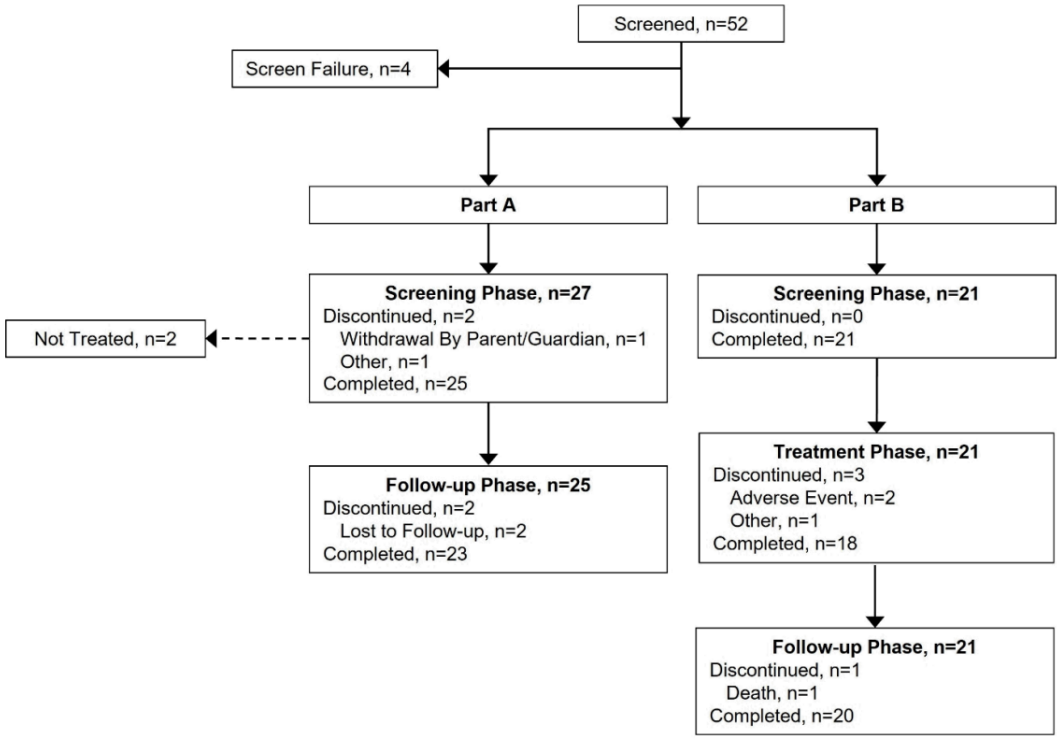
- The *ITT analysis set* was defined as all subjects who have been enrolled in each part of the study, regardless of whether or not treatment was received.
- The *MITT Analysis Set* included all subjects who received any amount of CAZ-AVI and who met minimal disease criteria described in the inclusion criteria defined as the presence of at least 1 clinical criterion and at least 1 laboratory criterion or 2 clinical criteria in the presence of, or as a result of suspected or proven bacterial infection requiring IV antibiotic therapy.
- The *Micro-ITT Analysis Set* included all subjects from the Part B ITT Analysis Set who had at least 1 Gram negative pathogen in an adequate initial/pre-study culture.

The *Safety Analysis Set* included those subjects who received any amount of the investigational drug (CAZ-AVI) in the respective part A and B.

The *Pharmacokinetic (PK) Analysis Set* for Part A was defined as subjects who received a single IV dose of CAZ-AVI in Part A. The PK analysis set for Part B was defined as subjects who received at least 3 consecutive doses of CAZ-AVI in Part B. In order for a subject to be part of the PK analysis sets he/she must have had at least 1 ceftazidime and/or avibactam plasma PK measurement available.

Results

Participant flow



Part A: single IV infusion of CAZ-AVI on Day 1. Part B: IV infusion of CAZ-AVI every 8 hours up to 14 days. Note: Discontinuation from the treatment phase indicates discontinuation from study intervention. Discontinuation from the Follow-up Phase indicates discontinuation from the study.

Figure 11. Participant disposition by Part

Of note, in Part B, discontinuation from the Treatment Phase indicated discontinuation from study intervention and not the study *per se,* while discontinuation from the Follow-up Phase indicated discontinuation from the study. Three patients discontinued the study intervention in the Treatment Phase (but continued the study); one patient in Cohort 2 due to "Other" which was pre-existing hypertransaminasemia (treated with cefazolin and commercial CAZ-AVI and thus excluded from any PK assessments or analysis of efficacy) and two patients in Cohort 3 due to adverse events (one was necrotising enterocolitis + septic shock with fatal outcome and the other was acute cardiac failure + sepsis). Only the patient with fatal outcome was later discontinued from the whole study (as indicated in the Follow-up Phase in the figure above).

Recruitment

The trial began 14 January 2020 (first participant first visit). Of note, the MAH decided to terminate the study early (after all treated subjects had reached their end-of-study) due to slow enrolment and as it was considered that sufficient PK data had been collected to support dose recommendations and safety/efficacy extrapolation for the neonatal age range. The MAH underlined that this decision was not due to safety issues. The date of study termination was 30 December 2022, which was also the date of the end of the study. The final CSR included all data as of study termination (30 December 2022).

The study was conducted in 8 countries: Estonia (2 patients), Greece (18 patients), Hungary (3 patients), India (1 patient), Italy (11 patients), Slovakia (2 patients), Taiwan (4 patients), and USA (7 patients).

Conduct of the study

Protocol deviations

Table 28. Summary of important deviations by Part - ITT Analysis Set

Protocol Deviation Category/ Subcategory	Part A (N=27) n (%)	Part B (N=21) n (%)	Part A + Part B (N=48) n (%)
Number of participants with at least 1 important protocol deviation	15	16	31
Inclusion/Exclusion	0	2 (9.5)	2 (4.2)
Did not meet Inclusion Criterion Qualifying age for one of the 3 age cohorts	0	1 (4.8)	1 (2.1)
Met Exclusion Criterion Receipt of more than 24 hours of nonstudy systemic antibacterial treatment for Gram-negative organisms after culture and before administration of study doses of CAZ-AVI - PART B ONLY	0	1 (4.8)	1 (2.1)
Informed Consent	3 (11.1)	5 (23.8)	8 (16.7)
Informed Consent Other	2 (7.4)	0	2 (4.2)
Subject/LAR did not sign the ICD but gave verbal consent	1 (3.7)	3 (14.3)	4 (8.3)
Subject/LAR signed a superseded/outdated version of the ICD	0	2 (9.5)	2 (4.2)
Subject/LAR signed and dated ICD after screen/enroll date	0	1 (4.8)	1 (2.1)
Subject/LAR signed consent but did not date it	0	1 (4.8)	1 (2.1)
Investigational Product	6 (22.2)	4 (19.0)	10 (20.8)
Dispensing error	1 (3.7)	1 (4.8)	2 (4.2)
Dosing/Administration error	5 (18.5)	3 (14.3)	8 (16.7)
Laboratory	7 (25.9)	10 (47.6)	17 (35.4)
Abnormal lab result not followed up appropriately	0	1 (4.8)	1 (2.1)
Lab not done	4 (14.8)	9 (42.9)	13 (27.1)
Lab not performed within pre-specified conditions	0	3 (14.3)	3 (6.3)
Lab performed out of window	1 (3.7)	0	1 (2.1)
PK/PD samples not done	1 (3.7)	0	1 (2.1)
PK/PD samples not properly collected, stored or handled	1 (3.7)	0	1 (2.1)
Specimen could not be analyzed	0	1 (4.8)	1 (2.1)
Other	0	3 (14.3)	3 (6.3)
Emergency Contact Card not provided to caregiver	0	2 (9.5)	2 (4.2)
Unassigned IP Vial for infusion	0	1 (4.8)	1 (2.1)
Procedures/Tests	7 (25.9)	14 (66.7)	21 (43.8)
Procedure/Test not done	2 (7.4)	10 (47.6)	12 (25.0)
Procedure/Test not performed per protocol	5 (18.5)	10 (47.6)	15 (31.3)
Procedure/Test performed out of window	0	2 (9.5)	2 (4.2)
Visit Schedule	1 (3.7)	2 (9.5)	3 (6.3)
Visit not done	0	1 (4.8)	1 (2.1)
Visit not performed per protocol	1 (3.7)	2 (9.5)	3 (6.3)

Part A: Single-Dose & Part B: Multi-Dose.
N = Number of participants in each part. n = Number of participants with the specified characteristic.
Percentages are based on the total number of participants in each specified characteristic and part
A participant with multiple deviations is counted in the corresponding categories and subcategories.

In addition, COVID-19-related protocol deviations were reported for 2 participants (Part B, Cohort 3) during the trial. The deviations were in the Informed Consent category: for 2 participants, verbal consent was obtained, but the ICD was not signed due to site adherence to COVID-19 protocols.

Protocol amendments

Changes in the conduct of the study were implemented by one protocol amendment (27 June 2019) and three protocol administrative change letters (dated 28 August 2020, 16 March 2022 and 02 June 2022, respectively).

Main changes are described below:

Amendment 1 (27 June 2019)

- Part B Cohort 3 enrolment sequence was revised as requested by the EMA Paediatric Committee (PDCO) on 19 Oct 2018. The purpose of this request was to ensure that enrolment of subjects in Part B Cohort 3, who represent the most vulnerable population based on their age (pre-term neonates [GA ≥26 to <37 weeks] from birth to ≤28 days), was initiated only after data from the first 4 subjects in Cohort 3 of Part A were evaluated.
- "Emergent infections" were added as secondary endpoint for Part B.

Protocol Administrative Change Letter (16 March 2022)

- Emphasised that corrected age applied only to the enrolment of preterm infants in Cohort 1 and not Cohort 3.

Protocol Administrative Change Letter (02 June 2022)

- Permitted enrolment of infants in Part B who may have been treated with ceftazidime prior to enrolment as it was considered that the assessment of plasma ceftazidime following 3 or more doses of CAZ-AVI, administered over at least 24 hours, would not be significantly affected by ceftazidime dosing prior to beginning CAZ-AVI (serum half-life of ceftazidime of ca. 2 hours in children > 2 months of age or up to 4.5 to 7.5 hours in preterm and term neonates).

Baseline data

Table 29. Demographic characteristics by Part - Safety Analysis Set

	Part A (N=25)	Part B (N=21)	Part A + Part B (N=46)
Age (Days)[a]			
n	25	21	46
Mean(SD)	32.1 (23.46)	30.0 (21.08)	31.1 (22.19)
Median (Min, Max)	25.0 (2, 89)	23.0 (6, 86)	23.5 (2, 89)
(Q1,Q3)	(19, 48)	(14, 42)	(15, 42)
Corrected Age (Days)[b]			
n	2	0	2
Mean(SD)	45.0 (15.56)	- (-)	45.0 (15.56)
Median (Min, Max)	45.0 (34, 56)	- (-, -)	45.0 (34, 56)
(Q1,Q3)	(34, 56)	(-, -)	(34, 56)
Inclusion Age (Days)[c]			
n	25	21	46
Mean(SD)	29.6 (19.83)	30.0 (21.08)	29.8 (20.18)
Median (Min, Max)	25.0 (2, 71)	23.0 (6, 86)	23.5 (2, 86)
(Q1,Q3)	(19, 46)	(14, 42)	(15, 42)
Sex, n (%)			
Male	10 (40.0)	11 (52.4)	21 (45.7)
Female	15 (60.0)	10 (47.6)	25 (54.3)
Total	25 (100.0)	21 (100.0)	46 (100.0)
Race, n (%)			
White	18 (72.0)	18 (85.7)	36 (78.3)
Black or African American	2 (8.0)	2 (9.5)	4 (8.7)
Asian	4 (16.0)	1 (4.8)	5 (10.9)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not reported	1 (4.0)	0	1 (2.2)
Total	25 (100.0)	21 (100.0)	46 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	2 (8.0)	0	2 (4.3)
Not Hispanic or Latino	21 (84.0)	21 (100.0)	42 (91.3)
Not reported	2 (8.0)	0	2 (4.3)
Total	25 (100.0)	21 (100.0)	46 (100.0)

Part A: Single-Dose & Part B: Multi-Dose. a. Age = Date of Screening - Date of Birth + 1. b. Corrected Age for pre-term participants in PART A COHORT 1 and PART B COHORT 1. Corrected Age = Age (days) + Gestational Age (days) – 280. c. Inclusion age is the analysis age for term infants and corrected age for pre-term infants. N = Number of participants in each part. n = Number of participants with the specified characteristic. Percentages are based on the total number of participants in each specified characteristic and part.

Primary diagnosis for infectious disease

In Part A the most common primary infectious diagnoses were sepsis (in total 7 subjects, 28.0%; 1 in Cohort 1 and 3 in each of the Cohorts 2 and 3) and UTI (in total 3 subjects, 12%; all in Cohort 1). The median time from primary infectious diagnosis to the study intervention administration (duration since onset) was 4.0 days.

For Part B, sepsis (in total 11 subjects, 52.4%; 1 in Cohort 1, 4 in Cohort 2 and 6 in Cohort 3) and UTI (in total 4 subjects, 19.0%; all in Cohort 1) were also the most common primary infectious diagnoses. The median time from primary infectious diagnosis to the study intervention administration (duration

since onset) was 2.0 days. The duration since onset for 1 participant (Part B, Cohort 2) was incorrectly reported as 23 days.

Table 30. Baseline characteristics - gestational age and infant feeding - Safety Analysis Set

Number (%) of Participants	Part A				Part B				Part A + Part B
	Cohort 1 (N=9) n (%)	Cohort 2 (N=8) n (%)	Cohort 3 (N=8) n (%)	Total (N=25) n (%)	Cohort 1 (N=8) n (%)	Cohort 2 (N=5) n (%)	Cohort 3 (N=8) n (%)	Total (N=21) n (%)	Total (N=46) n (%)
Gestational Age (weeks)									
< 26 weeks	0	0	0	0	0	0	0	0	0
26 - 29 weeks	0	0	0	0	0	0	0	0	0
30 - 33 weeks	0	0	7 (87.5)	7 (28.0)	0	0	5 (62.5)	5 (23.8)	12 (26.1)
34 - 36 weeks	2 (22.2)	0	1 (12.5)	3 (12.0)	0	0	3 (37.5)	3 (14.3)	6 (13.0)
>= 37 weeks	7 (77.8)	8 (100.0)	0	15 (60.0)	8 (100.0)	5 (100.0)	0	13 (61.9)	28 (60.9)
Breast Feeding									
Yes	5 (55.6)	2 (25.0)	2 (25.0)	9 (36.0)	6 (75.0)	2 (40.0)	3 (37.5)	11 (52.4)	20 (43.5)
No	4 (44.4)	6 (75.0)	6 (75.0)	16 (64.0)	2 (25.0)	3 (60.0)	5 (62.5)	10 (47.6)	26 (56.5)

Part A: Single-Dose & Part B: Multi-Dose. Cohort 1: > 28 days to < 3 months; Cohort 2: Full Term to <= 28 days; Cohort 3: Premature to <= 28 days. N = Number of participants in each cohort group. n = Number of participants with the specified characteristic. Percentages are based on the total number of participants in each cohort group and total (N).

Table 31. Summary of weight and body length at baseline - Safety Analysis Set

Measurement	Part A				Part B				Part A + Part B
	Cohort 1 (N=9)	Cohort 2 (N=8)	Cohort 3 (N=8)	Total (N=25)	Cohort 1 (N=8)	Cohort 2 (N=5)	Cohort 3 (N=8)	Total (N=21)	Total (N=46)
Weight (kg)									
n	9	8	8	25	8	5	8	21	46
Mean (SD)	4.81 (1.236)	3.51 (0.425)	1.78 (0.392)	3.43 (1.494)	4.18 (0.994)	2.87 (0.551)	1.85 (0.339)	2.98 (1.239)	3.22 (1.387)
Median (Min, Max)	4.93 (3.3, 6.4)	3.50 (3.1, 4.0)	1.69 (1.3, 2.6)	3.27 (1.3, 6.4)	4.27 (2.9, 6.0)	2.88 (2.2, 3.6)	1.81 (1.5, 2.5)	2.86 (1.5, 6.0)	3.12 (1.3, 6.4)
(Q1, Q3)	(3.5, 6.1)	(3.1, 3.9)	(1.6, 1.9)	(2.0, 4.0)	(3.4, 4.6)	(2.6, 3.1)	(1.6, 2.0)	(2.0, 3.7)	(2.0, 4.0)
Body Length (cm)									
n	9	8	8	25	8	4	8	20	45
Mean (SD)	55.33 (3.536)	50.50 (2.330)	43.88 (3.944)	50.12 (5.790)	54.50 (3.423)	46.50 (4.041)	42.38 (3.068)	48.05 (6.476)	49.20 (6.122)
Median (Min, Max)	55.00 (50.0, 59.0)	50.50 (46.0, 53.0)	45.00 (38.0, 48.0)	50.00 (38.0, 59.0)	54.00 (49.0, 61.0)	47.50 (41.0, 50.0)	41.50 (39.0, 48.0)	48.50 (39.0, 61.0)	50.00 (38.0, 61.0)
(Q1, Q3)	(52.0, 59.0)	(49.5, 52.5)	(40.5, 47.0)	(47.0, 53.0)	(53.0, 56.0)	(43.5, 49.5)	(40.0, 44.5)	(41.5, 53.5)	(45.0, 53.0)

Part A: Single Dose & Part B: Multi-Dose. Cohort 1: > 28 days to < 3 months; Cohort 2: Full Term to <= 28 days; Cohort 3: Premature to <= 28 days. N = Number of participants in each cohort group. n = Number of participants included in analysis.

In Part A, 23 participants (92.0%) reported concomitant antibiotic medications. The most frequently reported concomitant antibiotic medications were amikacin (6 participants [24.0%]), meropenem and vancomycin (4 participants [16.0%], each).

In Part B, 13 participants (61.9%) received concomitant antibiotic medications during the Treatment Phase and 17 participants (81.0%) received concomitant antibiotic medications during the Follow-Up Phase. Permissible concomitant antibiotics used by 13 participants during the Treatment Phase included those providing narrow spectrum Gram-positive coverage (linezolid or vancomycin), aminoglycosides (amikacin or gentamicin) for suspected multidrug resistance, metronidazole for anaerobe coverage, and amphotericin B for antifungal coverage.

Two participants received non-permitted concomitant antibiotics during the Treatment Phase. These included cefazolin, meropenem, and commercial CAZ-AVI.

Treatment duration and exposure

In Part A, the median duration of CAZ-AVI treatment was 2.00 hours (1.8, 2.4). In Part B, the median duration of CAZ-AVI treatment was 7.00 days (1.0, 12.0). Four of 21 participants in Part B switched to oral therapy (amoxicillin, cefixime, trimethoprim/sulfamethoxazole).

It was incorrectly reported that 4 participants in Cohort 1 switched to OPAT, however, these patients were all hospitalised during the time period noted as OPAT switch. This was not in line with the protocol requirement stating that when a patient is hospitalised, he/she cannot be switched to outpatient therapy. As the inclusion of these 4 patients, that had been switched from the study drug to different IV antibiotics, could have had an impact on the efficacy results, sensitivity analyses excluding these 4 participants from the efficacy analyses were performed. Please refer to "Outcomes and estimation" below for details.

Numbers analysed

A total of 48 participants were enrolled in the study and 46 participants were treated. The analysis sets are shown below.

Table 32. Participant evaluation groups by Part - all participants

	Part A (N=27) n (%)	Part B (N=21) n (%)	Part A + Part B (N=48) n (%)
Screened: 52 Screened Failure: 4			
Treated	25 (92.6)	21 (100.0)	46 (95.8)
Not Treated	2 (7.4)	0	2 (4.2)
Intent-to-Treat (ITT)	27 (100.0)	21 (100.0)	48 (100.0)
Safety Analysis Set (SAS)	25 (92.6)	21 (100.0)	46 (95.8)
Pharmacokinetic Analysis Set (PK)	25 (92.6)	20 (95.2)	45 (93.8)
Microbiological Intent-to-Treat (Micro-ITT)	0	10 (47.6)	10 (20.8)
Modified Intent-to-Treat (MITT)	0	16 (76.2)	16 (33.3)

Part A: Single-Dose & Part B: Multi-Dose. N = Number of participants in each part. n = Number of participants with the specified characteristic. Percentages are based on the total number of participants in each specified characteristic and part (N)

Eleven participants in Part B were excluded from the Micro-ITT Analysis Set because they did not have a Gram-negative pathogen at Screening: 1 participant in Cohort 1, all 5 participants in Cohort 2, and 5 participants in Cohort 3.

One participant in Part B, Cohort 2 did not have a plasma PK measurement and was excluded from the PK analysis set.

Five participants were excluded from the MITT Analysis Set, no details could be found regarding the reason for this.

Outcomes and estimation

In Study C3591024, efficacy was assessed as a secondary endpoint and the results presented below are descriptive. Only the results from Part B are shown here. The results from Part A are described and evaluated under Section 5.3.2. Pharmacokinetics further above.

All-cause mortality (Part B)

One participant (4.8%) (Part B, Cohort 3) died on Study Day 35 due to SAEs of necrotising colitis and septic shock which was considered not related to study intervention by the investigator.

In addition, 1 participant (Part B, Cohort 1) died on Study Day 67, after completing the LFU Visit. As this event occurred outside the active data collection period, it was not included in the analysis of all-cause mortality. Please also refer to the *Clinical Safety* section below for more information regarding these two deaths.

Clinical Outcome at EOIV, EOT, TOC and LFU (Part B)

Table 33. Clinical Outcome at EOIV, EOT, TOC and LFU (Part B) - ITT Analysis Set

Visit	Clinical Outcome	Part B			
		Cohort 1 (N=8)	Cohort 2 (N=5)	Cohort 3 (N=8)	Total (N=21)
End of IV Treatment (EOIV)	Favourable Outcome, n (%)	8 (100.0)	4 (80.0)	6 (75.0)	18 (85.7)
	Clinical Cure, n (%)	2 (25.0)	2 (40.0)	3 (37.5)	7 (33.3)
	Clinical Improvement, n (%)	6 (75.0)	2 (40.0)	3 (37.5)	11 (52.4)
	Clinical Failure, n (%)	0	0	1 (12.5)	1 (4.8)
	Indeterminate, n (%)	0	1 (20.0)	1 (12.5)	2 (9.5)
	Missing, n (%)	0	0	0	0
End of Treatment (EOT)	Favourable Outcome, n (%)	8 (100.0)	4 (80.0)	6 (75.0)	18 (85.7)
	Clinical Cure, n (%)	6 (75.0)	3 (60.0)	3 (37.5)	12 (57.1)
	Clinical Improvement, n (%)	2 (25.0)	1 (20.0)	3 (37.5)	6 (28.6)
	Clinical Failure, n (%)	0	0	1 (12.5)	1 (4.8)
	Indeterminate, n (%)	0	1 (20.0)	0	1 (4.8)
	Missing, n (%)	0	0	1 (12.5)	1 (4.8)
Late Follow-up (LFU)	Favourable Outcome, n (%)	8 (100.0)	4 (80.0)	6 (75.0)	18 (85.7)
	Clinical Cure, n (%)	8 (100.0)	4 (80.0)	6 (75.0)	18 (85.7)
	Clinical Improvement, n (%)	0	0	0	0
	Clinical Failure, n (%)	0	0	1 (12.5)	1 (4.8)
	Indeterminate, n (%)	0	1 (20.0)	0	1 (4.8)
	Missing, n (%)	0	0	0	0
Test of Cure (TOC)	Favourable Outcome, n (%)	7 (87.5)	3 (60.0)	7 (87.5)	17 (81.0)
	Clinical Cure, n (%)	7 (87.5)	3 (60.0)	7 (87.5)	17 (81.0)
	Clinical Improvement, n (%)	0	0	0	0
	Clinical Failure, n (%)	0	0	1 (12.5)	1 (4.8)
	Indeterminate, n (%)	0	2 (40.0)	0	2 (9.5)
	Missing, n (%)	0	0	0	0

Cohort 1: > 28 days to < 3 months; Cohort 2: Full Term to <= 28 days; Cohort 3: Premature to <= 28 days;
Data cut-off date: 18JAN2023

One participant (Cohort 3) had clinical failure reported at EOIV due to SAEs (necrotising colitis and septic shock with fatal outcome) leading to discontinuation of IV CAZ-AVI (the patient was later discontinued from the whole study due to death). Per protocol, a clinical failure at EOIV was carried forward as the clinical response for all subsequent visits.

Three participants had variable clinical outcome responses over time:

- 1 participant (Cohort 1) did not have a TOC visit and therefore had an indeterminate response at TOC, but with a favourable clinical outcome at the EOIV and LFU visits.
- 1 participant (Cohort 2) with a favourable response at EOIV and LFU was reported as indeterminate at TOC because at that time, the participant was being treated with oral cefalexin for a TEAE of postoperative wound infection. There was no culture-identified pathogen, so this event did not qualify as a new infection. The participant had a favourable response at the LFU visit at which time the TEAE had resolved, and the oral antibiotic was stopped.
- 1 participant (Cohort 3) discontinued study intervention on Day 7 due to an SAE of renal failure considered not related to study intervention by the investigator. The investigator reported the clinical response as indeterminate at EOIV because the participant was receiving IV meropenem after CAZ-AVI discontinuation, and the switch to meropenem was incorrectly reported as an OPAT switch. The investigator rated the clinical response as favourable at TOC because all antibacterial therapy had been stopped and all symptoms were resolved. The participant discontinued from the study due to death and did not complete the LFU visit. This participant was excluded in the sensitivity analysis due to the impact of the incorrectly reported OPAT switch on subsequent clinical outcome assessments.

Modified ITT analysis set

In the Modified-ITT Analysis Set, favourable clinical outcome rates of ≥81% were observed at the EOIV, EOT, and LFU Visits, and of 75.0% (12/16) at TOC.

Microbiological Response (Part B)

At TOC, a favourable per-participant microbiological response rate (eradication or presumed eradication) of 80.0% (8/10; 6 in Cohort 1 and 2 in Cohort 3) was observed in the Micro-ITT Analysis Set (N=21).

One patient had missing data and one patient (Cohort 3) experienced SAEs of cardiac failure acute and sepsis and received meropenem in conjunction with the study intervention being permanently discontinued. Per protocol, this participant was assessed as a clinical failure with presumed microbiological persistence at EOIV, although no pathogen was identified.

At TOC, favourable per-pathogen microbiological responses were observed for 88.9% of pathogens isolated in the Micro-ITT Analysis Set. An unfavourable microbiological response was reported for one pathogen because the participant was assessed as a clinical failure at EOIV (although the baseline pathogen was not culture-verified to be persistent).

Nine baseline *Enterobacteriaceae* were isolated in 10 participants. The most frequently reported baseline pathogen was *Escherichia coli* (6 isolates), and favourable microbiological responses were observed for all 6 (4 eradication and 2 presumed eradication).

In the Micro-ITT Analysis Set, 2 participants in Part B (Cohorts 1 and 3) had isolates that were resistant to ceftazidime (*Escherichia coli* and *Klebsiella pneumoniae*). There were no isolates tested that were reported as being resistant to CAZ-AVI.

Sensitivity analyses

Four participants were incorrectly reported as having switched to OPAT. All 4 participants were in the ITT Analysis Set, 3 of the participants were included in the Modified-ITT Analysis Set and 2 participants in the Micro-ITT Analysis Set.

For the sensitivity analysis performed on the Modified-ITT Analysis Set excluding 3 participants with invalid OPAT switch, favourable clinical outcome rates of ≥92% were observed at the EOIV, EOT, and LFU Visits, and with a favourable clinical outcome rate of 76.9% at TOC.

For the sensitivity analysis performed on the Micro-ITT Analysis Set excluding 2 participants with invalid OPAT switch, a favourable per-participant microbiological response rate (eradication or presumed eradication) of 75.0% was observed at TOC.

Emergent infections

None of the participants in Part B had an emergent infection.

2.4.1. Discussion on clinical efficacy

The MAH is seeking authorisation to extend the indication of Zavicefta (ceftazidime – avibactam) to include treatment of neonates and infants from birth to less than 3 months of age for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and infections due to aerobic Gram-negative organisms where the treatment options are limited. Zavicefta is already approved for these indications in adults and paediatric patients ≥ 3 months of age. Of note, in many European countries, ceftazidime (alone) is approved for use in paediatric patients from birth.

The current application relies on the concept of extrapolation of clinical efficacy based on comparable plasma exposures in children to those in adults. This is in line with the CHMP "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements" (EMA/CHMP/187859/2017). Hence, the solely descriptive nature of the efficacy data is acceptable.

Design and conduct of clinical studies

The MAH has submitted one Phase 2a, 2-part, open-label, non-randomised, multi-centre, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age. This study (study code C3591024) was conducted in 2 parts, Part A (single dose) and Part B (multiple dose). Efficacy data was obtained in Part B of the study and consequently only this part will be further discussed below.

The study enrolled patients in 3 age cohorts:

- Cohort 1: Full term infants (gestational age ≥37 weeks) with chronological age >28 days to <3 months (<89 days) or pre-term infants with corrected age >28 days to <3 months (<89 days).
- Cohort 2: Full term neonates (gestational age ≥37 weeks) from birth to ≤28 days.
- Cohort 3: Pre-term neonates (gestational age ≥26 to <37 weeks) from birth to ≤28 days.

To be included in Part B, patients were to be hospitalised with suspected or confirmed aerobic Gram-negative bacterial infection requiring intravenous antibacterial therapy. Of note, patients with moderate or severe renal impairment were excluded. Although there are no specific validated criteria for the rather non-specific condition "aerobic Gram-negative bacterial infection" required for inclusion, the criteria selected by the MAH seem to adequately reflect the target patient population. However, these criteria do not specifically reflect the approved indications (see also below).

Efficacy objectives and endpoints were secondary and merely descriptive. The endpoints included assessment of clinical response rate (comprised clinical cure or clinical improvement) at different

timepoints and microbiological response at TOC in addition to all-cause mortality and emergent infections.

The sample size was not based on any power calculations for hypothesis testing. The Intent-To-Treat (ITT) Analysis Set in addition to specified Modified-ITT (MITT) and Microbiological (Micro)-ITT populations were used for efficacy analyses. The study was open label, non-randomised, and no statistical testing was performed for the efficacy endpoints.

In total 5 participants were excluded from the MITT Analysis Set, however, no details for the reason for this could be found in the submitted documentation. It is assumed that they did not fulfil the minimal disease criteria as described in the inclusion criteria (i.e., presence of at least 1 clinical criterion and at least 1 laboratory criterion or 2 clinical criteria). Due to the descriptive nature of the efficacy data, this issue was not further pursued. Further, it is also noted that a majority of patients in Part B had an important protocol deviation (16/21; ca. 76%). The most common deviations were associated with the categories "lab not done" and "procedure/test not done/not performed per protocol". However, no details regarding what these deviations specifically comprised could be found in the submitted documentation. Considering that efficacy is a secondary objective and not critical for the overall assessment of the current application, this issue was not pursued.

Overall, the design of the study with the primary purpose of providing PK and safety data and only descriptive efficacy data from paediatric patients from birth to <3 months was considered acceptable.

Efficacy data and additional analyses

In total only 21 patients were included in Part B. The patients were distributed as follows; 8 patients in Cohort 1 (>28 days to <3 months), 5 patients in Cohort 2 (full term to ≤28 days) and 8 patients in Cohort 3 (premature to ≤28 days). Of note, the MAH decided to terminate the study early (after all treated subjects had reached their end-of-study) due to slow enrolment and as it was considered that sufficient PK data had been collected to support dose recommendations and safety/efficacy extrapolation for the neonatal age range. The MAH underlined that this decision was not due to safety issues.

Of the 21 enrolled patients, 16 patients received CAZ-AVI and met the minimal disease criteria described in the inclusion criteria and thus were included in the MITT Analysis Set.

Most of the participants were male (52.4%) and White (85.7%). The median (min, max) age was 23.0 (6, 86) days. All subjects in Cohorts 1 and 2 were ≥ 37 weeks gestational age (8 and 5 subjects, respectively). The majority of subjects in Cohort 3 were within the age group of 30 to 33 weeks gestational age (5 subjects [62.5%] in Part B). Sepsis (11/21 subjects) and UTI (4/21 subjects) were the most common primary infectious diagnoses. Provided that similar exposure is achieved, it is accepted that the efficacy of CAZ-AVI can be extrapolated from adults. Furthermore, according to the CHMP "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements" (EMA/CHMP/187859/2017), "*Extrapolation of efficacy against an infectious disease across age subgroups is possible based on similar pathophysiology and aetiology. This situation applies to the majority of infectious diseases*". This includes, among other infectious diseases, cIAI, cUTI and HAP/VAP.

Favourable clinical outcome rates (cure or improvement) of ≥80% were observed at the EOIV and EOT Visits (85.7%; 18/21) and were sustained through the TOC visit (81.0%; 17/21) and the LFU Visit (85.7%) for the ITT Analysis Sets. Similarly, in the Modified-ITT Analysis Set, favourable clinical

outcome rates (cure or improvement) of ≥81% were observed at the EOIV, EOT, and LFU Visits, and of 75.0% (12/16) at TOC.

In the Micro-ITT Analysis Set, a per-participant microbiological response rate (eradication or presumed eradication) of 80.0% (8/10) and a per-pathogen microbiological response of 88.9% of pathogens, were observed at TOC. However, these results were based on very scarce microbiological data.

Regarding all-cause mortality: 2 patients died (one on Study Day 35 and the other on Study Day 67 which was outside the active data collection period). No participant had emergent infections.

The number of patients in Study C3591024 was very limited and did not allow for any meaningful conclusions to be drawn regarding the efficacy of CAZ-AVI in neonates and infants < 3 months of age. However, this was not the intention of the study. Notwithstanding this, the efficacy results from Study C3591024 are, overall, considered consistent with data from studies in adults.

2.4.2. Conclusions on the clinical efficacy

Overall, available efficacy data from paediatric patients from birth to <3 month of age were very limited (in total 21 patients, whereof 13 were ≥ 37 weeks). These data did not allow any meaningful conclusions to be drawn in regard to the efficacy of CAZ-AVI in infants and neonates. Although the available data do not seem to deviate in any major way from the adult efficacy data, they are not intended for providing any sound evidence in support of efficacy and/or adequacy of the proposed dose regimen. The efficacy of CAZ-AVI is expected to be similar in children, given that available PK data indicate similar exposures in children and adults. Thus, the basis for approval of this variation lies on the PK and safety data.

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 SmPC for Zavicefta, there are warnings and precautions regarding hypersensitivity reactions, *Clostridioides 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.

The following adverse reactions have been reported with ceftazidime alone and/or identified during the abovementioned Phase 2 and Phase 3 trials with Zavicefta:

Table 34. Frequency of adverse reactions by system organ class

System Organ Class	Very common	Common	Uncommon	Very rare	Not known
Infections and infestations		Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	Clostridioides difficile colitis Pseudomembranous colitis		
Blood and lymphatic system disorders	Coombs direct test positive	Eosinophilia Thrombocytosis Thrombocytopenia	Neutropenia Leukopenia Lymphocytosis		Agranulocytosis Haemolytic anaemia
Immune system disorders					Anaphylactic reaction
Nervous system disorders		Headache Dizziness	Paraesthesia		
Cardiac disorders					Kounis syndrome[a,*]
Gastrointestinal disorders		Diarrhoea Abdominal pain Nausea Vomiting	Dysgeusia		

Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Gamma-glutamyltransferase increased Blood lactate dehydrogenase Increased			Jaundice
Skin and subcutaneous tissue disorders		Rash maculo-papular Urticaria Pruritus			Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders			Blood creatinine increased Blood urea increased Acute kidney injury	Tubulointerstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis Pyrexia			

* ADR identified post-marketing.
[a] Acute coronary syndrome associated with an allergic reaction.

An overview is given on the important potential risks and missing information in adults in the initial RMP submission and which were approved in the initial MAA in 2016. There are no safety concerns considered important identified risks.

Table 35. Safety concerns current RMP

Important potential risks	Hepatotoxicity Bacterial resistance development
Missing information	Pregnancy exposure Lactation exposure Immunocompromised population exposure

Since approval of the marketing authorisation for Zavicefta in adults, data in paediatric subjects have been collected from two paediatric studies conducted to evaluate the safety, tolerability, and efficacy profile of CAZ-AVI in paediatric subjects from 3 months to <18 years of age when given as treatment in subjects with cIAI (Study C3591004) and cUTI (Study C3591005):

- Study **C3591004** was a single-blind, randomised, multi-centre, active controlled trial that evaluated the safety, tolerability, pharmacokinetics (PK) and efficacy of CAZ-AVI when given in combination with metronidazole, as compared with meropenem, in paediatric subjects 3 months to less than 18 years of age with cIAI.
- Study **C3591005** was a single-blind, randomised, multi-centre, active controlled trial that evaluated the safety, tolerability, PK and efficacy of CAZ-AVI, as compared with cefepime, in paediatric subjects 3 months to less than 18 years of age with cUTI.

The safety assessment in paediatric patients from 3 months and above, is based on the safety data from two trials in which 61 patients (aged from 3 years to less than 18 years) with cIAI and 67 patients with cUTI (aged from 3 months to less than 18 years) received Zavicefta. Overall, the safety profile in these 128 paediatric patients was similar to that observed in the adult population with cIAI and cUTI.

Based on these data, the expansion of indications of CAZ-AVI to paediatric subjects from 3 months to <18 years of age for the treatment of cIAI, cUTI including pyelonephritis, HAP/VAP and treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options were accepted in October 2020.

PRESENT APPLICATION

The Summary of Clinical Safety presents data from one clinical study, Study **C3591024.**

This was a Phase 2a, 2-part, open-label, non-randomised, multi-centre, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from **birth to less than 3 months of age** with suspected or confirmed infections due to Gram-negative pathogens requiring intravenous antibiotic treatment.

New wording suggested in section 4.8 is as follows:

"*From birth to less than 3 months of age*

The safety assessment in neonates and infants less than 3 months of age is based on the safety data from one clinical trial in which 46 patients (from birth to less than 3 months of age) received Zavicefta. Overall, the adverse reactions reported in these 46 paediatric patients were consistent with the known safety profile of Zavicefta in older populations (i.e., paediatric patients from 3 months of age and adults)."

In addition to data from study C3591024, the applicant proposes extrapolation of clinical safety from previous studies with Zavicefta in adults and paediatric subjects >3 months of age.

Patient exposure

The current study **C3591024** was a Phase 2a, 2-part, open-label, non-randomised, multi-centre study which evaluated CAZ-AVI in infants and neonates. Single- and multiple-dose PK, safety, tolerability, and descriptive efficacy (Part B only) were assessed in newborns down to a gestational age of 26 weeks and infants <3 months of age, with suspected or confirmed infections due to Gram-negative pathogens requiring IV antibiotic treatment.

The study was conducted in 2 parts, **Part A** and **Part B**, which also were divided in 3 age cohorts each;

- Cohort 1: Full term infants (gestational age ≥37 weeks) with chronological age >28 days to <3 months (<89 days) or pre-term infants with corrected age [1] >28 days to <3 months (<89 days).
- Cohort 2: Full term neonates (gestational age ≥37 weeks) from birth to ≤28 days.
- Cohort 3: Pre-term neonates (gestational age ≥26 to <37 weeks) from birth to ≤28 days.

Part A was a non-randomised open-label, single-dose PK study.

Part B was a non-randomised open-label, multi-dose, single treatment arm PK/safety study.

Safety was evaluated as secondary endpoint in Part A of the study and as a primary endpoint in Part B of the study. In both parts of the study, the safety endpoint included AEs, SAEs, deaths, discontinuations due to AEs, and laboratory abnormalities.

For study outline and overview of cohort startup, please refer to Efficacy section Figure 9 and Figure 10.

A total of 48 participants were enrolled in the study and 46 participants were treated.

Table 36. Study C3591024: Subject Evaluation Groups

	Part A				Part B				Part A + B
	Cohort 1 (N = 10) n (%)	Cohort 2 (N = 8) n (%)	Cohort 3 (N = 9) n (%)	Total (N = 27) n (%)	Cohort 1 (N = 8) n (%)	Cohort 2 (N = 5) n (%)	Cohort 3 (N = 8) n (%)	Total (N = 21) n (%)	Total (N = 48) n (%)
Screened : 52									
Screened Failure: 4									
Treated	9 (90.0)	8 (100.0)	8 (88.9)	25 (92.6)	8 (100.0)	5 (100.0)	8 (100.0)	21 (100.0)	46 (95.8)
Not treated	1 (10.0)	0	1 (11.1)	2 (7.4)	0	0	0	0	2 (4.2)
Intent-to-treat (ITT)	10 (100.0)	8 (100.0)	9 (100.0)	27 (100.0)	8 (100.0)	5 (100.0)	8 (100.0)	21 (100.0)	48 (100.0)
Safety Analysis Set (SAS)	9 (90.0)	8 (100.0)	8 (88.9)	25 (92.6)	8 (100.0)	5 (100.0)	8 (100.0)	21 (100.0)	46 (95.8)

	Part A				Part B				Part A + B
Pharmacokinetic (PK) Analysis Set	9 (90.0)	8 (100.0)	8 (88.9)	25 (92.6)	8 (100.0)	4 (80.0)	8 (100.0)	20 (95.2)	45 (93.8)
Microbiological Intent-to-Treat (Micro-ITT)	0	0	0	0	7 (87.5)	0	3 (37.5)	10 (47.6)	10 (20.8)
Modified Intent-to-Treat (MITT)	0	0	0	0	8 (100.0)	3 (60.0)	5 (62.5)	16 (76.2)	16 (33.3)

Cross reference: Module 5.3.3.3 C3591024 Appendix Table 14.1.1.1

In Part A, the median duration of CAZ-AVI treatment was 2.0 hours.

In Part B, the median duration of CAZ-AVI treatment was 7.0 days. Four of 21 participants in Part B switched to oral therapy. No participant switched to outpatient parenteral antimicrobial therapy (OPAT).

Demographic and other characteristics of study population are presented in the efficacy section Table 30. Of note, all participants in Cohorts 1 and 2 were ≥37 weeks gestational age, with the exception of 2 participants in Part A, Cohort 1 who were 34 to 36 weeks gestational age, as allowed per the protocol.

The majority of participants in Cohort 3 were 30 to 33 weeks gestational age (7 participants [87.5%] in Part A, and 5 participants [62.5%] in Part B). The youngest participants were 31 weeks gestation, including 7 participants in Part A and 1 participant in Part B. The majority of participants (26 participants [56.5%]) were not breastfed.

Overall, sepsis (18 participants [39.1%]) and UTI (7 participants [15.2%]) were the most common primary infectious diagnoses. For Part B, the median time from primary infectious diagnosis to the study intervention administration (duration since onset) was 2.0 days.

Adverse events

The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of AEs, SAEs, and other reportable safety events) are detailed below.

Subjects must be evaluated by a physician or an appropriately trained health care professional at every visit, and the evaluation must be documented.

Blood samples and urine samples will be collected at screening baseline and EOIV, if applicable. Samples may also be collected at any time during the treatment period, at TOC and LFU if clinically indicated.

AEs collection: All directly observed AEs and all AEs spontaneously reported by the study subject's parent(s)/legal guardian/legally acceptable representative. In addition, each study subject's parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

An external drug monitoring committee (E-DMC) was responsible for ongoing monitoring of the safety of participants in the study. A safety review committee (SRC) consisting of the study team physician, international coordinating Investigator or delegate, global safety/risk lead or delegate, therapeutic area

director or delegate, and the clinical pharmacologist/pharmacometrician or delegate, assessed safety from each cohort.

Table 37. Overview of Treatment-Emergent Adverse Events up to LFU (All Causalities) by Part - Safety Analysis Set (Protocol C3591024)

Number (%) of Participants	Part A (N=25) n (%)	Part B (N=21) n (%)	Part A + Part B (N=46) n (%)
Participants evaluable for adverse events	25	21	46
Number of adverse events	26	45	71
Participants with adverse events	8 (32.0)	15 (71.4)	23 (50.0)
Participants with medication error events	0	0	0
Participants with serious adverse events	3 (12.0)	5 (23.8)	8 (17.4)
Participants with severe adverse events	1 (4.0)	4 (19.0)	5 (10.9)
Participants discontinued from study due to adverse events[a]	0	2 (9.5)	2 (4.3)
Participants discontinued study drug due to AE and continue Study[b]	0	0	0
Participants with dose reduced or temporary discontinuation due to adverse events	0	0	0

Part A: Single Dose & Part B: Multi-Dose.
N = Number of participants in each part; n = Number of participants with the specified characteristic.
Percentages are based on the total number of participants in each specified characteristic and total (N).
Serious Adverse Events - according to the investigator's assessment and include data up to Late Follow-Up (LFU).
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
a. Participants who have an AE record that indicates that the AE caused the Participant to be discontinued from the study.
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study.
PFIZER CONFIDENTIAL SDTM Creation: 23JAN2023 (03:37) Source Data: adae Table Generation: 06APR2023 (05:34)
(Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_CSR/adae_s010_a
Table 14.3.1.2.9 Ceftazidime-Avibactam is for Pfizer internal use.

Of note, there are two errors in the table above, both are commented by the MAH in Module 5.3.3.3 Study C3591024 Report Errata. Table 38 incorrectly reports that 2 participants discontinued from the study. One participant (Part B, Cohort 3) discontinued from the study due to SAEs of necrotising enterocolitis and septic shock with fatal outcome.

Table 38 also incorrectly reports that no participant discontinued from study intervention and continued the study, however 2 participants (Part B, Cohort 3) discontinued study intervention due to SAEs. However, one participant discontinued as a result of a severe SAE of renal failure that was considered not related to study intervention and one participant discontinued as a result of cardiac failure acute and sepsis that were considered not related to study intervention.

Common Adverse Events

All-Causality TEAEs up to LFU

Table 38. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term up to LFU (All Causalities) by Part - Safety Analysis Set (Protocol C3591024)

Number (%) of Participants Evaluable for AEs by SYSTEM ORGAN CLASS and Preferred Term	Part A (N=25) n (%)	Part B (N=21) n (%)	Part A + Part B (N=46) n (%)
With Any adverse event	8 (32.0)	15 (71.4)	23 (50.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (4.0)	5 (23.8)	6 (13.0)
Anaemia	0	3 (14.3)	3 (6.5)
Anaemia neonatal	1 (4.0)	0	1 (2.2)
Neutropenia	0	2 (9.5)	2 (4.3)
CARDIAC DISORDERS	2 (8.0)	1 (4.8)	3 (6.5)
Atrial tachycardia	1 (4.0)	0	1 (2.2)
Atrial thrombosis	1 (4.0)	0	1 (2.2)
Cardiac failure acute	0	1 (4.8)	1 (2.2)
Pericardial effusion	1 (4.0)	0	1 (2.2)
EYE DISORDERS	0	1 (4.8)	1 (2.2)
Retinopathy of prematurity	0	1 (4.8)	1 (2.2)
GASTROINTESTINAL DISORDERS	2 (8.0)	4 (19.0)	6 (13.0)
Diarrhoea	0	1 (4.8)	1 (2.2)
Necrotising colitis	1 (4.0)	1 (4.8)	2 (4.3)
Vomiting	1 (4.0)	2 (9.5)	3 (6.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (4.0)	2 (9.5)	3 (6.5)
Influenza like illness	0	1 (4.8)	1 (2.2)
Pyrexia	1 (4.0)	1 (4.8)	2 (4.3)
INFECTIONS AND INFESTATIONS	2 (8.0)	10 (47.6)	12 (26.1)
COVID-19	1 (4.0)	1 (4.8)	2 (4.3)
Candida sepsis	0	1 (4.8)	1 (2.2)
Enterobacter sepsis	0	1 (4.8)	1 (2.2)
Enterococcal sepsis	0	1 (4.8)	1 (2.2)
Infection	0	1 (4.8)	1 (2.2)
Oral candidiasis	1 (4.0)	0	1 (2.2)
Pneumonia aspiration	0	1 (4.8)	1 (2.2)
Postoperative wound infection	0	1 (4.8)	1 (2.2)
Rhinovirus infection	0	1 (4.8)	1 (2.2)
Sepsis	0	5 (23.8)	5 (10.9)
Septic shock	0	1 (4.8)	1 (2.2)
INVESTIGATIONS	4 (16.0)	6 (28.6)	10 (21.7)
Alanine aminotransferase increased	1 (4.0)	0	1 (2.2)
Blood potassium increased	0	1 (4.8)	1 (2.2)
Blood thyroid stimulating hormone increased	1 (4.0)	0	1 (2.2)
Cardiac murmur	1 (4.0)	0	1 (2.2)
Electrocardiogram QT prolonged	1 (4.0)	1 (4.8)	2 (4.3)
Hepatic enzyme increased	1 (4.0)	1 (4.8)	2 (4.3)
International normalised ratio increased	1 (4.0)	0	1 (2.2)
Oxygen saturation decreased	1 (4.0)	1 (4.8)	2 (4.3)

Transaminases increased	0	2 (9.5)	2 (4.3)
METABOLISM AND NUTRITION DISORDERS	3 (12.0)	1 (4.8)	4 (8.7)
Fluid retention	1 (4.0)	0	1 (2.2)
Hypercholesterolaemia	0	1 (4.8)	1 (2.2)
Hypermagnesaemia	1 (4.0)	0	1 (2.2)
Hypertriglyceridaemia	0	1 (4.8)	1 (2.2)
Hypoalbuminaemia	1 (4.0)	0	1 (2.2)
Hyponatraemia	1 (4.0)	0	1 (2.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (4.0)	0	1 (2.2)
Growth retardation	1 (4.0)	0	1 (2.2)
NERVOUS SYSTEM DISORDERS	0	1 (4.8)	1 (2.2)
Clonus	0	1 (4.8)	1 (2.2)
PSYCHIATRIC DISORDERS	1 (4.0)	0	1 (2.2)
Delirium	1 (4.0)	0	1 (2.2)
RENAL AND URINARY DISORDERS	2 (8.0)	2 (9.5)	4 (8.7)
Hydronephrosis	1 (4.0)	0	1 (2.2)
Oliguria	1 (4.0)	1 (4.8)	2 (4.3)
Renal failure	0	1 (4.8)	1 (2.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (4.0)	2 (9.5)	3 (6.5)
Acute respiratory failure	0	1 (4.8)	1 (2.2)
Bronchomalacia	1 (4.0)	0	1 (2.2)
Bronchopulmonary dysplasia	0	1 (4.8)	1 (2.2)
Pneumothorax	0	1 (4.8)	1 (2.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (4.0)	3 (14.3)	4 (8.7)
Decubitus ulcer	0	2 (9.5)	2 (4.3)
Dermatitis diaper	0	1 (4.8)	1 (2.2)
Erythema	1 (4.0)	0	1 (2.2)
VASCULAR DISORDERS	0	1 (4.8)	1 (2.2)
Hypertension	0	1 (4.8)	1 (2.2)

Part A: Single Dose & Part B: Multi-Dose.
N = Number of participants in each part. n = Number of participants with the specified characteristic.
Percentages are based on the total number of participants in each specified characteristic and total(N).
Participants are only counted once per treatment per event and include data up to Late Follow-Up (LFU).
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a Participant may report two or more different adverse events within the higher level category.
MedDRA v25.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 23JAN2023 (03:37) Source Data: adae Table Generation: 06APR2023 (02:23)
(Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_CSR/adae_s0311_a
Table 14.3.1.2.10 Ceftazidime-Avibactam is for Pfizer internal use.

Overall, up to late follow-up (LFU), the most frequently reported all-causality TEAEs by SOC from either Part A or B were from the SOCs Infections and Infestations, Investigations and Blood and lymphatic disorders.

The most frequently reported all-causality TEAEs by PT in 3 or more participants (≥5%) were sepsis, anaemia, and vomiting.

According to the MAH, the majority of all-causality TEAEs were mild or moderate in severity. Five participants (10.9%) reported severe all-causality TEAEs up to LFU, all of which were considered not related to study intervention by the investigator.

1 participant (Part B, Cohort 2) experienced severe SAEs of oliguria and acute respiratory failure during the Treatment Phase. Both events resolved.

1 participant (Part B, Cohort 3) experienced severe SAEs of cardiac failure acute and sepsis during the Treatment Phase that led to discontinuation of study intervention. Both events resolved.

1 participant (Part B, Cohort 3) experienced a severe SAE of renal failure during the Treatment Phase and severe SAEs of necrotising colitis and septic shock during the Follow-up Phase. The event of renal failure led to discontinuation of study intervention. The events of necrotising colitis and septic shock were fatal; refer to section on Deaths below.

1 participant (Part A, Cohort 1) experienced a severe TEAE of hyponatremia and a severe SAE of increased hepatic enzyme, both during the Follow-up Phase. The event of hyponatremia resolved, and the event of increased hepatic enzyme was ongoing.

1 participant (Part B, Cohort 1) experienced severe SAEs of Enterobacter sepsis and Candida sepsis during the Follow-up Phase. Both events were ongoing at the time of the LFU Visit.

All-Causality TEAEs up to EOIV

In Part B, up to EOIV, the most frequently reported all-causality TEAEs by SOC were Investigations and Blood and Lymphatic System Disorders. The most frequently reported all-causality TEAEs by PT were neutropenia and transaminases increased, experienced by 2 participants (9.5%) each. According to the MAH, the majority of all-causality TEAEs were mild or moderate in severity.

Table 39. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term up to EOIV (All Causalities) (Part B) – Safety Analysis Set (Protocol C3591024)

	Part B			
Number (%) of Participants Evaluable for AEs by SYSTEM ORGAN CLASS and Preferred Term	**Cohort 1 (N=8) n (%)**	**Cohort 2 (N=5) n (%)**	**Cohort 3 (N=8) n (%)**	**Total (N=21) n (%)**
With Any adverse event	3 (37.5)	3 (60.0)	5 (62.5)	11 (52.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (12.5)	1 (20.0)	1 (12.5)	3 (14.3)
Anaemia	0	0	1 (12.5)	1 (4.8)
Neutropenia	1 (12.5)	1 (20.0)	0	2 (9.5)
CARDIAC DISORDERS	0	0	1 (12.5)	1 (4.8)
Cardiac failure acute	0	0	1 (12.5)	1 (4.8)
GASTROINTESTINAL DISORDERS	1 (12.5)	0	0	1 (4.8)
Diarrhoea	1 (12.5)	0	0	1 (4.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (12.5)	0	1 (12.5)	2 (9.5)
Influenza like illness	1 (12.5)	0	0	1 (4.8)
Pyrexia	0	0	1 (12.5)	1 (4.8)
INFECTIONS AND INFESTATIONS	0	0	1 (12.5)	1 (4.8)
Sepsis	0	0	1 (12.5)	1 (4.8)
INVESTIGATIONS	3 (37.5)	1 (20.0)	1 (12.5)	5 (23.8)
Blood potassium increased	0	1 (20.0)	0	1 (4.8)
Electrocardiogram QT prolonged	0	0	1 (12.5)	1 (4.8)
Hepatic enzyme increased	1 (12.5)	0	0	1 (4.8)
Transaminases increased	2 (25.0)	0	0	2 (9.5)
METABOLISM AND NUTRITION DISORDERS	0	0	1 (12.5)	1 (4.8)
Hypercholesterolaemia	0	0	1 (12.5)	1 (4.8)
Hypertriglyceridaemia	0	0	1 (12.5)	1 (4.8)
NERVOUS SYSTEM DISORDERS	0	1 (20.0)	0	1 (4.8)
Clonus	0	1 (20.0)	0	1 (4.8)
RENAL AND URINARY DISORDERS	0	1 (20.0)	1 (12.5)	2 (9.5)
Oliguria	0	1 (20.0)	0	1 (4.8)
Renal failure	0	0	1 (12.5)	1 (4.8)

Number (%) of Participants Evaluable for AEs by SYSTEM ORGAN CLASS and Preferred Term	Part B Cohort 1 (N=8) n (%)	Part B Cohort 2 (N=5) n (%)	Part B Cohort 3 (N=8) n (%)	Total (N=21) n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (20.0)	1 (12.5)	2 (9.5)
Acute respiratory failure	0	1 (20.0)	0	1 (4.8)
Pneumothorax	0	0	1 (12.5)	1 (4.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (12.5)	0	1 (12.5)	2 (9.5)
Decubitus ulcer	0	0	1 (12.5)	1 (4.8)
Dermatitis diaper	1 (12.5)	0	0	1 (4.8)

Part B: Multi-Dose. Cohort 1: > 28 days to < 3 months; Cohort 2: Full Term to <= 28 days; Cohort 3: Premature to <= 28 days.
N = Number of participants in each cohort group. n = Number of participants with the specified characteristic.
Percentages are based on the total number of participants in each cohort group and total (N).
Participants are only counted once per treatment per event and include data up to End of IV (EOIV).
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a Participant may report two or more different adverse events within the higher level category.
MedDRA v25.1 coding dictionary applied.
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Table 14.3.1.2.3 Ceftazidime-Avibactam is for Pfizer internal use.

Treatment-related TEAEs

One participant (Part A, Cohort 3) experienced a mild treatment-related TEAE of oxygen saturation decreased during the Follow-up Phase. No other treatment-related TEAEs were reported up to LFU. In Part B, no treatment-related TEAEs were reported up to EOIV or up to LFU.

Serious adverse event/deaths/other significant events

Eight subjects experienced serious adverse events, 3 subjects in part A and 5 subjects in part B, none of which was considered treatment-related. The serious events consist of necrotising colitis, two subjects with sepsis (Enterobacter sepsis, Candida sepsis, sepsis, enterococcal sepsis), one subject with renal failure, electrocardiogram QT prolonged, septic shock and necrotising colitis, one subjects with sepsis and acute cardiac failure, one subject with acute respiratory failure, oliguria and neutropenia, one subject with Covid-19, and one subject with hepatic enzyme increased. Confounding factors, underlying illness and lack of time association with treatment are described in all cases.

Deaths

Two participant deaths were reported; 1 during the study and 1 after study completion.

- 1 participant (Part B, Cohort 3) died on Study Day 35 as a result of SAEs of necrotising colitis and septic shock considered not related to study intervention by the investigator.
- 1 participant (Part B, Cohort 1) died on Study Day 67 as a result of an SAE of Candida sepsis considered not related to study intervention by the investigator, after completing the LFU Visit. The death occurred outside the active data collection period for the study.

Laboratory findings

In Part A, no clinically meaningful mean changes from baseline were observed in haematology, blood chemistry, or urinalysis parameters. There were a few individual clinically significant laboratory abnormalities, which were considered unrelated to study intervention and related to the participants' underlying condition.

In Part B, elevated C-reactive protein levels were observed, consistent with signs of infection, which normalised during the course of treatment in most participants (where data were available).

In addition, increases in lymphocyte counts, lymphocyte/leukocyte ratio, eosinophil counts, and eosinophil/leukocyte ratio were observed in several participants, consistent with their underlying condition.

No clinically meaningful changes from baseline were observed in urinalysis parameters in Part B. Some laboratory abnormalities were reported as TEAEs, all of which were considered unrelated to study intervention by the investigator.

No clinically meaningful changes from baseline were observed in urine outputs in Parts A or B.

Vital Signs

A mild treatment-related TEAE of oxygen saturation decreased was reported for 1 participant. The event started on Study Day 1 and resolved within approximately 1 day. Otherwise, no clinically meaningful changes were observed in vital sign measurements (SBP, DBP, PR, oxygen saturation, weight, temperature, and respiratory rate) in Part A or Part B of the study.

Physical Examination Findings

In Part A, the majority of participants had normal physical examination findings at each study visit.

In Part B, the majority of participants had normal physical examination findings at each study visit with the exception of general appearance and skin (e.g., poor general clinical condition, appearance of ill neonate, and jaundiced skin), which is consistent with and not unexpected for hospitalised neonates and infants (up to 3 months of age) with suspected or confirmed aerobic Gram-negative bacterial infection requiring IV antibacterial therapy.

Safety in special populations

Safety by Age Cohort

The majority of participants in Part A with all causality TEAEs up to LFU occurred in Cohort 1 (4 (44.4%)) compared to Cohorts 2 and 3 (2 (25.0%), 2 (25.0%) respectively). The majority of participants in Part B with all causality TEAEs up to LFU occurred in Cohorts 2 and 3 (4 (80.0%), 7 (87.50%) respectively) compared to Cohort 1 (4 (50.0%)).

In Part A, the SOC with the most frequently reported all causality TEAEs was the SOC of Investigations, the majority of which were reported in Cohort 3 (2 (25%)) compared to Cohorts 1 (1 (11.1%)) and 2 (1 (12.5%)).

In Part B, the most frequently reported all-causality TEAEs by SOC were from SOC Infections and Infestations where the events were most frequently reported in Cohort 3 (5 (62.5%)) compared to Cohorts 1 (2 (25.0%)) and 2 (3 (60.0%)).

No other intrinsic factors such as sex or race were analysed in this study.

Extrinsic Factors were not applicable for this submission.

Safety related to drug-drug interactions and other interactions

Please refer to section 4.4 and 4.5 of the SmPC for information on interactions for CAZ-AVI.

Discontinuation due to adverse events

Two participants (Part B, Cohort 3) discontinued study intervention due to SAEs. The SAEs were considered not related to study intervention by the investigator.

One participant (Part B, Cohort 3) discontinued the study during the Follow-up Phase due to SAEs of necrotising colitis and septic shock with fatal outcome. Both events were considered not related to study intervention by the investigator.

Post marketing experience

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality. The safety database was searched applying PSUR (PBRER) criteria for all CAZ-AVI post-marketing cases reported cumulatively through 16 October 2023.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data.

Data results

Cumulatively, there have been approximately 12,538 patient-years of exposure or 558,476 patients exposed to CAZ-AVI from the post-marketing experience. CAZ-AVI received first regulatory approval on 25 February 2015 in the US and is marketed in the US by AbbVie Inc under the tradename Avycaz.

CAZ-AVI is approved in further 92 countries (EU approval on 24 June 2016) and is currently marketed in 82 countries.

Table 40. Cumulative Estimated Exposure for CAZ-AVI[a]

Region	Patient Treatment days	Patient-years	Number patients treated	Total vials containing 2.5 g CAZ + AVI each
US	995,080	2,724	121,351	2,985,241
EU	1,475,539	4,040	179,944	4,426,617
Rest of World	2,108,886	5,774	257,181	6,326,658
Total	4,579,505	12,538	558,476	13,738,516

a. Assuming 3 adult doses per day for 8.2 days

The reference safety information (RSI) for this post marketing information is the CAZ-AVI SmPC dated 11 February 2021. A type II variation procedure (EMEA/H/C/004027/II/0033) regarding inclusion of safety information about Kounis syndrome was finalised 24 January2024.

There were no actions taken regarding CAZ-AVI for safety reasons by either a health authority (HA) or by the marketing authorisation holder (MAH) from the latest submitted PSUR (data lock point of 24 Feb 2023) through 16 Oct 2023.

Post Marketing paediatric cases (from birth to less than 3 months of age)

Through 16 October 2023, a total of 54 post-marketing cases in paediatric patients aged from birth to 3 months of age were reported in Pfizer's safety database; six cases were serious, 48 non-serious. The majority of cases (> 90%) pertained to reports of off-label use. Forty-four cases (81.5%) reported the PT Off label use, 17 cases (31.5%) reported Product use issue and 3 cases (3.7%) reported drug effective unapproved indication. Only 2 clinical PTs were reported more than once (Drug induced liver injury (2), and Hypomagnesaemia (2)); the associated cases are summarised below.

Two cases of DILI (Drug induced liver injury) were received from Russia. The 2 case reports were received on the same day by a single reporter (a physician), both reporting the same events, whereby one case concerned a full-term baby, and the other a premature baby; in all other aspects, the available case information was identical for both cases. Available information was very limited (no indication, no treatment dose or duration, no specific age, no concomitant medication or medical history, or any details about the event), and insufficient for a meaningful case assessment. Event outcome or action taken in response to the event were both unknown. Standard follow-up attempts have been completed, and no further information was obtained or is expected for either of the cases.

The 2 cases of hypomagnesaemia were received from Greece and originated from the same literature article. The available case information is identical for both cases and very limited (no indication, no treatment dose or duration, no specific age, no concomitant medication or medical history, or any details about the event), and insufficient for a meaningful case assessment. It was only reported that both neonates developed hypomagnesemia during CAZ-AVI treatment, which was solved by increasing the intravenous administration of magnesium. Standard follow-up attempts were not possible, and no further information is expected for either of the cases.

2.5.1. Discussion on clinical safety

The proposed expansion of therapeutic indication for CAZ-AVI is for the treatment of paediatric patients (neonates and infants) from birth to <3 months of age with cIAI, cUTI, HAP/VAP and other infections due to aerobic Gram-negative organisms in patients with limited treatment options. The submission is based on data from study C3591024. Population PK models based on this study (PK-data for 44 subjects) and also study C3591025 (PK-data for 4 subjects) to predict exposure and PK/PD attainment for applied doses are assessed in the pharmacology section of this AR. Additionally, the MAH proposes extrapolation of clinical safety from previous studies with Zavicefta in adults and paediatric subjects >3 months of age.

According to the MAH, study C3591024 was terminated early, (30 December 2022), after all treated participants had reached their end-of-study. This decision was taken due to slow enrolment and a determination by the sponsor that sufficient PK data had been collected to support dose recommendations and safety/efficacy extrapolation for the neonatal age range.

The pivotal clinical study C3591024 was conducted in 2 parts. In Part A (single dose part) of the study safety was a secondary endpoint. In part B (multiple dose part) safety was the primary endpoint. In both parts safety and tolerability endpoints included AEs, SAEs, deaths, discontinuations due to AEs, and laboratory abnormalities. A total of 46 subjects were included in the safety analysis set, 25 subjects in part A and 21 subjects in part B.

Overall, 23 of 46 participants (50.0%) experienced TEAEs up to LFU, 8 of whom experienced SAEs.

In **part A**, there were 26 TEAEs in total, reported in 8 (32%) subjects. TEAEs occurred most frequently in the SOCs Investigations; 4 subjects (16%) and Metabolism and nutrition disorders, 3 subjects (12%). Only one of these TEAEs were considered treatment-related, namely 1 subject with oxygen saturation decreased. Of note, one subject had a TEAE of oral candidiasis, which is an ADR for Zavicefta.

In **part B**, there were 45 TEAEs in total, reported in 15 (71.4%) subjects. TEAEs occurred most frequently in SOCs Infections and infestations, (10 subjects, 47.6%), Investigations; 6 subjects (28.6%), Blood and lymphatic system disorders 5 (23.8%) subjects, Gastrointestinal disorders, 4 (19.0%) subjects, Skin and subcutaneous disorders 3 (14.3%) subjects and Renal and urinary disorders 2 (9.5%) subjects. None of the TEAEs were considered treatment related. Of note, 2 subjects in part B had neutropenia, 2 subjects experienced transaminase increased, 2 subjects experienced vomiting and one subject diarrhoea, all of which are listed ADRs for Zavicefta.

Eight subjects experienced serious adverse events, 3 subjects in part A and 5 subjects in part B, none of which was considered treatment related. None of these serious adverse events are sufficiently discussed in the Clinical Overview or Summary of Clinical Safety, however, narratives are presented in module 5. The serious events consist of necrotising colitis, two subjects with sepsis (Enterobacter sepsis, Candida sepsis, sepsis, enterococcal sepsis), one subject with renal failure, electrocardiogram QT prolonged, septic shock and necrotising colitis, one subjects with sepsis and acute cardiac failure, one subject with acute respiratory failure, oliguria and neutropenia, one subject with Covid-19, and one subject with hepatic enzyme increased. Confounding factors, underlying illness and lack of time association with treatment are described in all cases.

Two deaths were reported during the study. One subject in Part B died on study day 35 as a result of SAEs of necrotising colitis and septic shock. This case is discussed in narratives for SAEs, and according to investigator and sponsor, there was no compatible time association or reasonable pathophysiological evidence to attribute the fatal sepsis and necrotising colitis to the ceftazidime-avibactam treatment. The underlying sepsis and acute coronary syndrome are possible confounders.

One subject in part B died on study day 67 as a result of candida sepsis. Considering that event occurred after the active data collection period for the study, no further information is presented.

No clinically meaningful mean changes from baseline were observed in haematology, blood chemistry, or urinalysis parameters for Part A. In part B some laboratory abnormalities were reported as TEAEs, all of which were considered unrelated to study intervention by the investigator.

Discontinuation from study: One subject in Part B, Cohort 3 discontinued the study during the Follow-up Phase due to SAEs of necrotising colitis and septic shock with fatal outcome. This case is discussed under the SAEs section.

The MAH has also provided an overview of post-marketing data. Cases with age range from birth to less than 3 months consist of 54 cases; where 40 are aged 0-27 days, and 14 from 28 days to less than 3 months. Outcome is unknown in most cases. Nine cases are reported from literature and overall, 6 cases are reported as serious. The majority of cases (> 90%) pertained to reports of off-label use. Only 2 clinical PTs were reported more than once (Drug induced liver injury (2), and Hypomagnesaemia (2). The cases of drug induced liver injury (DILI) and hypomagnesaemia are reported with very limited information, and as such no meaningful conclusion can be drawn from these reports. Of note, hepatotoxicity is an important potential risk for CAZ-AVI.

Overall, study C3591024 provides data from a very limited number of subjects in the lowest age groups. However, no new safety findings were observed, and the safety profile of CAZ-AVI in

paediatric patients from birth to <3 months seem to be in line with findings in adults and in previous paediatric studies.

2.5.2. Conclusions on clinical safety

Based on data from study C3591024, where 46 subjects (neonates and infants from birth to less than 3 months of age) were included in the safety analysis set, no new safety findings were observed.

In total 71 TEAEs were reported in half (50%) of the participating subjects, however, only one of these was considered treatment-related, namely 1 subject with oxygen saturation decreased. Eight subjects experienced SAEs; 3 subjects in the single-dose part (A) of the study and 5 subjects in the multiple-dose part (B), but none was considered treatment-related.

Paediatric-specific adverse events are unlikely to be detected in this trial that is very limited in size and duration. However, the safety profile of Zavicefta in paediatric patients from birth to <3 months seem to be in line with findings in adults and previous paediatric studies in patients from 3 months of age and older.

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. Risk management plan

The MAH submitted an updated RMP version 3.3 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.3 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity Bacterial resistance development
Missing information	Pregnancy exposure Lactation exposure Immunocompromised population exposure

The list of safety concerns is unchanged, which is agreed.

Pharmacovigilance plan

Summary Table of Additional Pharmacovigilance Activities

On-Going and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of objectives	Safety concerns addressed	Due dates
Resistance Surveillance Programme An international antimicrobial surveillance programme Category 3 Ongoing	To track the longitudinal in vitro activity of CAZ-AVI and comparator agents against relevant clinical isolates (those pathogens identified in the SmPC against which CAZ-AVI demonstrated clinical efficacy) in cIAI, cUTI, and HAP.	Bacterial resistance development	Reports will be submitted annually for 5 years once CAZ-AVI is on the market in the EU; the final report will be Year 5.

CAZ-AVI = Ceftazidime-Avibactam; cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; HAP = Hospital-acquired Pneumonia; SmPC = Summary of Product Characteristics

Risk minimisation measures

Routine risk minimisation measures

Text revised to aligned with the updated text of the SmPC and proposed new wording in support of the EU submission for a paediatric indication neonates and infants from birth to less than 3 months of age.

Additional risk minimisation measures

No additional risk minimisation measures are proposed.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

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

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable, as 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 MAH has applied for an extension of indication to broaden the current indications of Zavicefta to include treatment of paediatric patients from birth to < 3 months of age with the following infectious diseases:

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Infections due to aerobic Gram-negative organisms where the treatment options are limited.

3.1.2. Available therapies and unmet medical need

Infections due to resistant Gram-negative bacteria are increasingly common in paediatric patients. Few antibiotics with activity against ESBL and carbapenemase producing Gram-negative bacteria are currently available. Furthermore, only a few antibacterial agents have had their safety and efficacy carefully evaluated in paediatric patients. Hence, there is an undisputable medical need for further treatment options for the paediatric patient population.

3.1.3. Main clinical study

Study C3591024

Clinical Phase 2a, 2-part, open-label, non-randomised, multi-centre, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime-avibactam in neonates and infants from birth to less than 3 months of age hospitalised with suspected or confirmed infections due to Gram-negative pathogens requiring intravenous antibiotic treatment. The study was conducted in 2 parts, Part A and Part B. Part A was a non-randomised, open-label and single-dose study with PK as primary endpoint and safety as secondary endpoint. Part B was a non-randomised, open-label, multi-dose and single treatment arm study with safety as primary endpoint. In this part efficacy together with PK were assessed as secondary objectives. Efficacy endpoints were merely descriptive in nature.

A total of 48 participants were enrolled in the study and 46 participants were treated with ceftazidime-avibactam, of which 45 patients were included in the PK analysis set. In Part A, 27 patients were included whereof 25 were treated. In Part B, 21 patients were included and of these, 16 patients received ceftazidime-avibactam and met the minimal disease criteria described in the inclusion criteria. These patients were included in the modified-ITT analysis set.

In both Part A and B, the majority of patients was ≥37 weeks (15 and 13 patients, respectively).

The application relies on the concept of extrapolation of clinical efficacy based on comparable plasma exposures in children to those in adults. The acceptance of extrapolation is based on assumptions that the disease, mechanism of action and thus PK/PD are the same in paediatric patients as in adults and

therefore the doses selected should achieve similar plasma exposures and probability of PK/PD target attainment (PTA) in children as in adults.

3.2. Favourable effects

An updated popPK analysis (PMAR-EQDD-C359m-sNDA-1155) was conducted to assess the PK of ceftazidime-avibactam in paediatric patients <3 months and to support that the proposed dose recommendations allow for PK bridging to adults for extrapolation of efficacy. Paediatric PK data from phase II study C3591024 were pooled with PK data from adults (phase I-III) and from patients aged 3 months to <18 years (phase I-II).

Simulated paediatric exposures and jPTA analyses for preterm (≥26 weeks GA) and term neonates and infants <3 months using the previously established joint PKPD target, demonstrated PTA achievement of >95% at the proposed dose regimens for the relevant paediatric subgroups with cIAI, cUTI and HAP/VAP.

Efficacy measures were defined as secondary endpoints in the phase II studies and evaluation of efficacy was based on descriptive statistics. *Favourable clinical outcome (cure or improvement) rates were 81.0% (17/21) and 75.0% (12/16) at TOC for the ITT and the modified-ITT analysis set, respectively. The microbiological eradication or presumed eradication rate at TOC (micro-ITT) was 80% (8/10). Regarding all-cause mortality: 2 patients died (one on Study Day 35 and the other on Study 67 which was outside the active data collection period).* No participant had emergent infections.

3.3. Uncertainties and limitations about favourable effects

Dose recommendations in the youngest age group 26- <31 weeks GA are based on extrapolation of ceftazidime-avibactam pharmacokinetics by modelling and simulation exercises.

The primary objective of Study C3591024 was to evaluate pharmacokinetics, safety and tolerability of ceftazidime-avibactam in neonates and infants from birth to <3 months of age. Hence, the study was not powered for a statistical analysis of efficacy and of limited size. As per the inclusion and exclusion criteria patients hospitalised with suspected or confirmed infections due to Gram-negative pathogens requiring intravenous antibiotic treatment were included.

3.4. Unfavourable effects

A similar safety profile is expected across age sub-groups whenever paediatric dose regimens achieve similar ceftazidime-avibactam systemic exposures to those in other age sub-groups.

Overall, 23 of 46 participants (50.0%) experienced TEAEs up to LFU, 8 of whom experienced SAEs.

In part A, there were 26 TEAEs in total, reported in 8 (32%) subjects. TEAEs occurred most frequently in SOCs Investigations; 4 subjects (16%) and Metabolism and nutrition disorders, 3 subjects (12%).

In part B, there were 45 TEAEs in total, reported in 15 (71.4%) subjects. TEAEs occurred most frequently in SOCs Infections and infestations, (10 subjects, 47.6%), Investigations; 6 subjects (28.6%), Blood and lymphatic system disorders 5 (23.8%) subjects, Gastrointestinal disorders, 4 (19.0%) subjects, Skin and subcutaneous disorders 3 (14.3%) subjects and Renal and urinary disorders 2 (9.5%) subjects.

Only one reported TEAE was considered related to treatment with ceftazidime-avibactam, namely 1 subject with oxygen saturation decreased, observed in part A.

Eight subjects experienced serious adverse events, 3 subjects in part A and 5 subjects in part B. The serious events consist of necrotising colitis, two subjects with sepsis (Enterobacter sepsis, Candida sepsis, sepsis, enterococcal sepsis), one subject with renal failure, electrocardiogram QT prolonged, septic shock and necrotising colitis, one subjects with sepsis and acute cardiac failure, one subject with acute respiratory failure, oliguria and neutropenia, one subject with Covid-19, and one subject with hepatic enzyme increased. None of the reported SAEs was considered treatment related.

Two deaths were reported during the study, none of which was considered treatment related.

3.5. Uncertainties and limitations about unfavourable effects

Dose recommendations in the youngest age group 26 to <31 weeks GA are based on modelling and simulation only, as no PK data is available in this population: ceftazidime and avibactam exposures are predicted to be similar to those in preterm neonates 31-<37 weeks GA, and within the adult 5th to 95th percentile reference range across the sought indications.

A limitation of the unfavourable effects is the very limited size of study C391024, with less than 20 subjects included in each of the three age cohorts.

None of the observed TEAEs in part B were considered treatment related. However, 2 subjects in part B had neutropenia, 2 subjects experienced transaminase increased, 2 subjects experienced vomiting and one subject diarrhoea, all of which are listed ADRs for Zavicefta.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

A popPK modelling approach was employed to identify appropriate doses of ceftazidime-avibactam to be used in (pre)term neonates and infants <3 months of age under the assumption that comparable PK exposure as in adults should lead to similar response to ceftazidime-avibactam. This strategy is accepted. Thus, the extension of the proposed indications to the paediatric patients depends on the adequacy of the proposed dose regimens in different age subgroups to achieve adult exposure matching, and whether the paediatric safety profile is acceptable (EMA/187859/2017).

The adequacy of proposed dose recommendations is demonstrated for the age groups ≥31 weeks GA based on PK data from study C3591024 and PK/PD modelling and simulation.

There is no PK data in the lowest age group 26-<31 weeks GA in study C3592024, and dose recommendations in this group is based only on PK/PD modelling and simulation. The PK-PD analyses show jPTA ≥98%, and efficacy in this youngest group is therefore expected to be adequate. Exposures of ceftazidime and avibactam are predicted to be similar to those in preterm neonates 31-<37 weeks GA, and within the adult 5th to 95th percentile reference range across the sought indications, which is reassuring from a safety perspective. Limited literature on clinical use is available, but there are, however, published case reports and (retrospective) studies on use of ceftazidime and ceftazidime-avibactam in preterm infants with similar or higher doses than those proposed in the current application, which report no major safety concerns. Furthermore, ceftazidime is a well-known active substance, for which there is extensive clinical experience, and ceftazidime monotherapy is used in comparable doses in neonates, as those proposed for ceftazidime-avibactam. The seriousness of the clinical indications in this vulnerable population, the short treatment duration and the potential for curative therapy, should also be taken into account. The totality of data support the currently proposed dose recommendations from 26 weeks PMA (with an extended dose interval).

The safety profile in all age groups is expected to be driven mainly by systemic exposure to the ceftazidime-avibactam. The safety profile of ceftazidime-avibactam in paediatric patients from birth to <3 months seem to be in line with findings in adults and previous paediatric studies in patients from 3 months of age and older. No new safety findings have been identified in study C3591024.

According to relevant guidance (EMA/187859/2017), no appropriately powered efficacy studies are required in the paediatric population as efficacy can be extrapolated from adults provided similar exposure is achieved in the paediatric population.

3.6.2. Balance of benefits and risks

The benefit/risk balance of ceftazidime-avibactam for treatment of paediatric patients from birth to <3 months is positive.

3.7. Conclusions

The overall benefit-risk of Zavicefta 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 and IIIB

Extension of indication to include treatment of paediatric patients from birth to less than 3-months of age in the following infections: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and in the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options, for Zavicefta, based on final results from study C3591024 and the population PK modelling/simulation analyses. Study C3591024 is a Phase 2a, 2-part, open-label, non-randomised, multicenter, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring intravenous antibiotic treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. A revised RMP version 3.3 has been approved. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0551/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Zavicefta-H-C-004027-II-0035’