17 September 2020
EMA/543616/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Zavicefta

International non-proprietary name: ceftazidime / avibactam

Procedure No. EMEA/H/C/004027/II/0015

Note

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

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List of abbreviations

% fT > CT	Percentage of time that free drug concentrations are above the threshold concentration
%fT > MIC	Percentage of time that free drug concentrations are above the minimal inhibitory concentration
%RSE	Percentage relative standard errors
ADR	Adverse drug reaction
AE	Adverse event
AEoSI	Adverse events of special interest
AmpC	Class C β-lactamase
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area under the plasma concentration versus time curve
AUC0-last	Area under the plasma concentration-time curve from zero to the last
AUCss,0-24	Area under the plasma concentration-time curve over 24 hours at steady state
AVI	Avibactam
BMI	Body mass index
BSA	Body surface area
CAZ	Ceftazidime
CAZ-AVI	Ceftazidime-avibactam
CAZ-NS	Ceftazidime-non-susceptible
CE	Clinically evaluable
CEF	Cefepime
cIAI	Complicated intra-abdominal infection
CL	Clearance
C_{max}	Maximum plasma drug concentration
Cmax,ss	Maximum plasma drug concentration at steady state
Cmin,ss	Minimum plasma drug concentration at steady state
CrCl	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Threshold concentration
cUTI	Complicated urinary tract infection
CV	Coefficient of variation
DAGT	Direct antiglobulin test
DCO	Data cut-off
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiogram
ECMA	Evaluability and clinical/microbiological assessment
Emax	Maximum efficacy
EOIV	End of intravenous treatment
EOT	End of treatment
ESBL	Extended-spectrum β-lactamases
FDA	Food and Drug Administration
FOCE-INTER	First Order Conditional Estimation with Interaction
FSFV	First Subject First Visit
HABP/VABP	Hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia
HAP	Hospital-acquired pneumonia
IB	Investigator's Brochure
ICSR	Individual case safety reports
IP	Investigational product
IRB	Institutional review board.
ITT	Intent-to-treat
IV	Intravenous
LFU	Late Follow up
LLN	Lower limit of normal
MAA	Marketing Authorization Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
ME	Microbiologically evaluable
MER	Meropenem
MIC	Minimum inhibitory concentration
micro-ITT	Microbiological intent-to-treat
M&S	modelling and simulation
MTZ	Metronidazole
NCrCl	body surface area normalised creatinine clearance
NOAEL	No observed adverse effect level
NONMEM	Nonlinear mixed effects modeling

NP	Nosocomial Pneumonia
PBRER	Periodic Benefit Risk Evaluation Report
PCS	Potentially clinically significant
pcVPC	Prediction-corrected visual predictive check
PD	Pharmacodynamic
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PMA	Post menstrual age
PND	Post-natal day
popPK	Population pharmacokinetics
PT	Preferred term
PTA	Probability of PK/PD target attainment
q8h	quaque octa hora (every 8 hours)
Q	Intercompartmental clearance
SAE	Serious adverse event
SAEM	Stochastic Approximation of Expectation-Maximisation
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
steady state	threshold concentration over a dose interval
TEAE	treatment emergent adverse events
TOC	Test of cure
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	Urinary tract infection
USPI	United States Prescribing Information
VAP	Ventilator-associated pneumonia
Vc	Central volume of distribution
Vp	Peripheral volume of distribution

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 29 March 2019 an application for a variation.

The following variation was requested:

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

Extension of indication to include paediatric patients aged 3 months to less than 18 years for Zavicefta (for the treatment of cIAI and cUTI), based on data from paediatric studies D4280C00014, C3591004 and C3591005 and the population PK modelling/simulation analyses (CAZ-MS-PED-01 and CAZ-MS-PED-02). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated in order to reflect this additional population, the paediatric posology, paediatric safety information, the description of the clinical trials and handling instructions for paediatric dosing. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct the sodium content to SmPC sections 2 and 4.4 and PL section 2 and the volumes of distribution of ceftazidime and avibactam in SmPC section 5.2.
The RMP version 3.0 has also been submitted.

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 the EMA Decision(s) P/0340/2018 of 8 November 2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some remaining measures in the PIP are still deferred. The current application is based on Study 3, 4, 5 and 7 in the PIP.

The PDCO concluded a partial compliance for the PIP (EMEA-C2-001313-PIP01-12-M08) with positive outcome.

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 regarding the paediatric development programme.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bjorg Bolstad Co-Rapporteur: Simona Stankeviciute

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	27 Apr 2019	27 Apr 2019
☐	CHMP Co-Rapporteur Assessment Report	21 Jun 2019	21 Jun 2019
☐	CHMP Rapporteur Assessment Report	21 Jun 2019	21 Jun 2019
☐	PRAC Rapporteur Assessment Report	28 Jun 2019	28 Jun 2019
☐	PRAC members comments	03 Jul 2019	03 Jul 2019
☐	Updated PRAC Rapporteur Assessment Report	04 Jul 2019	04 Jul 2019
☐	PRAC endorsed relevant sections of the assessment report	11 Jul 2019	11 Jul 2019
☐	CHMP members comments	15 Jul 2019	15 Jul 2019
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Jul 2019	18 Jul 2019
☐	Request for supplementary information	25 Jul 2019	25 Jul 2019
☐	Request for ext. on timetable	19 Sep 2019	19 Sep 2019
☐	Submission of responses	24 Jan 2020	23 Jan 2020
☐	Restart	27 Jan 2020	27 Jan 2020
☐	CHMP Rapporteur Assessment Report	25 Feb 2020	28 Feb 2020
☐	PRAC Rapporteur Assessment Report	28 Feb 2020	27 Feb 2020
☐	PRAC members comments	04 Mar 2020	04 Mar 2020
☐	Updated PRAC Rapporteur Assessment Report	05 Mar 2020	06 Mar 2020
☐	PRAC endorsed relevant sections of the assessment report	12 Mar 2020	12 Mar 2020
☐	CHMP members comments	16 Mar 2020	16 Mar 2020
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 Mar 2020	20 Mar 2020
☐	Request for supplementary information	26 Mar 2020	26 Mar 2020
☐	Submission of responses	20 May 2020	19 May 2020
☐	Restart	25 May 2020	25 May 2020
☐	CHMP Rapporteur Assessment Report	23 Jun 2002	23 Jun 2020

Status of this report and steps taken for the assessment			
☐	PRAC Rapporteur Assessment Report	26 Jun 2020	26 Jun 2020
☐	PRAC members comments	01 Jul 2020	01 Jul 2020
☐	Updated PRAC Rapporteur Assessment Report	02 Jul 2020	n/a
☐	PRAC endorsed relevant sections of the assessment report	09 Jul 2020	09 Jul 2020
☐	CHMP members comments	13 Jul 2020	13 Jul 2020
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 Jul 2020	16 Jul 2020 23 Jul 2020
☐	3RD Request for supplementary information	23 Jul 2020	23 July 2020
☐	Submission of responses	18 Aug 2020	18 Aug 2020
☐	Restart	19 Aug 2020	19 Aug 2020
☐	CHMP Rapporteur Assessment Report	02 Sep 2020	02 Sep 2020
☐	CHMP members comments	07 Sep 2020	07 Sep 2020
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 Sep 2020	10 Sep 2020
☒	Opinion	17 Sep 2020	17 Sep 2020

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 drug 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, approved in the EU for the treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), nosocomial pneumonia (NP) and a range of other

infections. It has no noticeable antibacterial activity against Gram-positive pathogens, with the exception of some streptococci, or anaerobes.

Zavicefta (CAZ-AVI) is currently approved for adults in complicated intra-abdominal infection, complicated urinary infection and hospital-acquired pneumonia, including ventilator-associated pneumonia. Furthermore, ceftazidime (CAZ) is well-known from clinical practice also in the paediatric population and is approved from the age of 2 months.

This application was initially intended to extend the approved treatment of cIAI and cUTI indications to children aged from 3 months to less than 18 years of age, including the appropriate dose recommendations for this age subgroup. The CHMP, during the variation procedure, suggested that the application would be extended to include the indications HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options, in addition to cIAI and cUTI. The MAH provided therefore further analyses, updated Clinical Summary and RMP as part of the responses to the first RSI.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application. However, a non-clinical safety assessment specific for paediatric patients ≥3 months of age has been conducted, which was considered acceptable by the CHMP.

2.2.1. Introduction

In the approved PIP (EMEA-001313-PIP01-12-M08) targeting the indications cIAI and cUTI, a 14-day toxicity study in juvenile rats is included in the measures.

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.

Compared to the initial MAA, no new non-clinical data have been generated for this extension of indication application. General non-clinical characteristics for avibactam and the combination are briefly summarised below (source: EPAR for Zavicefta). The definitive juvenile rat toxicity study is presented in more detail in connection with the non-clinical safety assessment specific for paediatric patients ≥ 3 months of age.

2.2.2. Pharmacology

Avibactam does not adversely affect the antibacterial activity of ceftazidime and restores the activity of ceftazidime against beta-lactamase-producing bacteria within its spectrum of activity and within the range of inhibition of avibactam.

Intravenous administration of avibactam had no clinically relevant effects on the cardiovascular, respiratory, gastrointestinal or renal systems in animal models. There was also no effect on the hERG channel in a GLP compliant study at avibactam concentrations up to 1000 µM.

2.2.3. Pharmacokinetics

Avibactam had no effect on plasma protein binding and has low penetration into blood cells. Avibactam is widely distributed across tissues and organs and evidence showed that avibactam crosses the placenta and is also excreted in rat milk.

Metabolism of avibactam is very low in both animals and humans. Avibactam is readily excreted in urine and is also eliminated by OAT1 and OAT3 transport across the renal epithelium (but not ceftazidime). Blood concentrations of avibactam may therefore be affected by other drugs which induce or inhibit OAT1 and/or OAT3 transportation.

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

2.2.4. Toxicology

Repeat dose toxicity

Following daily intravenous administration of avibactam for 4-weeks the No Observed Adverse Effect Level (NOAEL) was deemed to be 250 mg/kg/day in both rat and dog. No major systemic toxicity was observed in adult animals with avibactam or ceftazidime either alone or in combination; the main issue identified was local tolerance at the injection site in all non-clinical species used. Adverse drug reactions were seen in the clinical trials with avibactam but there were no reports of severe reactions or patient discontinuations due to injection site tolerability.

Genotoxicity and Carcinogenicity

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

Reproduction toxicity

Avibactam did not affect female fertility/reproductive performance or embryo-foetal development following repeat IV administration to rats at doses up to 250 mg/kg/day (AA39554 (DS0021)). Two malformed foetuses at 500 mg/kg/day (one with domed head, protruding tongue, malrotated right hindlimb and hyperextension of the right forepaw and a second with scoliosis) and at 1000 mg/kg/day (anophthalmia) were reported in the rat embryo-foetal development study. Since there were no malformations and no overall effects on embryo-foetal development at 250 mg/kg/day, the exposures at this dose were considered as an appropriate reference for a no observed effect level (NOEL) for embryo-foetal changes in the rat.

In the rabbit embryo/foetal development study (AA39552 (DS0024)), there was an increased post-implantation loss at 1000 mg/kg/day and lower mean foetal weights with slightly retarded ossification of the metacarpal of the first digit, tarsal bone and sixth sternebra was observed at 300 mg/kg/day and above. These findings have been adequately addressed in the Zavicefta SmPC. There were no other overt findings at 100 mg/kg/day and this dose is therefore deemed to be the NOEL for embryo-foetal changes in the rabbit and the NOAEL for maternal toxicity.

Avibactam administered alone during pregnancy and lactation to F0 rats was associated with a dose related increase in the incidence of F1 renal pelvic dilatation (without recovery) and ureter dilatation in less than 10% of the pups, with no associated pathological changes to the renal parenchyma (AB04834 (3225WR)). The effect was seen at maternal exposure levels ≥ 1.5 times human therapeutic exposures. Ureter dilatation was reversible and not seen in the young adult offspring. The dose of 120 mg/kg/day was considered to be the NOEL.

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;

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

The 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.

For the paediatric population, the recommended maximum dosage is similar to the adult population.

Zavicefta was first approved in Europe in 2016. In the current submission, an extension of the indication to include paediatric use for the indications cIAI and cUTI 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 3. 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	0.0015	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.**		

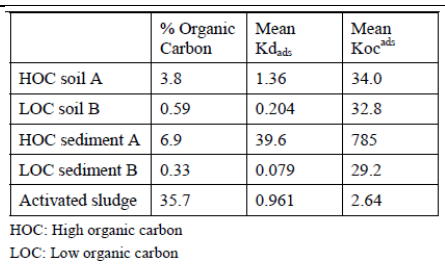
Phase I

- Ceftazidime

Table 4. 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- logD_{ow}[a]	OECD107	$LogD_{ow}$ < -2.20 (pH5) $LogD_{ow}$ < -2.21 (pH7) $LogD_{ow}$ < -2.17 (pH9)	Potential PBT **No**
PBT-statement:	**The log D values for ceftazidime are < 4.5 at all environmentally relevant pHs, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined	0.12	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 anticipated not persisting in the aquatic environment.
Outcome of Phase IIA Physical-chemical properties and fate:	**The adsorption coefficient ($Kd_{(ads)}$) is < 3700 L/Kg and therefore a Tier B assessment of the terrestrial compartment is not required. As greater than 10% of the radioactivity was associated with the sediment phase, the effect of ceftazidime on sediment-dwelling organisms is required.**			

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 32[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*
$PEC_{surfacewater}$ $PNEC_{surfacewater}$ **$PEC/PNEC_{surfacewater}$**			0.11 1.3 **0.085**	µg/L µg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{groundwater}$ $PNEC_{groundwater}$ **$PEC/PNEC_{groundwater}$**			0.028 920 **0.00003**	µg/L µg/L	Unlikely to represent a risk to the aquatic environment

$PEC_{microorganisms}$ $PNEC_{microorganisms}$ **$PEC/PNEC_{microorganisms}$**			0.11 32 000 **3.4×10^{-6}**	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

The CHMP considered that issues with the calculation of the Fpen for avibactam and ceftazidime and the prevalence/ consumption data were resolved in the last revision of the environmental risk assessment.

The PECsurfacewater for both substances are now accepted, as well as the prevalence/consumption data.

Ceftazidine is not considered a PBT and does not need to be classified as such.

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 in table 2 are copied from the previous assessment report.

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

The calculation of the $PEC_{sediment}$ is slightly different from the previous application (the Kp_{susp} is calculated using the weight fraction organic carbon in susp. solids (default value) and the K_{OC} rather than using the Kd value).

The CHMP considered the use of the weight fraction organic carbon in susp. solids (default value) and the K_{OC} rather than using the Kd value in the calculation of the Kp_{susp} acceptable. The $RQ_{sediment}$ is 0.00043, which is under the action limit of 1 and no further testing is required.

2.2.6. Discussion on non-clinical aspects

Findings in juvenile toxicity studies

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), the CHMP 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. Considering that this dose-related and irreversible finding has been seen in two different studies involving juvenile animals, and that the intended patient population includes children from 3 months of age with UTI infections, the MAH was requested to discuss the potential clinical relevance for the human paediatric population. 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 AUC_{0-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

suggest 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

The issues with the calculation of the Fpen for avibactam and ceftazidime and the prevalence/ consumption data have been resolved in the last revision of the environmental risk assessment. The PECsurfacewater for both substances are now accepted, as well as the prevalence/consumption data. Ceftazidine is not considered a PBT and does not need to be classified as such.

2.2.7. Conclusion on the non-clinical aspects

The MAH submitted results from a juvenile animal toxicity study, in compliance with the non-clinical measures in the approved PIP. There are no outstanding concerns from a non-clinical point of view.

The environmental risk assessment is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The paediatric data program for Zavicefta (including the completed/submitted and the planned/ongoing clinical trials and pharmacokinetic studies), is summarised in the tabular overview below.

Table 5. Listing of new clinical pharmacokinetic studies

Study ID	Objective(s) of the study	Study design	Dosage regimens of ceftazidime and avibactam	Number of subjects with PK data	Subjects
Submitted CAZ-AVI paediatric studies					
D4280C00014 **PIP study 3**	To characterize the pharmaco-kinetics of single-dose ceftazidime and avibactam in a pediatric population	Phase 1, open-label, single-dose study	≥12 years or ≥40 kg, 2000 mg CAZ and 500 mg AVI, 2-hour IV infusion <12 years and/or weight <40 kg: 50 mg/kg CAZ and 12.5 mg/kg AVI, 2-hour IV infusion	≥12-<18 years; ≥6-<12 years; ≥2-<6 years; >3 month-<2 years: 8 subjects in each age cohort	Male/female children aged ≥3 months to <18y, any suspected or confirmed infection
C3591004/ D4280C00015 **PIP study 4**	To evaluate the safety, tolerability, efficacy and pharmaco-kinetics of ceftazidime and avibactam Primary endpoints: safety, tolerability	Phase 2, single-blind, randomised, multi-centre, and actively controlled study	≥12 years or ≥40 kg, 2000 mg CAZ and 500 mg AVI q8h for ≥72h ≥2 years to <12 years and/or weight <40 kg: 50 mg/kg CAZ and 12.5 mg/kg AVI q8h for ≥72h Moderate renal insufficiency: 50% of doses above	≥2 years to <6 Years: 6 subjects ≥6 years to <12 years: 33 subjects ≥12 years to <18 years: 21 subjects	Male/female patients aged ≥2 to <18y with cIAI
C3591005/ D4280C00016 **PIP study 5**	To evaluate the safety, tolerability, efficacy and pharmaco-kinetics of ceftazidime and avibactam Primary endpoints: safety, tolerability	Phase 2, single-blind, randomised, multi-centre, and actively controlled study	≥12 years or ≥40 kg, 2000 mg CAZ and 500 mg AVI q8h for ≥72 hours ≥ 6 months to <12 years and/or weight <40 kg: 50 mg/kg CAZ and 12.5 mg/kg AVI q8h for ≥72h ≥ 3 months to <6 months: 40 mg/kg CAZ and 10 mg/kg AVI q8h for ≥72h Moderate renal insufficiency: 50% of doses above	≥3 months to <2 years: 26 subjects ≥2 years to <6 years: 11 subjects ≥6 years to <12 years: 17 subjects ≥12 years to <18 years: 13 subjects	Male/female patients aged ≥3 months to <18y with cUTI
Planned CAZ-AVI paediatric studies					
C3591024/ D4280C00017 **PIP study 6**	Primary endpoint: PK Secondary endpoints: safety, tolerability	Phase 2A, 2-part, open-label, non-randomised, multicentre, single-dose study (part A) and multiple dose (part B)	Cohort 1: full-term infants aged >28d to <3 months or preterm infants with corrected age <28d to <3 months Cohort 2: full-term neonates ≤28d Cohort 3: preterm neonates ≤28d	Planned number of patients: At least 24 patients, 8 per cphort in both part A and B	Male/female patients aged <3 months to <18y hospitalised with suspected or confirmed bacterial infections
C3591025/ D4280C00028 **PIP study 8**	Primary endpoint: PK Secondary endpoints: safety, tolerability	Phase 1, open-label, single-dose study	Cohort 1: ≥12 to <18 y Cohort 2: ≥6 to <12 y Cohort 3: ≥2 to <6 y Cohort 4: full-term infants ≥3 months to <2years	Planned number of patients: At least 32 patients, 8 per cphort	Male/female patients aged ≥3 months to <18 years with suspected or confirmed HAP/VAP

IV: intravenous, cIAI: complicated intraabdominal infection, cUTI: complicated urinary tract infection

2.3.2. Pharmacokinetics

This application to extend all adult indications to children and adolescents ≥3 months to <18 years is supported by one phase I (D4280C00014) and two phase II studies (D4280C00015/Pfizer reference C3591004; D4280C00016/Pfizer reference C3591005) (Table 5). An updated population PK (popPK) analysis was conducted to assess the PK of ceftazidime (CAZ) and avibactam (AVI) in paediatric patients and to support the paediatric dose recommendations (CAZ-MS-PED-02).

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 proposed CAZ-AVI dose in patients aged 6 months to <18 years is 50/12.5 mg/kg q8h (capped at the adult dose of 2 g/0.5 g) as a 2-hour infusion. In patients aged 3 to <6 months, the proposed dose is 40/10 mg/kg q8h as a 2-hour infusion. Dose adjustments are recommended for paediatric patients ≥2 years with impaired renal function (31 to <50 mL/min/1.73m^2). The proposed paediatric doses were used in the clinical phase II studies (C3591004 and C3591005) in cIAI and cUTI patients, respectively. The formulation used for the Phase II paediatric studies is identical to the final drug product for commercial use.

The CHMP acknowledged that, in accordance with the EMA guideline on medicinal products to treat bacterial infections (EMA/CHMP/187859/2017), extrapolation of efficacy to the paediatric populations could be made provided similar exposures (and similar safety profile) to those in adults. One phase I study investigating CAZ and AVI PK in paediatric patients with suspected or confirmed infection, two phase II safety studies in target populations cIAI and cUTI, and popPK models incorporating all available paediatric PK data have been submitted in support of the current variation application. These investigations were conducted as part of the agreed CAZ-AVI Paediatric Investigation Plan, and the phase II studies have been submitted in previous procedures (C3591004 in EMEA/H/C/4027/II/09 and C3591005 in EMEA/H/C/4027/P46/003). The formulation used for the Phase II paediatric studies is identical to the final drug product for commercial use. The proposed CAZ doses are similar to approved doses for CAZ single substance products.

The agreed PIP includes nosocomial pneumonia (NP, HAP/VAP) in patients from 3 months to less than 18 years of age, and aerobic Gram-negative infections in patients from birth to less than 3 months of age, in addition to the cUTI and cIAI indications in patients from 3 months to <18 years as initially sought for this paediatric indication. During the variation procedure, the CHMP suggested that the application would be extended to the HAP/VAP indication as well as aerobic Gram-negative infections in patients with limited treatment options. The MAH agreed to this, and the Clinical Summary was re-submitted with the inclusion of the above-mentioned additional indications. A PK study on NP, HAP/VAP requested by PDCO as part of the PIP is ongoing, and no PK data is presently available. This means that approval of these indications will be based on extrapolation using popPK and simulations without a supportive PK bridge. When the HAP/VAP exposure data becomes available the dosing recommendation and PK bridge must be reassessed.

Analytical methods

Validated analytical methods

Bioanalytical methods used to analyse samples from clinical studies and information regarding the pharmaceutical formulation for the combined CAZ and AVI drug product were included in the original MAA. No changes have been made to the CMC information in support of the present variation application. The validated bioanalytical methods used in the clinical development programs and the assay validation characteristics were acceptable for all applications. There is no new biopharmaceutical information

generated during this submission and no new bioanalytical methods were used for the analysis of samples from studies C3591004 (cIAI) or C3591005 (cUTI).

Acceptance criteria of analytical runs/within study validation

The CAZ and AVI concentrations were analysed by Covance Laboratories Ltd (Harrogate, UK), using a validated liquid chromatography with tandem mass spectrometric detection method (Covance HB-13-001 [8280474], Pfizer reference C359901). For all pediatric studies, the LLOQ was 50 ng/mL for CAZ and 10 ng/mL for AVI. ULOQ was 10000 ng/mL and 20000 ng/mL for CAZ and AVI, respectively.

- 1004 Bioanalytical report (cIAI study)

Total number of samples analysed were 179 for both CAZ and AVI, respectively. Eight CAZ (4.5%) and three AVI (1.7%) samples were re-analysed due to high IS response or a result >ULOQ. Two samples were received outside the established AVI stability period. Incurred sample reanalysis were performed for >10% of samples (20 CAZ and 20 AVI), where 80% of CAZ repeat and original results were within 20% of the mean of the two values. The corresponding number for AVI was 85%. To dilute study samples with high CAZ concentrations into the validated range, a larger dilution factor (100-fold) was successfully validated. For AVI, the overall %RSD value at the LoQC level (19.3%) was outside the mean QC sample acceptance criteria (±15%) due to one an individual LoQC value (run 20). All reported runs met acceptance criteria, including run 20, and the overall %RSD value is therefore considered to have no impact on the integrity of the QC data generated. Analytical run 19 was repeated twice before calibration and QC acceptance criteria were met. Carry-over was <5% of peak area of subsequent samples.

Calibration standard data, QC sample data, incurred sample reanalysis data and chromatograms indicate that the method performed acceptably during the sample analysis.

- 1005 Bioanalytical report (cUTI study)

Total number of samples analysed were 183 for both CAZ and AVI, respectively. Twelve CAZ (6.6%) and nine AVI (4.9%) samples were re-analysed due to high IS response, a result >ULOQ or failure to meet acceptance criteria when analysed with dilution. Sixteen samples were received/analysed outside the established CAZ stability period. Incurred sample reanalyses were performed for >10% of samples (24 CAZ and 24 AVI), where 91.7% of CAZ repeat and original results were within 20% of the mean of the two values. The corresponding number for AVI was 95.8%. Runs 15 and 16 did not meet acceptance criteria and were re-analysed. Carry-over was <5% of peak area of subsequent samples.

Calibration standard data, QC sample data, incurred sample reanalysis data and chromatograms indicate that the method performed acceptably during the sample analysis.

The CHMP considered that the analytical methods submitted to support the new phase II clinical studies C3591004 and C3591005 had been adequately validated in accordance with the EMA bioanalytical guideline (EMEA/CHMP/EWP/192217/2009 Rev. 1). These methods were assessed in the original MAA, and no new bioanalytical methods were used for the analysis of samples from studies supporting the current variation application. The analysis of PK study samples (studies C3591004 and C3591005) are acceptable.

The bioanalytical method used in the phase I study D4280C00014 investigating single-dose PK profile was missing in the initial submission of this procedure, but it was provided as response to the first RSI. Based on the review of the submitted report, the bioanalytical methods used to analyse PK samples from paediatric patients in the above-mentioned studies are considered by the Committee to be adequately validated.

Pharmacokinetic data analysis

The PK data analyses were performed using non-compartmental analysis. Population PK (popPK) analyses were performed using nonlinear mixed effects modelling (NONMEM) with First Order Conditional Estimation with Interaction (FOCE-INTER) and Stochastic Approximation of Expectation-Maximisation estimation (SAEM) methods.

The CHMP considered that acceptable methods were used.

Evaluation and qualification of models

popPK model CAZ-MS-PED-02

Methodology

Prior modelling

Prior popPK modeling	Purpose/objectives	Data set	Comments
CAZ-MS-06	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	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	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 **(current/main model)**	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.

The CHMP noted that several popPK models have been developed throughout Zavicefta product development, with separate models for each active substance. The preceding models are overall similar to the most recent ones (CAZ-MS-PED-02) in the structural and co-variate models, *i.e.* linear two-compartmental models with first order elimination) and with CLCr and body weight as important covariates on CL and V, respectively, for both CAZ and AVI models. Patient population (cIAI and cUTI) was identified as a significant covariate impacting CL and/or Vc of CAZ and AVI, independent of any demographic differences. In general, the models were found to describe the data well (MAA assessment and EMEA/H/C/4027/II/02).

Two popPK models were submitted in this application (CAZ-MS-PED-01 and -02). This assessment report focuses on the latter, which is the main model incorporating all available paediatric PK data and supporting the proposed paediatric dose recommendations. The main model is considered by the CHMP to be of medium regulatory impact.

Objectives

- Describe the popPK of CAZ and AVI in pediatric patients with cIAI and cUTI, including subject covariate effects.
- Evaluate current pediatric dose recommendations for cUTI, cIAI, and NP through simulations from the final CAZ and AVI PK models, and explore alternative CAZ-AVI dose regimens in the event that serious deficiencies were noted in the exposures achieved by the currently proposed regimens.
- Confirm the recommended dosing regimen of the current pediatric studies C3591004 and C3591005 and support the dosing regimen selection for two pediatric studies C3591024 (neonatal sepsis) and C3591025 (NP).

Model development process

The CAZ and AVI models from CAZ-MS-09 were refined and updated. Body weight and renal function (including a renal maturation function) were taken into account in the base model. The impacts of selected covariates on CL and Vc were tested using a forward inclusion/backward elimination procedure (acceptance criteria $\alpha = 0.05$). All covariates, except the allometric body weight scaling, body size-normalised CrCL (NCrCL), and the renal maturation effect, were then subjected to a backward elimination procedure (acceptance criteria $\alpha = 0.01$).

Continuous covariate relationships were primarily modelled using power models. Other structural models, *e.g.* Emax model for weight on CL, were also examined if deemed necessary based on graphical analysis of EBE of the base model vs the individual covariate. Categorical covariate relationships were modelled as follows:

$$\theta_{ij} = 1 + \theta_x$$

As a last step, various variance-covariance matrices of random effect were evaluated, beginning with the most parsimonious case of a diagonal structure and subsequently increasing in complexity to include off-diagonal covariances if supported by the data. A cross-drug scatterplot matrix of the random effects was used to examine the correlation structure of both models.

Dataset

Individuals were defined as evaluable if they had at least one CAZ or AVI dose administration and one corresponding post-dose plasma sample of CAZ or AVI (>LLOQ). The total dataset consisted of 9674 CAZ observations from 2135 subjects and 14254 AVI observations from 2409 subjects. Of these, 519 CAZ observations and 518 AVI observations were from 160 paediatric patients. Of the paediatric patients, 32 were from Study D4280C00014 with any type of suspected or confirmed infection, 60 were cIAI patients

(C3591004), and 67 were cUTI patients (C3591005). Eleven paediatric patients were excluded from analysis.

Table 6. Number of patients by infection and age range

Age Group	Infection	N
12 to <18 years	**Total**	**42**
	Any suspected/confirmed infection Study D4280C00014	8
	cIAI Study C3591004	21
	cUTI Study C3591005	13
6 to <12 years	**Total**	**58**
	Any suspected/confirmed infection Study D4280C00014	8
	cIAI Study C3591004	33
	cUTI Study C3591005	17
2 to <6 years	**Total**	**25**
	Any suspected/confirmed infection Study D4280C00014	8
	cIAI Study C3591004	6
	cUTI Study C3591005	11
3 months to < 2 years	**Total**	**34**
	Any suspected/confirmed infection Study D4280C00014	8
	cIAI Study C3591004	0
	cUTI Study C3591005	26

Source: CAZ-MS-PED-02 Table 10, CAZ-MS-PED-02 Table 11 and CAZ-MS-PED-02 Table 12

The majority of the paediatric patients were Caucasian/white (79%), median age was 7.57 years (range: 0.25 to 17.67 years) and 56% were females. Weight, height, and BMI were in line with expected baseline characteristics of this paediatric population overall and within each age cohort (Olsen, 2010). Study C3591004 had a greater proportion of males (73%) and study C3591005 of Chinese/Taiwanese (18%) subjects. The median baseline NCrCL was 104 mL/min/1.73 m2 (range 43 - 489 mL/min/1.73 m2). Based on reasonable physiologic values, the upper range for NCrCL was capped to a maximum value of 150 mL/min/1.73 m2 for NONMEM modeling in 10, 12, and 2 patients in studies D4280C00014, C3591004, and C3591005, respectively.

Data missingness

Missing NCrCL values were imputed for subjects (N=2) by using CrCL, body surface area (BSA), weight, and height (Gehan and George, 1970). Missing PMA values for study D4280C00014 were imputed based on the assumption that subjects were born at full term. PMA (weeks) was imputed as 52 × AGE (y) + 40 for eight subjects. BLQ were either excluded (pre-dose samples) or imputed to LLOQ/2 (adults only).

Outliers

The final models were rerun with the total dataset to assess impact of excluded outliers (N=33 CAZ and N= 17 AVI excluded observations, outliers defined as |CWRES|>4). A total of 3 CAZ and 17 AVI outlier observations were excluded from paediatric studies. Data cleaning for the adult dataset is described in the popPK report CAZ-MS-09.

Assumptions

Table 7. Model key assumptions (CAZ-MS-PED-02)

Class	Assumptions	Justification
PK - Avibactam	Two compartment PK disposition with first order disposition	The model has been used across previous adult and pediatric modeling
	Dose proportionality	The model has been used across previous adult and pediatric modeling
	Renal maturation function is appropriate to describe the maturation of renal function in subjects ≤ 2 years.	Rhodin et al (Rhodin et al, 2009)
	Allometric scaling exponents of 0.67 for CL and Q, and 1 for V_c and V_p	Hu et al (Hu et al, 2001) based on renal route as main route of elimination. Tested in current analyis
	All other structural covariates in the previously developed model.	Those covariates were identified in previous pediatric and/or adult PK analyses.
	Pediatric population for cIAI is similar to adult Phase 3 population rather than Phase 2 cIAI	Prior analysis CAZ-MS-PED-01, re-tested in current analysis
PK - Ceftazidime	Two compartment PK disposition with first order disposition	The model has been used across previous adult and pediatric modeling
	Dose proportionality	The model has been used across previous adult and pediatric modeling
	Renal maturation function is appropriate to describe the maturation of renal function in subjects ≤ 2 years.	Rhodin et al (Rhodin et al, 2009)
	Allometric scaling exponents of 0.67 for Q, and 1 for V_c and V_p, respectively	Hu et al (Hu et al, 2001) based on renal route as main route of elimination. Tested in current analysis
	Allometric scaling function for CL was an E_{max} model	Addressed model bias in the youngest subjects in current analysis
	All other structural covariates in the previously developed model	Those covariates were identified in previous pediatric and adult analyses

Abbreviations: cIAI = complicated intra-abdominal infection; CL = clearance; E_{max} model = nonlinear maximum efficacy; PK = pharmacokinetic(s); Q = intercompartmental clearance; V_c = apparent volume of the central compartment; V_p = apparent volume of the peripheral compartment.

Co-variate considerations

Allometric body weight effects on clearance (CL) and volume, and a renal maturation function for children ≤2 years were incorporated a priori (Table 7). The CrCL effect on CL from the preceding adult models was replaced with NCrCL[1] while keeping prior fixed the adult parameter estimates for the CrCL effect (for CAZ). The NCrCL was capped at an upper bound of 150 mL/min/1.73m^2. The impact of renal maturation on CL was accounted for by a sigmoidal function of post-menstrual age (PMA) effect on CL with parameters fixed to the values reported in the literature reference[2].

The following covariates were considered for CAZ and AVI models: sex, race (Caucasian/White, Black, Asian, American Indian/Alaskan Native, Japanese, Chinese/Taiwanese, other Asians), age, body weight, APACHE II score (≤10 vs >10), ESRD, dialysis, augmented renal clearance (ARC), presence of ventilator in hospital room on PK day, population (healthy, cUTI, cIAI, NP, general infection), study phase, pediatric effect.

Diagnostics/GoF evaluation

Base and final models were evaluated by standard diagnostic plots (*e.g.* DV vs. PRED/IPRED, IWRES vs. IPRED, CWRES vs. PRED, WRES vs. TIME, IWRES vs. IPRED, VPCs, individual random effect values η vs. covariates). Also, successful convergence, OFV (or corrected AIC), precision of parameter estimates,

[1] Peadiatric BSA-NCrCL were calculated using the "bedside" Schwartz formula (*i.e.* NCrCL mL/min/1.73m2 = 0.413 x height or length/serum creatinine mg/dL). Adult NCrCL was computed using BSA-normalised CrCL (NCrCL = CrCL x 1.73/BSA where Cokcroft Gault formula were used to compute CrCL and Gehan and George formula to compute BSA).
[2] Rhodin et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pedatr Nephrol, 2009; 24, 67-6.

plausibility of and uncertainty in parameter estimates, and degree of parsimony were assessed. pcVPCs were stratified by paediatric versus adult subjects, age, weight, NCrCL, and disease indication to assess the predictive performance of the model in each stratum.

Simulations to support dose recommendations in special populations and for PTA analysis

The final CAZ-AVI popPK models (CAZ-MS-PED-02) were used to conduct simulations (1000 subjects per age group, indication and renal function group) to support paediatric dose recommendations. In this updated popPK model, the paediatric PK data from phase 2 studies (C3591004 and C3591005) and Study D4280C00014 were pooled with PK data from adults (phase 1 to phase 3). This results in a total number of 9628 observations and 2130 subjects in the final ceftazidime dataset, and 14223 observations and 2403 subjects in the final avibactam dataset. Of the CAZ-AVI paediatric patients, 32 were from Study D4280C00014 with any type of suspected or confirmed infection, 59 were cIAI patients from Study C3591004, and 63 were cUTI patients from Study C3591005. A range of mg/kg doses were simulated, with the total dose capped at the adult CAZ-AVI label doses (*e.g.* 2 / 0.5g q8h over a 2-hour infusion for normal renal function). Given ongoing renal maturation in paediatric patients ≤2 years of age, definitions of renal impairment based on adult CrCL ranges do not necessarily translate directly to children. Subjects with renal impairment were not simulated for subjects ≤2 years of age.

A demography dataset (of 457 patients, 363 had NCrCL ≥80 mL/min/1.73 m^2) was constructed for the simulations for patients from 2 to <18 years by pooling covariate values (*i.e.* age, weight, height, and NCrCL) from the CAZ-AVI paediatric studies with values from paediatric studies from another antibiotic program (ceftaroline fosamil). Simulations for all children <2 years of age were based on demography from Centers for Disease Control and Prevention growth charts. For adults, demographics were first stratified by indication followed by an approach subsetting for NCrCL ≥80 mL/min/1.73 m^2, Phase III-only, non-Asian, and non-Japanese. For each indication, adults were resampled with replacement within the resulting indication specific groups (*i.e.* 271 adults with cUTI, 353 adults with cIAI, and 161 adults with HAP/VAP).

PTA was determined as the percent of 1000 patients meeting PKPD targets for both CAZ and AVI, using the joint PKPD target of 50% fT>MIC at an MIC of 8 mg/L for CAZ and 50% fT>CT at a CT of 1 mg/L for AVI. The joint target was employed for PTA simulations for all site-specific indications (i.e. cIAI, cUTI and HAP/VAP). In addition, PTA at an MIC range of 0.125 to 128 mg/L was assessed. Free plasma concentration of CAZ and AVI were calculated using unbound percentages of 85% and 92%, respectively.

The CHMP noted that CAZ and AVI model datasets are based on sparse and intensive sampling in phase I-III clinical studies in healthy subjects, adult and paediatric patients. Sparse sampling was conducted in phase II multiple dose paediatric clinical studies (three sampling periods at on Day 3 of treatment *i.e.* after nine administered doses) and, as the applicant has clarified during the procedure, in the phase I single dose study for patients aged ≥3 months to <6 years (cohorts 3 and 4). Paediatric studies are further described below under the Section "Special populations".

The MAH clarified the numbers used in the final population PK analyses (for CAZ 2130 individuals, 154 of whom were paediatric patients, for AVI 2403 individuals, 153 of whom were paediatric patients), and the reasons for the exclusions are described.

Regarding the paediatric dataset, more than 25 patients are providing PK data per age cohort (12- <18y; 6- <12y; 2- <6y; 3months- <2y). However, cIAI patients were primarily older (54 patients ≥6 years) with only six patients aged 2-6 years and none below 2 years. The cUTI patients were more evenly distributed across age cohorts. According to the EMA guideline EMEA/CHMP/EWP/147013/2004, PK information from one indication can be extrapolated to another indication if it can be assumed that the diseases and commonly used concomitant medications are not affecting the PK of the drug. The MAH showed that there is overlap by indication and similar concentration ranges by age group for the doses, and assessment of the paediatric dose normalized concentration data suggests that extrapolation across indications and age ranges is

supported. However, the risk remains that optimal dosing was not established in the age group of 3 months to <6 months. The MAH informed that there was no evidence of overexposure or underexposure in this age group, and hence routine PhV was considered appropriate for monitoring. Besides, the information regarding the limited experience in this age group included in the SmPC Section 4.2 can mitigate the risk. The criteria of inclusion in the RMP as an important potential risk was thus not considered to be met.

Only one paediatric patient with moderate renal impairment (NCrCL 30-50 mL/min/1.73m^2, cohort 4, cUTI) was included in the phase II studies. Nine cIAI patients and 23 cUTI patients had mild renal impairment (≥50 to <80 mL/min/1.73 m^2). Twelve of the 23 cUTI patients were in cohort 4 where renal function maturation may be ongoing. No PK information is available for paediatric patients with severe renal impairment.

In general, the allometric scaling of PK parameters (CL, V, Q) and the renal maturation function on CL in subjects <2 years is supported. During model development, the theoretically based allometric exponent of 0.75 for CL and Q was changed to 0.67 – according to the Applicant – to better reflect the renal characteristics of CAZ and AVI in paediatric subjects (Hu et al. 2001). The allometric function for CL in the CAZ model was then further changed to an E_{max} model. However, theory and extensive confirmatory observation support an exponent of 0.75 that is believed to provide a stronger basis for predictions, especially for extrapolation from adults to children and small infants (Anderson and Holford 2009, EMA M&S Q&A[3]). The available paediatric data are likely too limited to confidently conclude that the allometric exponent is different from the theoretical value. Furthermore, the improved fit was apparently based only on statistical terms in terms of reduction in OFV, and was not supported by visual examinations (*i.e.* better predicted performance). As the final models appear to describe the data reasonably well (see below), the issue was not further pursued.

Renal function maturation was modelled using the approach described by Rhodin et al. 2009, where the covariate CrCL on CAZ-AVI clearance is replaced with post-menstrual age (PMA). The current model is thus not able to account for changes in CrCL beyond what is expected based on PMA, and can only predict exposures in paediatric patients aged <2 years with CrCL values already represented in the popPK dataset. The issue is further addressed below, in the section "Special populations".

The division of APACHE II score into a binary variable of <10 vs ≥10 (as a marker of disease severity) was used in the prior adult modelling database. This was considered appropriate by the CHMP.

For the simulations performed, it seems that representative in silico populations with variability in co-variates representing what is observed in studies or what would be expected in the target populations has been used, however the full range of covariates have clearly not been included (ie. renal function etc). Simulation results are presented further below under "Special populations".

For PTA simulations, the joint PKPD target of 50% fT>MIC at an MIC of 8 mg/L for CAZ and 50% fT>CT at a CT of 1 mg/L for AVI was employed for indications cIAI, cUTI and HAP/VAP. This is in line with the PKPD targets employed for the above-mentioned indications in adults.

[3] Modelling and simulation: questions and answers.
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers

Results

Final model

CAZ:

The pooled paediatric and adult PK data for ceftazidime were described by a 2-compartment PK model with first-order elimination from the central compartment following IV infusion. Final popPK model (Run 77 and 121) parameter estimates are presented in Table 8.

Run 121 was a re-parameterised version of Run 77 (*i.e.* Emax covariate model constrained to 1 when WT was 70 kg). Run 121 achieved a lower condition number, reflecting a more precise determination of CL for the typical individual (7.75 L/h with an RSE of 1.56%). The OFV for Run 77 and 121 were similar (189896.2313 vs. 189896.2304, respectively) implying that the fits to the data were essentially the same. A subset of PK simulations and PTA calculations were re-run using Model 121 and confirmed that there were no numerical changes.

The dependence of CL on kidney function as measured by NCrCL was modelled as a piecewise linear function derived from literature information (using CrCL):

$$CLCLCr = \begin{cases} NCrCL \cdot 0.01030 \cdot & \text{NCrCL} < 100, \text{Age} > 2 \\ 100 \cdot 0.01030 \cdot + (NCrCL - 100) \cdot 0.00125 & \text{NCrCL} \geq 100, \text{Age} > 2 \\ 1 & otherwise \end{cases}$$

Table 8. Parameter estimates for the final ceftazidime popPK model (Run 77 and Run 121)

Parameter	Estimate (Run 77/ Run 121)	%RSE (Run 77/ Run 121)	BSV (%CV) (Run 77/ Run 121)
NCrCL Effect on CL			
Slope 1: NCrCL <100 mL/min, Slope 1 x NCrCL	0.01030360 (Fixed)	-	-
Slope 2: NCrCL ≥ 100 mL/min, Slope 1 x 100 + Slope 2 x (NCrCL - 100)	0.00125182 (Fixed)	-	-
NONMEM Fixed Effects			
θ_1: CL (L/h)	9.13 / 7.75[a]	35.6 / 1.56[a]	40.8 / 40.8[a]
θ_2: V_c (L)	11.2 / 11.2	3.54 / 3.54	33.9 / 33.8
θ_3: Q (L/h)	5.33 / 5.33	6.54 / 6.52	47.5 / 47.5
θ_4: V_p (L)	6.53 / 6.52	3.12 / 3.12	15.4 / 15.4
θ_{13}: Maximum covariate effect for WT on CL as an E_{max} function	1.5 / -[a]	38.2 / -[a]	-
θ_{15}: WT at half-maximal effect of WT on CL (kg) as part of an E_{max} function	53.4 / 53.5	8.87 / 8.81	-
θ_{16}: Population effect on CL for patients with cIAI, CL x θ_{16}	1.33 / 1.33	2.37 / 2.37	-
θ_{17}: Population effect on CL for patients with NP, CL x θ_{17}	1.1 / 1.1	2.96 / 2.96	-
θ_{18}: Race effect on CL for ASN, CL x (1 + θ_{18})	-0.136 / -0.136	20.3 / 20.3	-
θ_{19}: Race effect on CL for CHN, CL x (1 + θ_{19})	-0.0843 / -0.0844	29.2 / 29.1	-
θ_{20}: Population effect on V_c for patients with cUTI, V_c x θ_{20}	1.5 / 1.49	4.58 / 4.57	-
θ_{21}: Population effect on V_c for patients with cIAI or NP, V_c x θ_{21}	1.84 / 1.83	3.98 / 3.97	-
θ_{22}: Population effect on V_c for presence of ventilator, V_c x (1 + θ_{22})	0.202 / 0.202	33.5 / 33.5	-
θ_{23}: Race effect on V_c for ASN, CHN, and JPN, V_c x (1 + θ_{23})	-0.135 / -0.135	23.2 / 23.2	-
			Shrinkage (%)
ηCL^2	0.154 / 0.154	2.618 / 2.62	10.5 / 10.5
ηV_c^2	0.109 / 0.108	11.76 / 11.76	50.1 / 50.1
ηQ^2	0.203 / 0.203	18.99 / 18.98	79.7 / 79.7
ηV_p^2	0.0236 / 0.0236	21.13 / 21.12	83.2 / 83.2
Residual Error			
θ_8: Proportional variability, Phase 1	0.172 / 0.172	10.4 / 10.4	-
θ_9: Additive variability, Phase 1 (ng/mL)	125 / 125	15.9 / 15.9	-
θ_{10}: Proportional variability, Phase 2 or 3	0.374 / 0.374	2.21 / 2.21	-
θ_{11}: Additive variability, Phase 2 or 3 (ng/mL)	2560 / 2560	23.1 / 23.1	-

Notes: The Slope1 and Slope2 parameter estimates were obtained from CAZ-MS-06
η = individual random subject effect; θ = typical value of PK parameter; ASN = non-Chinese, non-Japanese Asian; BSV = between-subject variability; CHN = Chinese; CL = clearance; E_{max} = maximum efficacy; JPN = Japanese; NCrCL = BSA-normalised creatinine clearance; NP = nosocomial pneumonia; Q = intercompartmental clearance; RSE = relative standard error; V_c = central volume of distribution; V_p = peripheral volume of distribution; WT = weight
[a] Run 121 incorporated a reparameterisation that recentered θ_1 and eliminated θ_{13}
Source: CAZ-MS-PED-02 report, Table 14

The median values of all the structural and covariate parameters from bootstrap resampling (N=200) were consistent with the original population PK estimates; all estimates were within the 90% confidence intervals. In the sensitivity analysis performed by including outliers (N=33), parameter estimates changed by <15%, however the additive error for phase II or III subjects changed by 44% and random effects on Vc, Q and Vp increased >40%. This significant impact of outliers on parameter estimates justified their continued exclusion.

AVI:

The pooled paediatric and adult PK data for avibactam were described by a 2-compartment disposition model with first-order elimination from the central compartment following IV infusion.

Table 9. Parameter Estimates for the Final Avibactam PopPK Model (Run 198)

Parameter	Estimate	%RSE	BSV (CV%)
θ_1: CL (L/h)	10.7	3.74	58.8
θ_2: V_c (L)	11.5	4.31	107
θ_3: V_p (L)	7.56	14.1	108
θ_4: Q (L/h)	6.94	18.5	234
θ_5: Relative CL estimate for patients with ESRD, CL x θ_5	0.0674	23.7	
θ_6: CL estimate for dialysis patients (L/h)	21.1	9.5	
θ_7: Power NCrCL (<80 mL/min/1.73 m^2) on CL	0.986	6.34	
θ_8: Linear NCrCL (≥80 mL/min/1.73 m^2) on CL	0.00344	11.6	
θ_9: Population effect on V_c (cIAI) Phase 2, V_c x (1 + θ_9)	2.17	24.8	
θ_{10}: Population effect on CL (cIAI) adult, Phase 2, CL x (1 + θ_{10})	0.431	33.4	
θ_{11}: Population effect on V_c (cUTI), V_c x (1 + θ_{11})	0.412	19.6	
θ_{12}: Population effect on V_c (cIAI Phase 3, NP, paediatric cIAI), V_c x (1 + θ_{12})	0.214	26.8	
θ_{15}: APACHE II on CL, CL x (1 + θ_{15})	-0.192	15.4	
θ_{28}: Presence of ventilator (POP5) on V_c, V_c x (1 + θ_{28})	0.267	55.6	
			Shrinkage (%) or correlation[a]
ηCL^2	0.3453	6.743	6.8
ηV_c-ηCL	0.1305	169.8	r = 0.21[a]
ηV_c^2	1.139	25.91	32.4
ηV_p-ηCL	0.5397	13.8	r = 0.85[a]
ηV_p-ηV_c	-0.3397	40.12	r = -0.29[a]
ηV_p^2	1.156	17.21	12.3
ηQ-ηCL	1.178	13.78	r = 0.86[a]
ηQ-ηV_c	-0.7016	103.8	r = -0.28[a]
ηQ-ηV_p	2.495	35.26	r = 0.99[a]
ηQ^2	5.487	47.83	12.6
Residual Error			
θ_{17}: Proportional variability, Phase 1	0.174	8.09	
θ_{18}: Additive variability, Phase 1 (ng/mL)	43.8	23.9	
θ_{19}: Proportional variability, Phase 2	0.498	4.83	
θ_{20}: Proportional variability, Phase 3	0.364	2.6	

η = individual random subject effect; θ = typical value of PK parameter; POP5 = population with presence of ventilator
BSV CV% expressed as a variance.
[a] Correlation coefficient (r) between random effects.
Source: CAZ-MS-PED-02 report, Table 19

A piecewise function with an inflection point at 80 mL/min/1.73 m2 was employed to describe the relationship between NCrCL and CL:

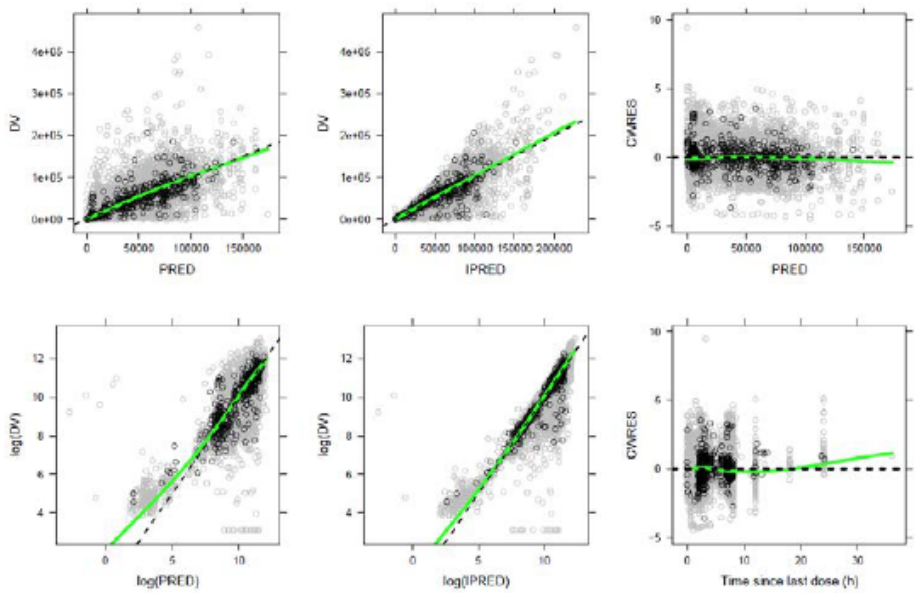
$$CLCLCr = \begin{cases} (NCrCL/80)^{0.99} & NCrCL < 80, No\ ESRD, Age > 2 \\ 1 + 0.00344 \cdot (NCrCL - 80) & NCrCL \geq 80, No\ ESRD,\ Age > 2 \end{cases}$$

The avibactam CL estimate was 101% of the estimate in CAZ-MS-PED-01 and not statistically different.

The median values of all the structural and covariate parameters from bootstrap resampling (N=200) were consistent with the original population PK estimates; all estimates were within the 90% confidence intervals. In the sensitivity analysis performed by including outliers (N=17), most parameter estimates changed by <15%. However, θ11 (population effect of cUTI on Vc) and θ12 (population effect of cIAI and NP Phase 3, and cIAI pediatric patients on Vc) changed by approximately 16% and 44%, respectively. This significant impact of outliers on parameter estimates justified their continued exclusion.

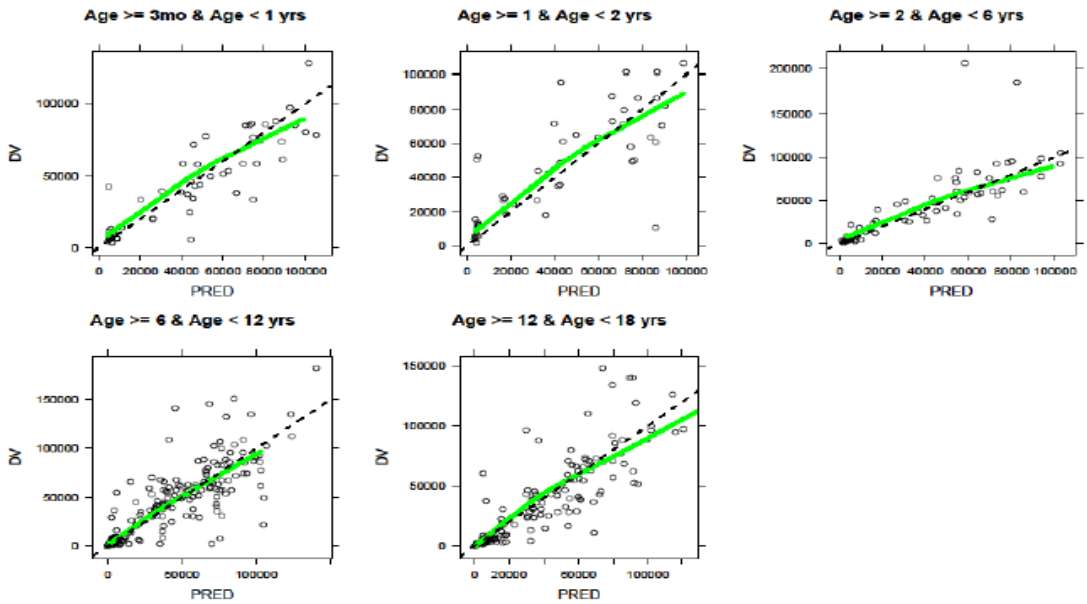
Model diagnostics

Figure 1. Goodness-of-Fit Plots for the Final CAZ PK Model (CAZ-MS-PED-02, Figure 6)

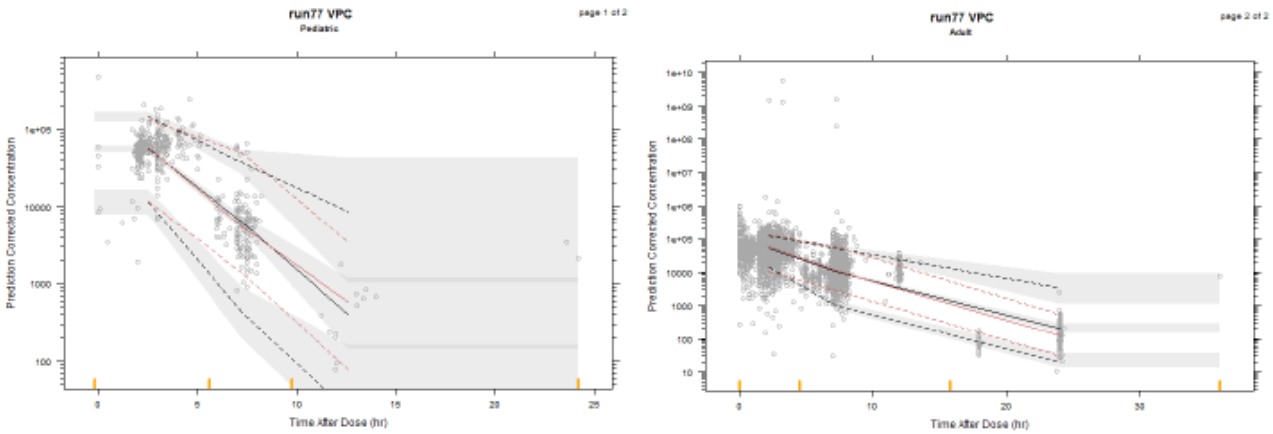


Abbreviations: CWRES = conditional weighted residual; DV = dependent variable; IPRED = individual prediction; PK = pharmacokinetic; PRED = population prediction.
Source: \Scripts\2018-02-21_CAZ_GOF_Final_PED-02.R
Each symbol represents an individual PK observation. Gray circles represent adult patients while black circles represent pediatric patients. The solid green line is a loess smooth to the data.

Figure 2. DV Versus PRED Plots for the Final CAZ Population PK Model Stratified by Pediatric Age Cohorts (CAZ-MS-PED-02, Figure 8)



Abbreviations: CAZ = ceftazidime; DV = dependent variable; PK = pharmacokinetic; PRED = population prediction.
Source: \Scripts\2018-02-21_CAZ_GOF_Final_PED-02.R
Each symbol represents an individual PK observation. The solid green line is a loess smooth to the data.



Abbreviations: CAZ = ceftazidime; PK = pharmacokinetic; VPC= visual predictive check.
Source: PsN_vpc_plots_PED2.R
Each symbol represents an individual PK observation, which is prediction corrected. The solid red line connects the median concentrations while the solid black line is the simulated median or the 50th percentile. The shaded region represents the 5th to 95th prediction interval for the median based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.

Figure 3. Prediction-corrected VPC for the final CAZ PK model – Stratified into Pediatric and Adult Subjects (CAZ-MS-PED-02, Figure 9)

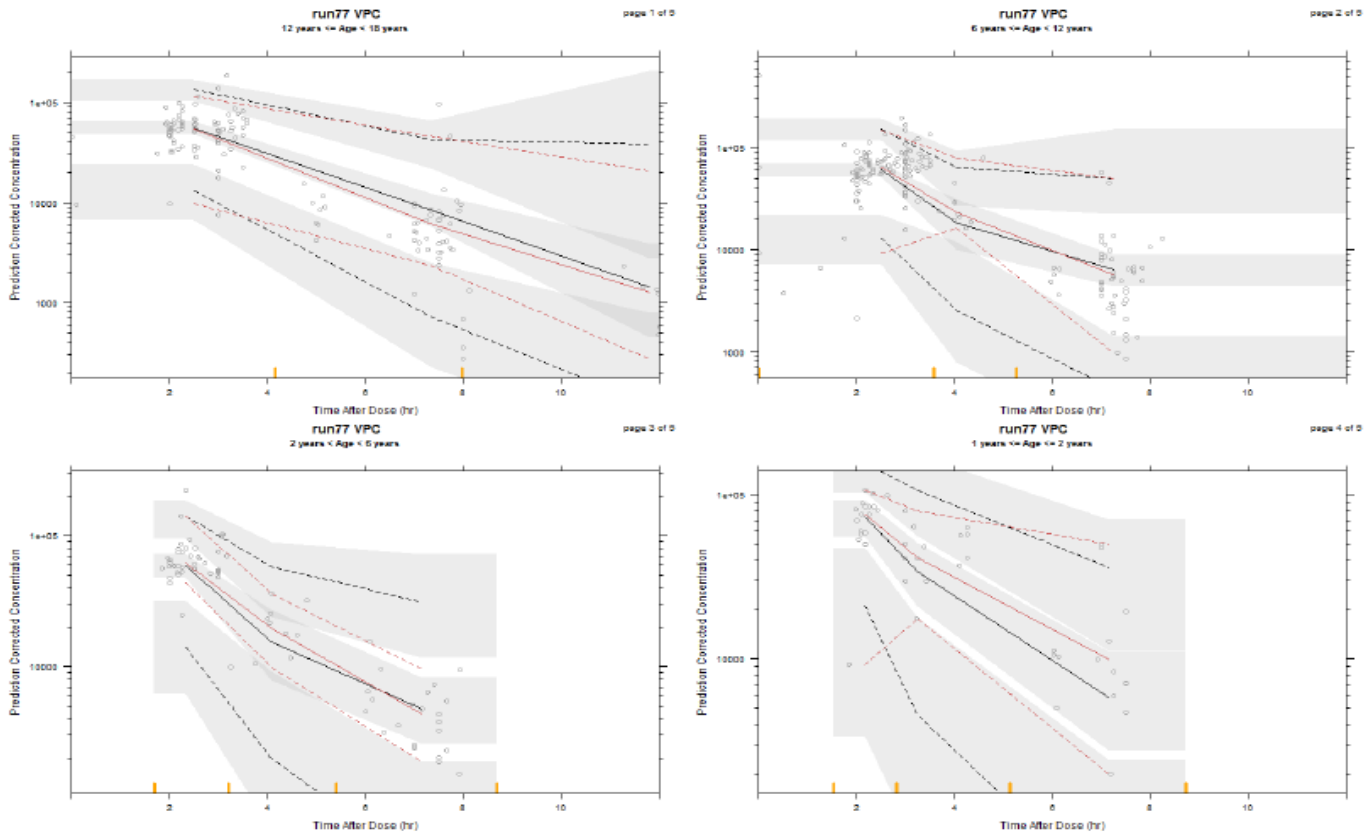
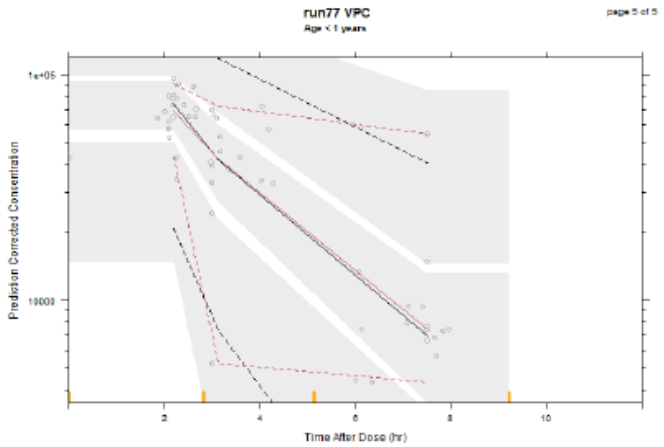
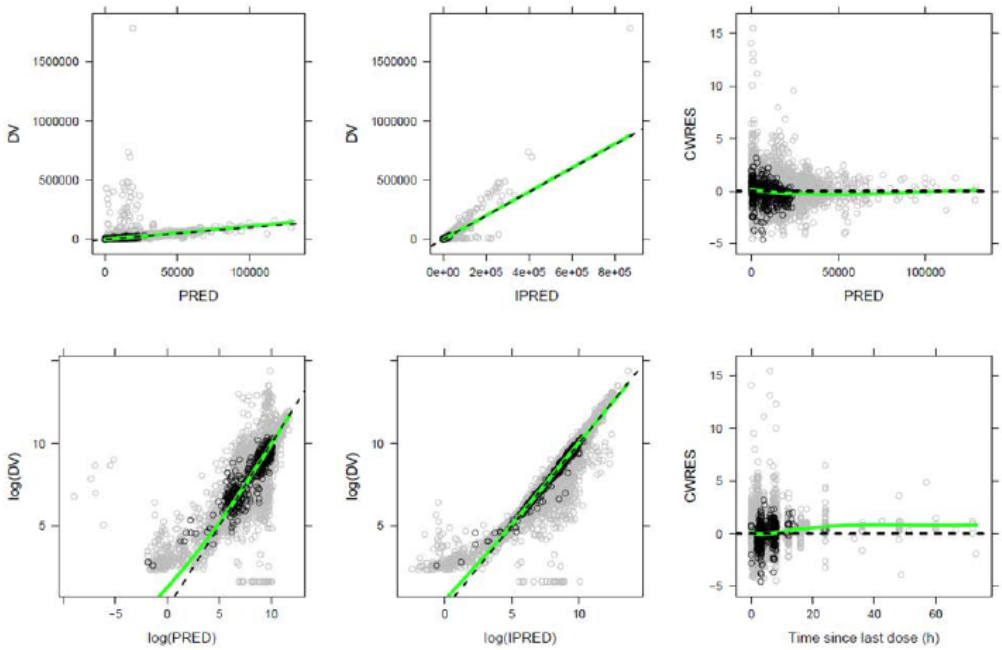


Figure 4. Prediction-corrected VPC for the Final CAZ PK model – Stratified by Age Group for Pediatric Subjects (CAZ-MS-PED-02, Figure 10)



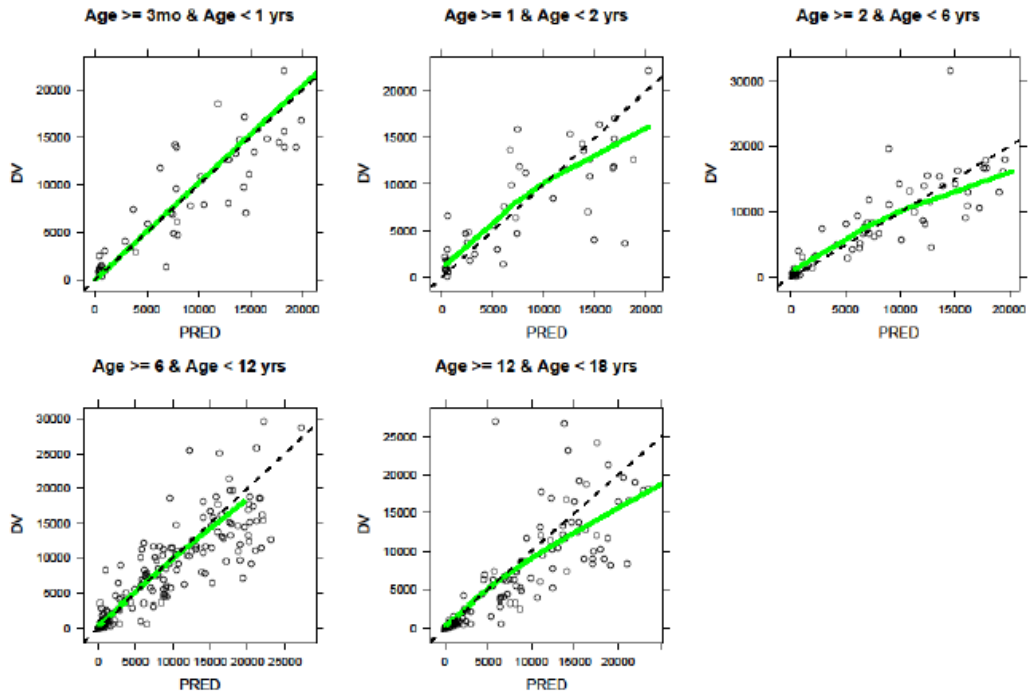
Abbreviations: CAZ = ceftazidime; PK = pharmacokinetic; VPC = visual predictive check.
Source: PsN_vpc_plots_PED_AGE2.R
Each symbol represents an individual PK observation, which is prediction corrected. The solid red line connects the median concentrations while the solid black line is the simulated median or the 50th percentile. The shaded region represents the 5th to 95th prediction interval for the median based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.

Figure 5. Goodness-of-Fit Plots for the Final AVI Population PK Model (CAZ-MS-PED-02, Figure 16)



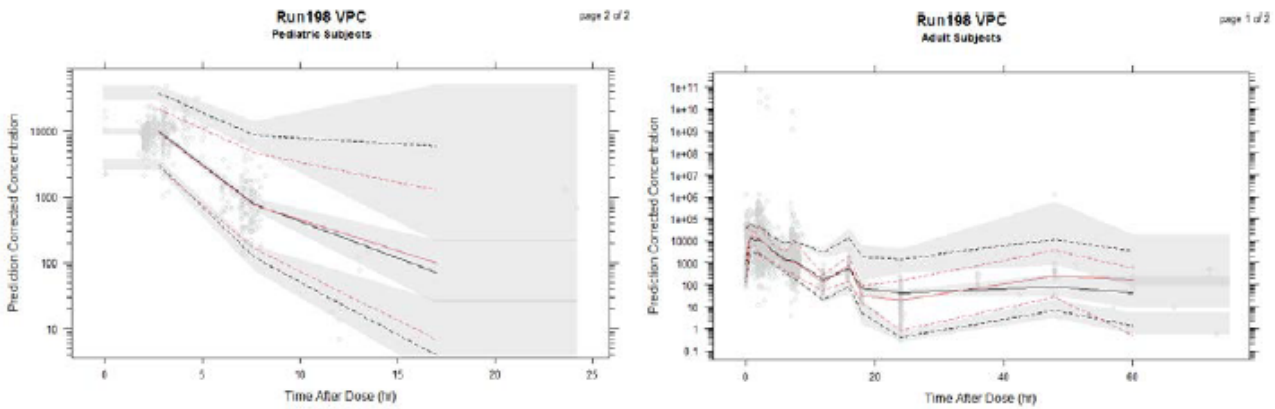
Abbreviations: AVI = avibactam; CWRES = conditional weighted residual; DV = dependent variable; IPRED = individual prediction; PK = pharmacokinetic; PRED = population prediction.
Source: 2018-02-21_AVI_GOF_Finalrun198_PED-02.R
Each symbol represents an individual PK observation. Gray circles represent adult patients while black circles represent pediatric patients. The solid green line is a loess smooth to the data.

Figure 6. DV Versus PRED Plots for the final AVI popPK model stratified by pediatric age cohorts (CAZ-MS-PED-02, Figure 18)



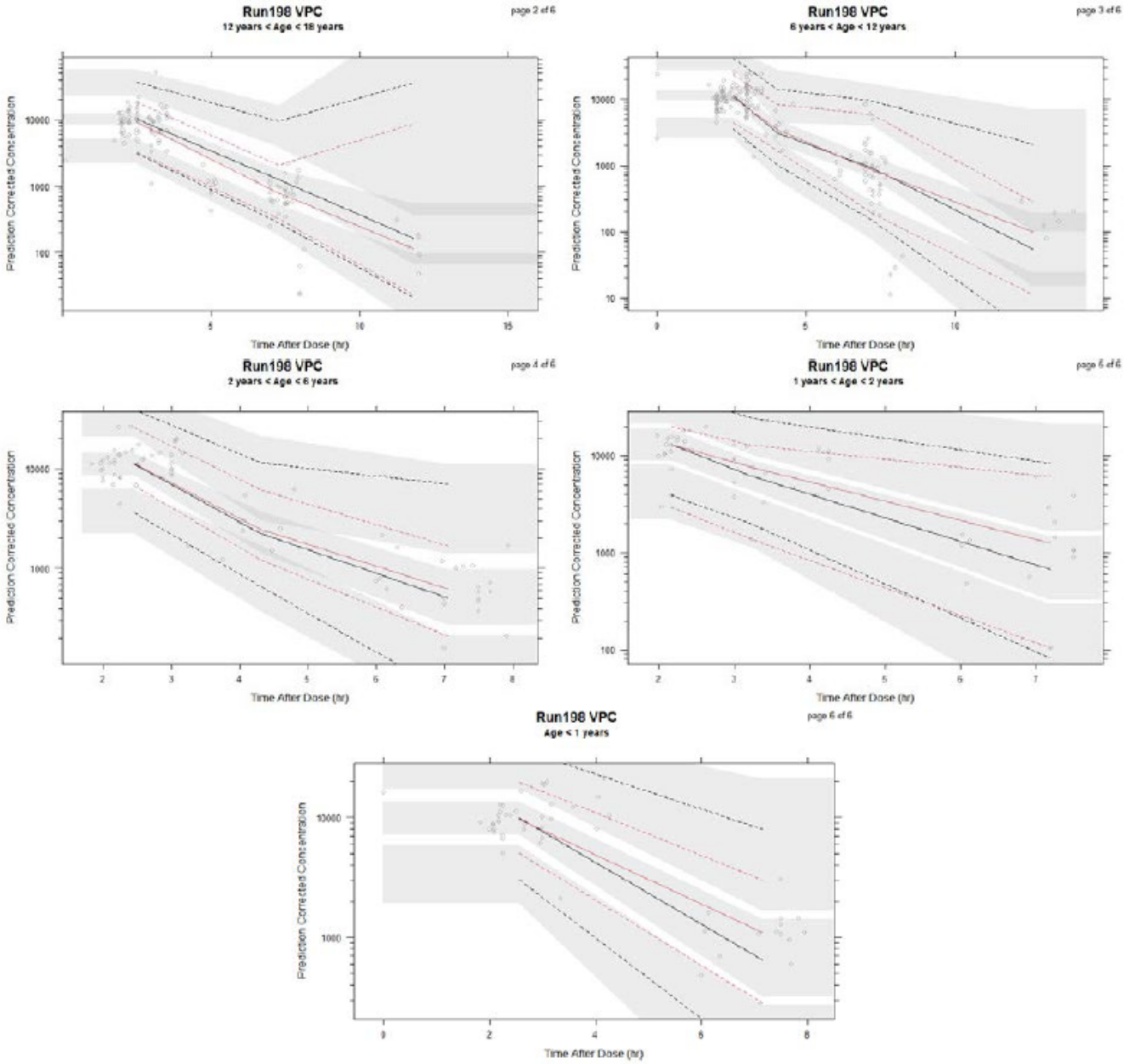
Abbreviations: AVI = avibactam; DV = dependent variable; PK = pharmacokinetic; PRED = population prediction.
Source: 2018-02-21_AVI_GOF_Finalrun198_PED-02.R
Each symbol represents an individual PK observation. The solid green line is a loess smooth to the data.

Figure 7. Prediction-corrected VPC for the final AVI PK model – stratified into pediatric versus adult subjects (CAZ-MS-PED-02, Figure 19)



Abbreviations: AVI = avibactam; PK = pharmacokinetic; VPC = visual predictive check.
Source: Source: analysis-script-report-draft-1-mar-2018.R
Each symbol represents an individual PK observation, which is prediction corrected. The solid red line connects the median concentrations while the solid black line is the simulated median or the 50th percentile. The shaded region represents the 5th to 95th prediction interval for the median based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.

Figure 8. Prediction-corrected VPC for the final AVI PK model – stratified by pediatric age cohort (CAZ-MS-PED-02, Figure 20)

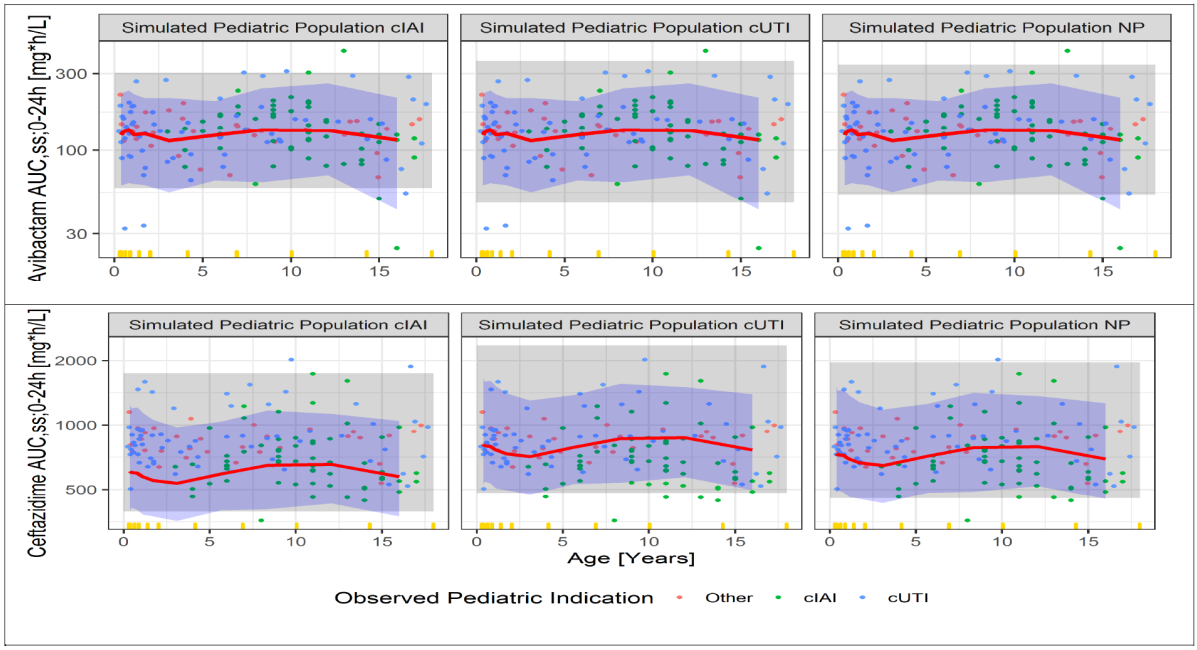


Abbreviations: AVI = avibactam; PK = pharmacokinetic; VPC = visual predictive check.
Source: Source: analysis-script-report-draft-1-mar-2018.R
Each symbol represents an individual PK observation, which is prediction corrected. The solid red line connects the median concentrations while the solid black line is the simulated median or the 50th percentile. The shaded region represents the 5th to 95th prediction interval for the median based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.

Graphical presentations of the predicted exposure metrics (AUC0-24 and Cmax) by age, weight and renal function have been provided by the MAH for all indications. Two figures on the AUC0-24 for paediatric patients with normal and mild reduction in renal function, respectively, are given below.

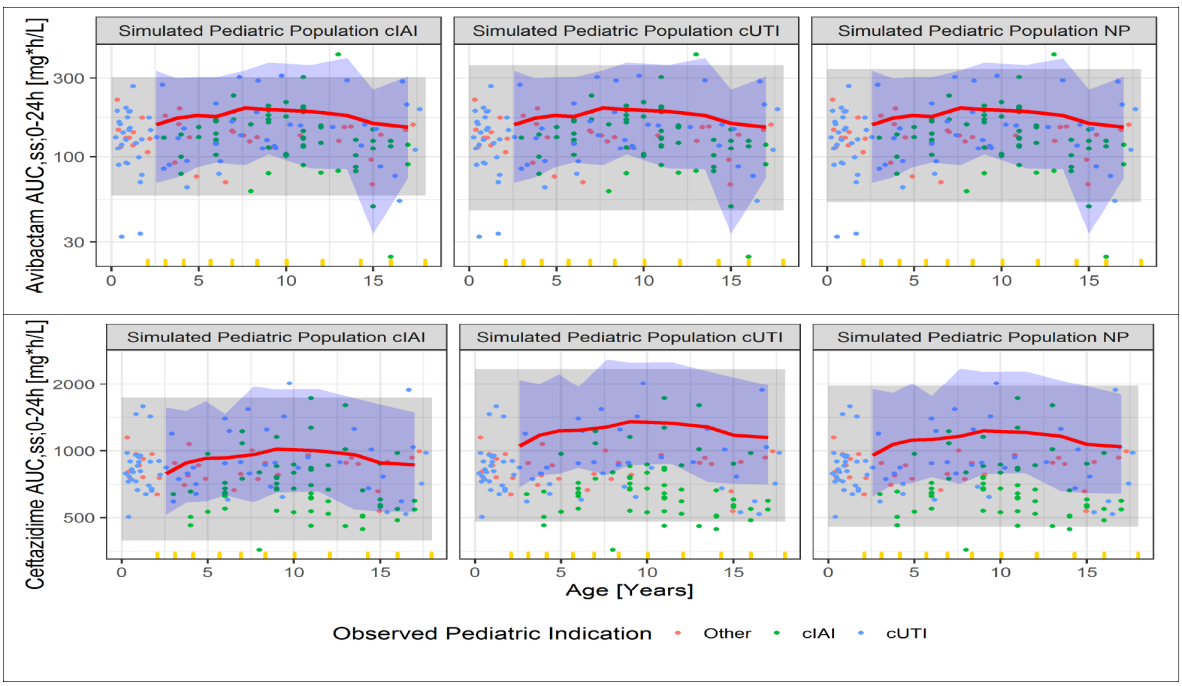
Figure 10. AUCss,0-24h by Age (Continuous) and Indication for AVI and CAZ in Paediatric Patients with Mild Renal Impairment. (90% PI, blue shaded area = paediatrics mild and grey shaded area = adults normal and mild)

Figure 9. AUCss,0-24h by Age (Continuous) and Indication for AVI and CAZ in Paediatric Patients with Normal Renal Function. (90% PI, blue shaded area = paediatrics normal and grey shaded area = adults normal and mild)



Dose: Paediatric dose: 40/10 mg/kg CAZ/AVI for 3 to<6 months and 50/12.5 mg/kg CAZ/AVI for ≥6 months capped at 2000/500 mg CAZ/AVI (adult dose) over 2 hrs, every 8 hrs. Source: CP1:FI-1239831-1 and CP1:FI-1239839-1

Figure 10. AUCss,0-24h by Age (Continuous) and Indication for AVI and CAZ in Paediatric Patients with Mild Renal Impairment. (90% PI, blue shaded area = paediatrics mild and grey shaded area = adults normal and mild)



Dose: Paediatric dose: 40/10 mg/kg CAZ/AVI for 3 to<6 months and 50/12.5 mg/kg CAZ/AVI for ≥6 months capped at 2000/500 mg CAZ/AVI (adult dose) over 2 hrs, every 8 hrs. Source: CP1:FI-1239829-1 and CP1:FI-1239837-1

The CHMP noted that both CAZ and AVI models were described by a 2-compartment PK model with first-order elimination from the central compartment following IV infusion. Body weight and renal function were taken into account in the model and were the major covariates impacting on CAZ-AVI clearance and volume of distribution. Disease status (cIAI) resulted in a higher CL (33%/43%) compared to healthy subjects. Disease status (cIAI, cUTI) also affected central volumes of distributions for both models.

Overall, fixed effects parameters were estimated with moderate precision (%RSE <30-40%). The 90% confidence intervals for final parameter estimates (see CAZ-MS-PED-02, Tables 15 and 20) would provide useful information about data consistency for covariate parameters from bootstrap resampling.

The 90% confidence intervals for the final parameter estimates (see CAZ-MS-PED-02, Tables 15 and 20) were provided.

Acceptable shrinkages were reported for CL in the CAZ-ASVI models (10.5%/6.8%) and for Vp in the AVI model (12%). However, the relatively high shrinkages of the central (50%/32%) and the peripheral (83%/-) volumes of distribution for CAZ-AVI, have not been discussed with respect to the potential impact on the eta-based diagnostics or the PTA simulations. The high shrinkage for volume of distribution was also observed in the original MAA, and was attributed to limited PK sampling in phase II-III clinical studies. The shrinkage in volume of distribution was at the time thought to mainly affect predicted concentrations in the elimination phase with limited impact on the validity of predictions. However, as 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, the high shrinkages confer uncertainty on the parameter and variability estimates and consequently to the results of the PTA analysis in the paediatric population. Shrinkage in the parameter estimates (although likely to be higher in children than adults due to sparser PK sampling) has been handled by re-inflating the post hoc etas for all subjects. With re-inflation, PTA increased by 2.5-5%, indicating that shrinkage has not had major influence on the conclusions derived from the PTA analyses.

The continued exclusion of CAZ and AVI outliers, which comprised <0.1% of data, was supported by sensitivity analysis. Standard plots have been provided to evaluate the models. No obvious trends were observed in the random effects estimates vs continuous covariate plots for either model (not shown). The GoF plots indicate no major misfit of the CAZ model, however there is some indication of overestimation of variability, and the model performs less well over time (>1 dose interval). The clinical impact of the latter is not assumed to be of great importance as initial concentrations are the most important for PTA assessment. For the AVI model GoF plots similar observations are made. These tendencies are also visualised in the CAZ-AVI pcVPCs, with an overestimation of variability that is somewhat greater for the AVI model compared to the CAZ model. In general, the pcVPCs demonstrate a reasonable fit to the observed data for the overall adult and the paediatric population, and the median tendency is adequately predicted. pcVPCs, stratified by paediatric versus adult subjects, age, weight, NCrCL, and indication to assess the predictive performance of the model in each stratum, also demonstrate that the models overall capture the observed PK data (only pcVPCs stratified by age are shown). As discussed above, the shrinkage in the parameter estimates (although likely to be higher in children than adults due to sparser PK sampling) has been handled by re-inflating the post hoc etas for all subjects. With re-inflation, PTA increased by 2.5-5%, indicating that shrinkage has not had major influence on the conclusions derived from the PTA analyses. However, the Applicant then raised a different concern: that variability may rather be under-estimated because the methodology used for simulations was based on bootstrapping of post-hoc values, which are affected by parameter shrinkage. Potentially under-estimated variability is more concerning than potentially over-estimated variability because it will cause over-estimation of PTA. To account for this, the Applicant re-inflated all the random effects prior to using them for simulations. 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. Furthermore, the shrinkage adjustment was based on the model-reported shrinkage value, which is directly calculated from the model-estimated variability (which was overestimated) and should therefore be considered somewhat unreliable. Thus, there is some uncertainties with the PTA analyses. However, further analyses are not requested as part of this variation application as this is not expected to affect the overall conclusion. However, when the data from the ongoing HAP/VAP study becomes available and the PK bridge re-assessed, it is expected that this will be further addressed. The PTA analysis should then be conducted with further increased re-inflation of the random effects prior to PTA simulations to account for the likely underestimated PK variability. A discussion of relevant degrees of inflation should then be presented and it is recommended that a range of inflations is then explored to understand the sensitivity of the PTA simulations towards the variability.

Special populations

- Paediatrics

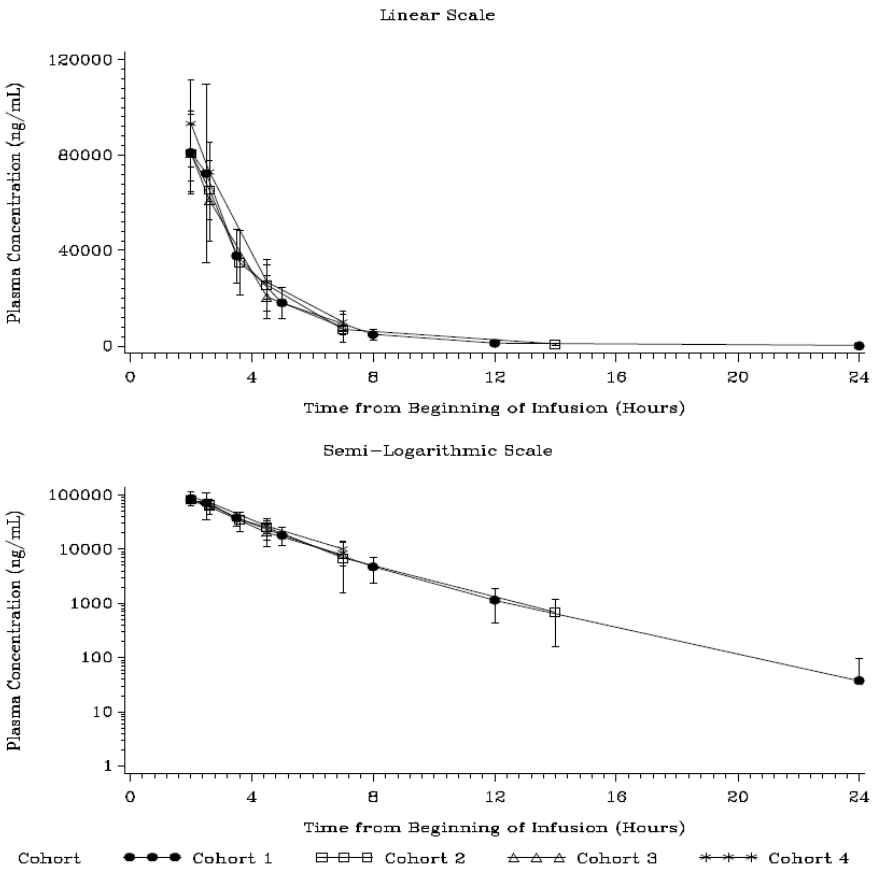
Non-compartmental analysis

D4280C00014 was a phase I, open-label, single-dose study in hospitalised paediatric patients from 3 months to <18 years of age receiving systemic antibiotic therapy for suspected or confirmed infection, conducted to characterise the PK of CAZ and AVI and to assess the safety and tolerability following a single IV dose of CAZ-AVI.

The study included four cohorts, each consisting of at least eight evaluable paediatric patients, aged ≥3 months to <18 years, who were hospitalised with infections. Cohort 1 consisted of patients aged ≥12 to <18 years, cohort 2 included patients aged ≥6 to <12 years, cohort 3 included patients aged ≥2 to <6 years, and cohort 4 patients aged ≥3 months to <2 years. A total of 35 patients were enrolled in the study and 32 patients were included in in the PK analysis set. Each patient received a single IV dose of CAZ-AVI administered as a continuous infusion over a 2-hour period.

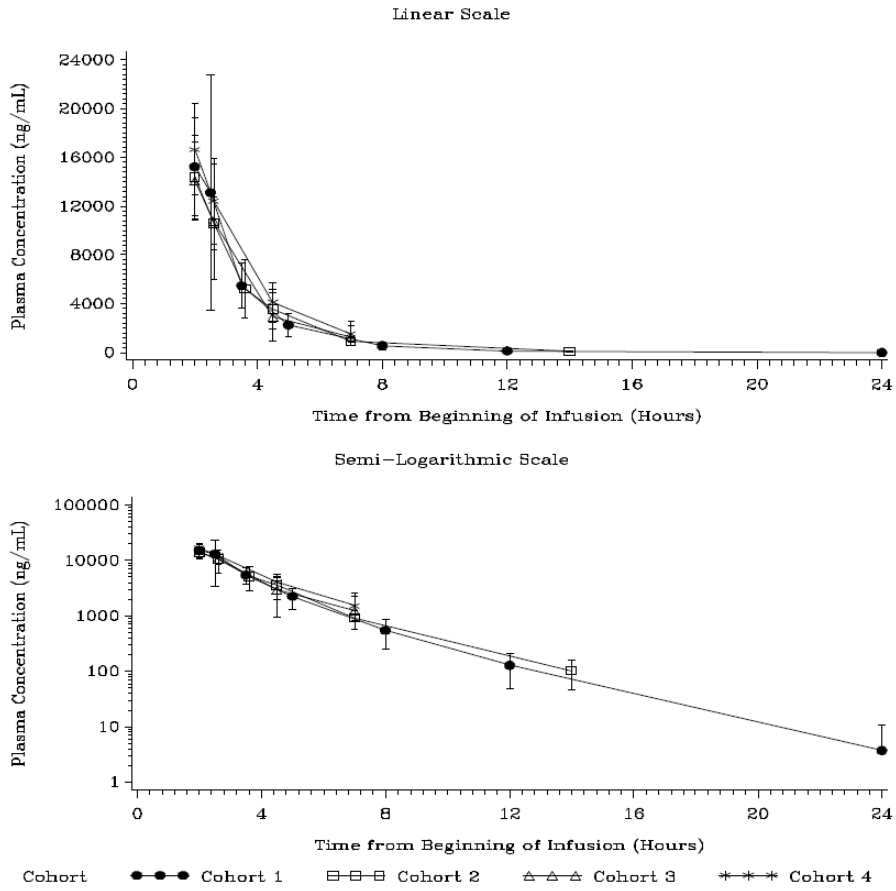
The dose regimens of cohorts 1 and 2 were determined by Monte Carlo simulation of the CAZ and AVI exposure to approximately match that observed in adults. For cohorts 3 and 4, the PK data of CAZ-AVI from cohorts 1 and 2 of this study were used to update the PK model and determine the dose to be administered to younger patients (see section 5.3.4). Dosing regimens used in the study are listed in Table 5. All patients received concomitant antibiotic medication, most commonly clindamycin (15 patients), cephalosporins (11 patients) and penicillins with or without beta-lactamase inhibitors (9 patients).

The mean±SD plasma concentration-time profiles for CAZ overlapped and were comparable for each cohort 1 to 4 (Figure 11). Mean plasma concentrations peaked at approximately 2 hours, which was at end of infusion. Also the mean±SD plasma concentration-time profiles for AVI overlapped and were comparable for each cohort 1 to 4 and mean plasma concentrations peaked at approximately 2 hours (Figure 12).



Cohort 1: patients aged ≥12 to <18 years; Cohort 2: patients aged ≥6 to <12 years; Cohort 3: patients aged ≥2 to <6 years; Cohort 4: patients aged ≥3 months to <2 years.
Source data: Figure 11.2.4.2

Figure 11. Overlay plots of mean (±SD) plasma concentrations (ng/mL) of ceftazidime versus time for cohorts 1 to 4 from study D4280C00014 (CSR Figure 1)



Cohort 1: patients aged ≥12 to <18 years; Cohort 2: patients aged ≥6 to <12 years; Cohort 3: patients aged ≥2 to <6 years; Cohort 4: patients aged ≥3 months to <2 years.
Source data: Figure 11.2.4.1

Figure 12. Overlay plots of mean (±SD) plasma concentrations (ng/mL) of avibactam versus time for cohorts 1 to 4 from study D4280C00014 (CSR Figure 2)

As shown in Figures above, the observed concentration profiles of ceftazidime and avibactam were similar in all four cohorts across sampling time points.

PK parameters of CAZ and AVI for cohorts 1 and 2 are summarised below. In cohorts 1 and 2 CAZ had similar geometric mean C_{max} and AUC values and the t1/2 of ceftazidime was similar; however, the CL, Vz, and Vss values were higher in cohort 1 than in cohort 2; the geometric mean body weight-normalised CL, Vz, and Vss values of CAZ appeared to be comparable for cohorts 1 and 2, although large variability was observed. In cohorts 1 and 2 AVI had similar geometric mean C_{max} and AUC values and the t1/2 of avibactam was similar; however, the CL, Vz, and Vss values were higher in cohort 1 than in cohort 2; the geometric mean body weight-normalized CL, Vz, and Vss values of AVI appeared to be comparable for cohorts 1 and 2, although large variability was observed.

Table 10. Pharmacokinetic parameters of ceftazidime and avibactam for cohort 1 and cohort 2 from study D4280C00014 (CSR Table 12)

PK Parameter (Units)	Statistic	Cohort 1 (N=8)		Cohort 2 (N=8)	
		Ceftazidime	Avibactam	Ceftazidime	Avibactam
$AUC_{(0-8)}$ (h*ng/mL)	n	8	8	8	8
	Arithmetic mean	230800	37590	215000	34560
	Geometric mean	219100	35140	212400	33590
	CV%	29.69	33.11	16.28	22.15
$AUC_{(0-t)}$ (h*ng/mL)	n	8	8	8	8
	Arithmetic mean	242600	38930	221400	35520
	Geometric mean	229200	36250	217800	34380
	CV%	30.86	33.70	18.36	23.37
$AUC_{(0-inf)}$ (h*ng/mL)	n	8	8	8	8
	Arithmetic mean	243900	39100	224400	35890
	Geometric mean	230600	36430	221200	34820
	CV%	30.70	33.61	17.38	22.62
C_{max} (ng/mL)	n	8	8	8	8
	Arithmetic mean	87000	17190	82490	14550
	Geometric mean	79750	15090	81270	14140
	CV%	41.81	52.42	17.81	22.96
t_{max} (h)	n	8	8	8	8
	Median	2.02	2.02	2.05	2.05
	Minimum, Maximum	1.93, 2.58	1.93, 2.58	1.93, 2.42	1.93, 2.42
t_{last} (h)	n	8	8	8	8
	Median	12.0	12.0	13.0	13.0
	Minimum, Maximum	8.00, 24.2	8.00, 24.2	5.97, 14.0	5.97, 14.0
$t_{1/2}$ (h)	n	8	8	8	8
	Median	1.65	1.59	1.63	1.66
	Minimum, Maximum	0.937, 2.83	0.887, 2.76	0.917, 1.79	0.893, 2.02

Table 10. Continued.

PK Parameter (Units)	Statistic	Cohort 1 (N=8)		Cohort 2 (N=8)	
		Ceftazidime	Avibactam	Ceftazidime	Avibactam
CL (L/h)	n	8	8	8	8
	Arithmetic mean	9.332	15.10	5.667	9.199
	Geometric mean	8.673	13.72	5.608	8.906
	CV%	45.47	52.56	15.95	30.17
V_z (L)	n	8	8	8	8
	Arithmetic mean	23.45	35.15	12.20	19.87
	Geometric mean	22.47	33.23	11.87	19.08
	CV%	31.42	36.92	22.70	26.85
V_{ss} (L)	n	8	8	8	8
	Arithmetic mean	23.67	34.11	13.18	19.88
	Geometric mean	22.23	31.02	12.97	19.26
	CV%	42.00	53.30	17.78	27.04
MRT (h)	n	8	8	8	8
	Arithmetic mean	2.582	2.276	2.335	2.181
	Geometric mean	2.564	2.260	2.313	2.162
	CV%	12.78	13.01	14.40	14.09
λz (1/h)	n	8	8	8	8
	Arithmetic mean	0.4091	0.4367	0.4862	0.4852
	Geometric mean	0.3859	0.4130	0.4726	0.4667
	CV%	38.47	37.17	27.51	32.08
CL/W (L/kg/h)	n	8	8	8	8
	Arithmetic mean	0.1784	0.2874	0.2298	0.3743
	Geometric mean	0.1686	0.2668	0.2262	0.3592
	CV%	37.91	44.15	20.03	35.76
V_z/W (L/kg)	n	8	8	8	8
	Arithmetic mean	0.4490	0.6754	0.4866	0.7910
	Geometric mean	0.4369	0.6460	0.4786	0.7696
	CV%	26.05	32.83	17.92	23.36

The CHMP noted that PK sampling in study D4280C00014 appeared to be less frequent in the two youngest cohorts. The PK sampling strategy for this study was outlined by the MAH as requested during the procedure. Caused by sparse sampling, CAZ-AVI PK parameters were not calculated for patients aged ≥3 months to <6 years (cohorts 3 and 4) in the study, however acceptable model-derived population PK parameters were presented.

C3591004/D4280C00015 was a phase II, single-blind, randomised, multi-centre, and actively controlled trial conducted in paediatric patients diagnosed with cIAIs of sufficient severity to require hospitalisation and treatment with IV antibiotics. Patients aged from 3 months to less than 18 years with cIAIs were randomised in a 3:1 ratio to receive CAZ-AVI plus metronidazole or meropenem. Patients were allocated to 1 of 4 cohorts based on age (cohort 1: 12 to <18 years; cohort 2: 6 to <12 years; cohort 3: 2 to <6 years; cohort 4: 3 months to <2 years). A total of 83 patients were enrolled, 61 were randomised to CAS-AVI plus metronidazole and 60 patients were included in the PK analysis.

Patients received IV treatment for a minimum of 72 hours (3 full days, *i.e.* 9 doses) before having the option to switch to an oral therapy on day 4. The total period of treatment (*i.e.* IV drug and oral switch treatment) was to be between 7 and 15 days. Patients could have remained on IV study treatment for the full 7 to 15 days. Dosing regimens of CAZ-AVI in the study are listed in Table 5.

Sparse PK sampling was conducted. On day 3 following a dose administration, blood samples (1 mL per sample for cohorts 1 and 2, and 0.5 mL per sample for cohort 3 and 4) for determination of ceftazidime and avibactam concentrations in plasma were obtained at the following time points: within 15 minutes prior to or after stopping CAZ-AVI infusion, between 30 and 90 minutes after stopping CAZ-AVI infusion, and between 5 and 6 hours after stopping CAZ-AVI infusion.

Median plasma concentrations of CAZ and AVI at Day 3 were similar across age cohorts 1 to 3 (Table 11 and Table 12). No patients from cohort 4 received CAZ-AVI, therefore no plasma concentration data are available for this cohort.

Table 11. Plasma concentrations (ng/mL) of ceftazidime on day 3 from study C3591004/D4280C00015 (CSR Table 32)

	15 minutes prior to/after stopping CAZ-AVI + MTZ infusion			30 to 90 minutes after stopping CAZ-AVI + MTZ infusion			300 to 360 minutes after stopping CAZ-AVI + MTZ infusion		
Cohort	Geometric mean	CV%	Median	Geometric mean	CV%	Median	Geometric mean	CV%	Median
Cohort 1 (N = 21)	50111.9	107.3	55300.0	30401.3	71.6	30600.0	4898.3	82.5	5140.0
Cohort 2 (N = 33)	70884.4	118.5	66700.0	43860.4	42.9	43500.0	4807.0	99.9	4230.0
Cohort 3 (N = 6)	77121.8	53.7	67900.0	38176.2	35.5	40400.0	2916.9	41.9	3370.0
All cohorts (N = 60)	63565.5	109.4	62300.0	38048.0	55.8	39450.0	4603.0	89.5	4420.0

Source: Table 14.4.3.1
Blood samples for PK (1 mL per sample for Cohorts 1 and 2, and 0.5 mL per sample for Cohorts 3 and 4) were collected from patients randomised to CAZ-AVI plus metronidazole treatment on Day 3 following a dose administration that is convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.
CAZ-AVI = ceftazidime-avibactam; CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; CV = coefficient of variation; PK = pharmacokinetic.

Table 12. Plasma concentrations (ng/mL) of avibactam on day 3 from study C3591004/D4280C00015 (CSR Table 33)

Cohort	15 minutes prior to/after stopping CAZ AVI + MTZ infusion			30 to 90 minutes after stopping CAZ-AVI + MTZ infusion			300 to 360 minutes after stopping CAZ-AVI + MTZ infusion		
	Geometric mean	CV%	Median	Geometric mean	CV%	Median	Geometric mean	CV%	Median
Cohort 1 (N = 21)	10010.3	113.1	10950.0	5525.8	88.6	6010.0	803.4	87.8	644.0
Cohort 2 (N = 33)	13200.1	140.2	13200.0	7138.0	64.2	7610.0	893.5	114.1	758.0
Cohort 3 (N = 6)	15126.2	63.2	13400.0	7385.9	39.1	8215.0	559.7	47.3	608.5
All cohorts (N = 60)	12186.2	122.9	12400.0	6548.6	71.3	7325.0	821.5	98.9	670.5

Source: Table 14.4.3.2

Blood samples for PK (1 mL per sample for Cohorts 1 and 2, and 0.5 mL per sample for Cohorts 3 and 4) are collected from patients randomised to CAZ-AVI plus metronidazole treatment on Day 3 following a dose administration that is convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.

CAZ-AVI = ceftazidime-avibactam; CAZ-AVI +MTZ = ceftazidime-avibactam plus metronidazole; CV = coefficient of variation; PK = pharmacokinetic.

C3591005/D4280C00016 was a phase 2, single-blind, randomised, multi-centre, and actively controlled trial conducted in hospitalised paediatric patients diagnosed with cUTIs. Patients aged from 3 months to <18 years with cUTI were randomised in a 3:1 ratio to receive CAZ-AVI or cefepime. Patients were allocated to 1 of 4 cohorts based on age (cohort 1: 12 to <18 years; cohort 2: 6 to <12 years; cohort 3: 2 to <6 years; cohort 4: 3 months to <2 years). A total of 101 patients were enrolled and 68 were randomised to CAS-AVI. Patients received IV treatment for a minimum of 72 hours. CAZ-AVI doses were based on the age and weight of the patient with adjustment according to renal function and were designed to match adult exposures and PK/PD target attainment.

In this study, sparse PK sampling was included, too. On day 3 following a dose administration, blood samples were obtained within 15 minutes prior to or after stopping CAZ-AVI infusion, between 30 and 90 minutes after stopping CAZ-AVI infusion, and between 5 and 6 hours after stopping CAZ-AVI infusion.

Median observed plasma concentrations of CAZ and AVI on Day 3 were similar across age cohorts, although concentrations were lower for trough samples in Cohort 3 and lower for samples taken near the end of infusion in Cohort 4 (Table 13 and Table 14).

Table 13. Plasma concentrations (ng/mL) of ceftazidime on day 3 from study C3591005/D4280C00016 (Module 2.7.2 cUTI, Table 2)

Cohort	15 minutes prior to/after stopping CAZ-AVI infusion			30 to 90 minutes after stopping CAZ-AVI infusion			300 to 360 minutes after stopping CAZ-AVI infusion		
	Geometric mean	CV%	Median	Geometric mean	CV%	Median	Geometric mean	CV%	Median
Cohort 1 (N = 12)	73628.9	133.3	98000.0	52141.4	61.8	44650.0	6364.8	42.3	6600.0
Cohort 2 (N = 16)	69835.3	106.2	86300.0	63551.4	59.4	56600.0	8134.1	134.3	8095.0
Cohort 3 (N = 10)	55220.1	182.5	92600.0	41427.9	34.0	39850.0	4433.7	27.3	4360.0
Cohort 4 (N = 26)	53865.2	91.4	63400.0	39841.7	64.2	43400.0	8663.3	93.9	7450.0
All cohorts (N = 64)	61411.2	112.8	78350.0	47638.5	61.8	47100.0	7285.7	90.4	6905.0

Source: Module 5.3.5.1 Study D4280C00016 CSR Table 14.4.3.1

Blood samples for PK (1 mL per sample for Cohorts 1 and 2, and 0.5 mL per sample for Cohorts 3 and 4) were collected from patients randomised to CAZ-AVI treatment on Day 3 following a dose administration that is convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.

Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years of age; Cohort 3: ≥2 years to <6 years of age; Cohort 4: ≥3 months to <2 years of age.

CAZ-AVI = ceftazidime-avibactam; CV = coefficient of variation; N = number of patients; PK = pharmacokinetic.

Table 14. Plasma concentrations (ng/mL) of avibactam on day 3 from study C3591005/D4280C00016 (Module 2.7.2 cUTI, Table 3)

Cohort	15 minutes prior to/after stopping CAZ-AVI infusion			30 to 90 minutes after stopping CAZ-AVI infusion			300 to 360 minutes after stopping CAZ-AVI infusion		
	Geometric mean	CV%	Median	Geometric mean	CV%	Median	Geometric mean	CV%	Median
Cohort 1 (N = 12)	11900.5	167.5	17800.0	7668.6	76.2	6780.0	748.7	39.1	743.5
Cohort 2 (N = 16)	11234.5	134.7	14550.0	9683.5	71.4	8210.0	1002.4	143.3	1034.5
Cohort 3 (N = 10)	8433.7	255.4	14200.0	6010.6	42.0	6450.0	606.0	29.0	582.0
Cohort 4 (N = 26)	8156.4	115.9	11900.0	5838.8	92.8	6635.0	1167.1	112.7	991.0
All cohorts (N = 64)	9577.4	144.1	13200.0	7046.4	80.3	6880.0	936.3	99.9	884.0

Source: Module 5.3.5.1 Study D4280C00016 CSR Table 14.4.3.2
Blood samples for PK (1 mL per sample for Cohorts 1 and 2, and 0.5 mL per sample for Cohorts 3 and 4) were collected from patients randomised to CAZ-AVI treatment on Day 3 following a dose administration that was convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.
Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years of age; Cohort 3: ≥2 years to <6 years of age; Cohort 4: ≥3 months to <2 years of age.
CAZ-AVI = ceftazidime-avibactam; CV = coefficient of variation; N = number of patients; PK = pharmacokinetic.

The CHMP acknowledged that in cIAI patients (study C3591005) median plasma concentrations of CAZ and AVI at Day 3 were similar across age cohorts 1 to 3. There were no patients in cohort 4 and only 6 patients in cohort 3 receiving CAZ-AVI, thus very limited PK data from patients < 6 years with cIAIs are available. In the PK model, patients with cIAI had higher CL for both CAZ and AVI compared to healthy subjects.

In cUTI patients (study C3591005) median observed plasma concentrations of CAZ and AVI on Day 3 were similar across age cohorts, although concentrations were lower for trough samples in Cohort 3 and lower for samples taken near the end of infusion in Cohort 4.

popPK

Individual model-predicted exposures

Individual model predicted exposures and PTA (using joint PKPD target) in paediatric patients from the two phase II studies are presented below (Table 16 and Table 17). Model-predicted $AUC_{ss,0-24}$ values for both CAZ and AVI were generally similar to the corresponding adult population, with geometric mean values from most study cohorts deviating from adults by ± 15%. Mean $C_{min,ss}$ values were lower in all paediatric cohorts than in the corresponding adult reference populations, and mean $C_{max,ss}$ values for CAZ and AVI tended to be higher in paediatric patients than in adults.

In study **C3591004**, model-predicted CAZ geometric mean $C_{max,ss}$ for each age cohort ranged from 102% (12 to <18 years) to 122% (6 to <12 years) and $AUC_{ss,0-24}$ ranged from 84% to 101% of corresponding values for adults with cIAI. Model-predicted AVI geometric mean $C_{max,ss}$ for each age cohort ranged from 89% to 128% and $AUC_{ss,0-24}$ ranged from 79% to 110% of corresponding values for adults with cIAI.

In study **C3591005**, model-predicted CAZ geometric mean $C_{max,ss}$ for each age cohort ranged from 114% to 145% and $AUC_{ss,0-24h}$ ranged from 76% to 102% of corresponding values for adults with cUTI.
Model-predicted AVI geometric mean $C_{max,ss}$ for each age cohort ranged from 102% to 139% and $AUC_{ss,0-24h}$ ranged from 81% to 110% of corresponding for adults with cUTI.

Table 15. Individual predicted geometric mean ceftazidime and avibactam exposures ($C_{max,ss}$, $AUC_{ss,0-24}$) in paediatric patients as percent of corresponding adult exposures following 2 g/0.5 g CAZ-AVI q8h (2-hour infusion)

Study/age groups	Dose regimen[a]	Ceftazidime			Avibactam		
		Percent of adult exposure (geom.means)			Percent of adult exposure (geom.means)		
		$C_{max,ss}$	$C_{min,ss}$	$AUC_{ss,0-24}$	$C_{max,ss}$	$C_{min,ss}$	$AUC_{ss,0-24}$
Study C3591004 (cIAI)							
≥12 to <18y	50 / 12.5 mg/kg	102%	21-55% (only a range given for whole population combined)	[b]	89%	[b]	79%
≥6 to <12y	50 / 12.5 mg/kg	122%		101%	128%	60%	110%
≥2 to <6y	50 / 12.5 mg/kg	[b]		84%	112%	31%	[b]
Study C3591005 (cUTI)							
≥12 to <18y	50 / 12.5 mg/kg	145%	[b]	[b]	[b]	[b]	[b]
≥6 to <12y	50 / 12.5 mg/kg	[b]	49%	102%	[b]	[b]	110%
≥2 to <6y	50 / 12.5 mg/kg	114%	22%	[b]	139%	31%	[b]
≥1 to <2y	50 / 12.5 mg/kg	114%	[b]	[b]	102%	[b]	[b]
≥6 months to <1y	50 / 12.5 mg/kg	[b]	[b]	[b]	102%	[b]	81%
≥3 to <6 months	40 / 10 mg/kg	97%	[b]	76%	[b]	60%	[b]

a. Doses administered q8h as a 2-hour infusion.
b. Value not stated, but presumably within the range of the other given values for the corresponding exposure metric.

Table 16. Summary of model predicted AUCss,0-24, Cmax,ss, and Cmin,ss for avibactam and ceftazidime and PTA in paediatric patients with cIAI (study C3591004) by age cohort (Module 2.7.2, Table 5)

Parameter[a]	≥2 Years to <6Years[c]	≥6 Years to <12 Years[c]	≥12 Years to <18 Years[c]
Number of subjects	6	33	19
Avibactam			
$AUC_{ss,0-24}$ (mg•h/L)	119 (24.7)	147 (34.5)	105 (59.1)
$C_{min,ss}$ (mg/L)	0.35 (58.6)	0.67 (119)	0.57 (62.5)
$C_{max,ss}$ (mg/L)	14.4 (24.6)	16.5 (32.9)	11.5 (77.5)
Ceftazidime			
$AUC_{ss,0-24}$ (mg•h/L)	607 (27.1)	729 (31.6)	642 (33.3)
$C_{min,ss}$ (mg/L)	1.71 (82)	3.85 (123)	4.55 (105)
$C_{max,ss}$ (mg/L)	75.6 (19.2)	81 (17.8)	67.7 (17.4)
PK/PD Target Attainment[b]	100	97	94.7

[a] Values are the geometric mean (%CV). $AUC_{ss,0-24}$ is obtained by multiplying AUC_{ss0-8} from a single steady-state dose by 3. $C_{max,ss}$ is obtained at the end of infusion. $C_{min,ss}$ is obtained 8 hours after the start of infusion.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% $fT > C_T$ of 1 mg/L for avibactam.
[c] There were no patients <2 years in this study. The dose was 50 mg/kg ceftazidime and 12.5 mg/kg avibactam q8h given as a 2-hour IV infusion, with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
Source: CAZ-MS-PED-02 report, Table 3

Table 17. Summary of model predicted AUCss,0-24, Cmax,ss, and Cmin,ss for avibactam and ceftazidime and PTA in paediatric patients with cUTI (Study C3591005) by age cohort (Module 2.7.2, Table 6)

Parameter[a]	≥3 Months to <6 months[c]	≥6 Months to <1 Year[c]	≥1 Year to <2 Years[c]	≥2 Years to <6 Years[c]	≥6 Years to <12 Years[c]	≥12 Years to <18 Years[c]
Number of subjects	5	9	11	10	16	12
Avibactam						
$AUC_{ss,0-24}$ (mg•h/L)	132 (30.5)	113 (58.3)	117 (62.2)	123 (43.3)	153 (43.4)	139 (55.3)
$C_{min,ss}$ (mg/L)	0.91 (17)	0.55 (85.2)	0.6 (254)	0.47 (47.4)	0.76 (110)	0.66 (65.6)
$C_{max,ss}$ (mg/L)	13.8 (36.8)	12.5 (63.1)	12.5 (46.8)	14.6 (50.5)	17.1 (38.3)	16.4 (60.9)
Ceftazidime						
$AUC_{ss,0-24}$ (mg•h/L)	736 (24.4)	859 (23.1)	883 (30.8)	789 (19.7)	993 (35.6)	843 (39.1)
$C_{min,ss}$ (mg/L)	4.68 (78.6)	5.14 (80.9)	5.57 (121)	3.18 (50.3)	7.02 (109)	6.06 (84.9)
$C_{max,ss}$ (mg/L)	78.1 (15.9)	92.3 (9.72)	92.8 (12.9)	94.1 (15)	104 (22)	92.4 (27.4)
PK/PD Target Attainment [b]	100	100	90.9	100	100	100

[a] Values are the geometric mean (%CV). $AUC_{ss,0-24}$ is obtained by multiplying $AUC_{ss,0-8}$ from a single steady-state dose by 3. $C_{max,ss}$ is obtained at the end of infusion. $C_{min,ss}$ is obtained 8 hours after the start of infusion.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% $fT > C_T$ of 1 mg/L for avibactam.
[c] The dose for patients from 3 to <6 months was 40 mg/kg ceftazidime and 10 mg/kg avibactam q8h. Doses for patients 6 months and older was 50 mg/kg ceftazidime and 12.5 mg/kg avibactam q8h, with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam. All doses were given as a 2-hour IV infusion.
Source: CAZ-MS-PED-02 report, Table 4

Simulations to support paediatric dose recommendations

Simulated CAZ and AVI exposures (1000 subjects per age group, indication and renal function group) are presented in the Tables below. In the updated popPK model (CAZ-MS-PED-02), the paediatric PK data from phase 2 studies (C3591004 and C3591005) and Study D4280C00014 were pooled with PK data from adults (phase 1 to phase 3). Overall, the predicted exposures for CAZ and AVI at the proposed dose regimens were similar to the predicted exposures in adult patients receiving the labelled CAZ-AVI dose.

Table 18. Simulated geometric mean ceftazidime and avibactam exposures ($C_{max,ss}$, $AUC_{ss,0-24}$) in paediatric patients with normal renal function as percent of corresponding adult exposures

Age groups	Dose regimen*	Ceftazidime Percent of adult exposure (geom.means)		Avibactam Percent of adult exposure (geom.means)	
		$C_{max,ss}$	$AUC_{ss,0-24}$	$C_{max,ss}$	$AUC_{ss,0-24}$
6months to <18 y	50 mg/kg / 12.5 mg/kg	110-124%	92-110%	117-148%	104-130%
3 to <6 months	40 mg/kg / 10 mg/kg	109%	99-102%	115-118%	107-113%

* Doses administered q8h as a 2-hour infusion.

Table 19. Mean ceftazidime and avibactam Cmax,ss and AUCss,0-24 in 1000 simulated patients with cIAI, cUTI, or HAP/VAP and normal renal function following repeated administration with CAZ-AVI by age group (Module 2.7.2, Table 7)

Age Group	Dose [a] (CAZ/AVI)	cIAI		cUTI		HAP/VAP	
		$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)
Ceftazidime							
12 to <18 yrs	50/12.5 mg/kg q8h	64.6 (24.1)	618 (30.4)	81.5 (23.9)	821 (30.4)	71.8 (24.1)	747 (30.4)
6 to <12 yrs	50/12.5 mg/kg q8h	72.4 (19.6)	650 (29.8)	91.5 (19.4)	864 (29.8)	80.8 (19.6)	785 (29.8)
2 to <6 yrs	50/12.5 mg/kg q8h	68.2 (21.1)	572 (29.9)	86.3 (20.8)	760 (29.9)	76.4 (21.0)	691 (29.9)
1 to <2 yrs	50/12.5 mg/kg q8h	68.1 (19.4)	577 (29.8)	86.0 (19.1)	767 (29.8)	76.2 (19.2)	698 (29.8)
6 to <12 mths	50/12.5 mg/kg q8h	72.1 (19.5)	637 (29.9)	90.8 (19.2)	846 (29.9)	80.4 (19.4)	769 (29.9)
3 to <6 mths	40/10 mg/kg q8h	64.2 (19.4)	617 (30.2)	80.7 (19.2)	820 (30.2)	71.4 (19.4)	745 (30.2)
Adults	2000/500 mg q8h	58.9 (30.4)	602 (40.7)	74.0 (29.9)	828 (47.8)	65.1 (31.0)	712 (41.8)
Avibactam							
12 to <18 yrs	50/12.5 mg/kg q8h	12.3 (67.7)	121 (51.1)	11.9 (68.0)	121 (51.1)	13.0 (67.5)	121 (51.1)
6 to <12 yrs	50/12.5 mg/kg q8h	14.2 (44.3)	136 (36.0)	13.7 (44.7)	136 (36.0)	15.1 (43.2)	136 (36.0)
2 to <6 yrs	50/12.5 mg/kg q8h	13.0 (49.8)	118 (41.3)	12.5 (50.6)	118 (41.3)	13.8 (48.9)	118 (41.3)
1 to <2 yrs	50/12.5 mg/kg q8h	13.6 (53.5)	125 (42.8)	12.9 (53.9)	125 (42.8)	14.4 (52.8)	125 (42.8)
6 to <12 mths	50/12.5 mg/kg q8h	14.0 (53.7)	132 (43.2)	13.3 (54.1)	132 (43.2)	14.9 (53.1)	132 (43.2)
3 to <6 mths	40/10 mg/kg q8h	12.1 (54.1)	121 (43.5)	11.5 (54.4)	121 (43.5)	12.9 (53.6)	121 (43.5)
Adults	2000/500 mg q8h	10.5 (81.7)	107 (68.8)	9.73 (65.7)	113 (69.9)	10.2 (77.6)	105 (71.8)

[a] All doses as a 2-hour IV infusion with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
Source: CAZ-MS-PED-02 Report Table 25, Table 26, Table 29, Table 30, Table 33, and Table 34

The CHMP noted that the aim of the dose selection in paediatric patients was to achieve comparable exposures to that of adult patients with cIAI, cUTI and HAP/VAP. For ceftazidime-avibactam, limited PK sampling was performed in paediatric subjects with cIAI and cUTI, and comparisons rely on individual model-predicted exposures and simulations for cIAI and cUTI indications, and only on simulations for HAP/VAP indication.

Of note, no PK data are currently available in paediatric patients with HAP/VAP. An ongoing study will provide exposure data from HAP/VAP patients 3 months old to 18 years of age. The applicant's extrapolation strategy for this indication was thus based on popPK/PTA simulations, using adult datasets across 3 approved indications (cIAI, cUTI, and HAP/VAP) and PK data from paediatric patients with cUTI and cIAI. Of note, paediatric patients with cUTI had severe infections requiring IV treatment. This strategy is acceptable to the CHMP, as paediatric PK data for at least two type of infections are available, including from cUTI patients with severe infections.

Overall, individually predicted and simulated paediatric exposures do not differ greatly from that of adults for cIAI and cUTI. For HAP/VAP, simulated paediatric exposures were also overall comparable to the adult exposures.

The cIAI population aged 1-6 years appears to have the lower exposure than the other subgroups, which is also reflected in the PTA analysis. For both active compounds the predicted exposures show a higher Cmax

and lower Cmin (trough) in the paediatric population compared to the adult population, although the total exposure (AUC) seem to be similar. This can be interpreted as the time above MIC is shorter which in turn could be the reason for the lower PTA in the age group 1-6 years. See below for further assessment.

The requested graphical presentations of simulated exposure metrics (AUC0-24 and Cmax) by age, body weight and renal function were provided by the MAH. In retrospect, they are not considered very informative. Rather Cmin should have been presented, and sensitivity analysis on the PTA simulations with higher shrinkage adjustments, than the used adult values, should have been performed to explore the potential impact of the uncertainties. However, this was not further pursued, as it was not expected to further inform the conclusion on the dosing regimen.

The MAH has not pre-specified acceptance limits for similarity of exposure. In general, such acceptance limits should be discussed, and pre-set, in relation to the therapeutic window of the medicinal product. Additional considerations toward the variability in a sparse sampling setting in a paediatric population must also be made. The MAH selected AUC0-24 and Cmax as the primary exposure metrics. However, in smaller children there is a risk that similar AUC may be observable, while Cmax may be higher and Cmin lower. As this may affect the PTA, it is of value to compare the simulated PTAs for the various cohorts.

Even so, the comparability of exposure levels in children does demonstrate roughly similarity of exposures. In brief, the MAH provided several methods of comparing the exposure profiles in children of the various age cohorts to that of adults;

- observed plasma concentrations,

- estimated NCA for cohorts 1 and 2,

- simulated exposure metric data (AUC0-24 and Cmax) for all cohorts,

- simulations of PTA for all cohorts.

The two latter comparisons depend on a credible model (population-PK model) for the simulations. The MAH provided model diagnostics for the paediatric model, which was assessed as part of the initial AR. The model is considered low to moderately credible for its context of use. With this background, the exposure metrics and the PTA does support that the proposed posology will provide adequate exposure levels, while not exceeding the exposure to a level where harm to patients is expected. While the exposure-response relationship of ceftazidime/avibactam is not explicitly presented, the therapeutic window of ceftazidime is known to be rather wide and the main risk to patients and society is underexposure (lack of effect and risk of bacterial resistance). However, there are sources of uncertainty on 1) the exposure levels in the younger age cohorts, 2) specifically in cIAI below 2 years and 3) in patients with moderate to severely reduced renal function that cannot be relieved by the available data.

The totality of the data and the consideration that ceftazidime is approved for use in children, with dosing recommendations down to birth, allows for concluding that the proposed dosing recommendations are adequate and that the exposures are sufficiently similar to allow preceding with extrapolation of safety and efficacy.

- Renal impairment

Non-compartmental analysis

CAZ and AVI are eliminated by the kidneys, therefore, the dose should be reduced according to the degree of renal impairment (SmPC, Zavicefta). In the studies **D4280C00014** and **C3591004**, all patients had normal or mildly reduced renal function (CrCl values $\geq$ 50 mL/min/1.73 m^2). In study **C3591005** the majority of patients (66.3%) had CrCl values at baseline in the normal range of $\geq$ 80 mL/min/1.73 m^2,

31.6% of the patients had mild renal insufficiency with CrCl values ≥50 to <80 mL/min/1.73 m^2 and 2.1% had CrCl values ≥30 to <50 mL/min/1.73 m^2. No patients had a CrCl value <30 mL/min/1.73 m^2. Thus, the experience with pediatric patients with moderately or severe reduced renal function is limited.

popPK

Simulations to support paediatric dose recommendations in renal impairment

Simulated mean CAZ-AVI $C_{max,ss}$ and $AUC_{ss,0-24}$ in peadiatric patients with mild and moderate renal impairment are compared to adults exposures in the below table. Mean CAZ $C_{max,ss}$ and $AUC_{ss,0-24}$ values in paediatric patients with moderate renal impairment receiving the proposed dose were 91-107% and 117-140%, respectively, of the mean values in adults with normal renal function. Corresponding AVI values were 93-120% and 116-148%, respectively.

Mean CAZ $C_{max,ss}$, $C_{min,ss}$ and $AUC_{ss,0-24}$ values in paediatric patients (cUTI, cIAI, NP) with severe renal impairment receiving 18.75 / 4.75 mg / kg q12h were 78-95%, 176-271% and 104-124%, respectively, of the mean values in adults with normal renal function. Corresponding mean AVI values were 83-104%, 190-330% and 104-131%, respectively.

No dosage adjustment is considered necessary for paediatric patients with cIAI or cUTI and mild renal impairment.

Table 20. Simulated geometric mean ceftazidime and avibactam exposures ($C_{max,ss}$, $AUC_{ss,0-24}$) in paediatric patients 2-<18 years with impaired renal function as percent of those in adults with mild renal impairment

Degree of renal impairment[a]	Dose regimen[b]	Ceftazidime		Avibactam	
		Percent of adult exposure[c] (geom.means)		Percent of adult exposure[c] (geom.means)	
		$C_{max,ss}$	$AUC_{ss,0-24}$	$C_{max,ss}$	$AUC_{ss,0-24}$
cIAI					
Mild	50 / 12.5 mg/kg	109-125%	97-111%	116-137%	111-130%
Moderate	25 / 6.25 mg/kg	72-83%	79-90%	77-91%	89-105%
cUTI					
Mild	50 / 12.5 mg/kg	109-125%	96-109%	120-142%	108-126%
Moderate	25 / 6.25 mg/kg	73-83%	78-89%	80-95%	86-102%

a Mild renal impairment: NCrCL 50 to <80 mL/min/1.73 m^2; moderate renal impairment: NCrCL 30 to <50 mL/min/1.73 m^2.
b Doses administered q8h as a 2-hour infusion. Maximum paediatric dose = recommended adult dose in each renal function category.
c Reference exposures were simulated in adults with mild renal impairment receiving the 2 g / 0.5 g q8h dose.

Table 21. Mean ceftazidime and avibactam Cmax,ss and AUCss,0-24 in 1000 simulated patients with cIAI, cUTI or HAP/VAP and mild renal impairment following repeated administration with CAZ-AVI by age group (Module 2.7.2, Table 9)

Age Group	Dose [a] (CAZ/AVI)	cIAI		cUTI		HAP/VAP	
		$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)
Ceftazidime							
12 to <18 yrs	50/12.5 mg/kg q8h	81.6 (25.6)	940 (34)	103 (25.5)	1250 (34)	90.9 (25.7)	1140 (34)
6 to <12 yrs	50/12.5 mg/kg q8h	93.4 (20.5)	1020 (32.1)	118 (20.4)	1350 (32.1)	104 (20.6)	1230 (32.1)
2 to <6 yrs	50/12.5 mg/kg q8h	88.2 (21.7)	892 (31.8)	111 (21.5)	1190 (31.8)	98 (21.8)	1080 (31.8)
Adults	2000/500 mg q8h	74.9 (31.9)	917 (42.1)	94.3 (32.6)	1240 (49.5)	83.8 (33)	1100 (43.9)
Avibactam							
12 to <18 yrs	50/12.5 mg/kg q8h	14.7 (68.4)	164 (54.2)	14.2 (68.3)	164 (54.2)	15.5 (68.7)	164 (54.2)
6 to <12 yrs	50/12.5 mg/kg q8h	17.4 (45.2)	192 (37.4)	16.7 (45.3)	192 (37.4)	18.5 (44.5)	192 (37.4)
2 to <6 yrs	50/12.5 mg/kg q8h	15.9 (51)	167 (42.9)	15.3 (51.5)	167 (42.9)	17 (50.4)	167 (42.9)
Adults	2000/500 mg q8h	12.7 (83.8)	148 (69.7)	11.8 (66.7)	152 (71)	12.5 (79.5)	147 (72.6)

[a] All doses as a 2-hour IV infusion with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
Source: CAZ-MS-PED-02 Report Table 37, Table 38, and Table 39

Table 22. Mean ceftazidime and avibactam Cmax,ss and AUCss,0-24 in 1000 simulated patients with cIAI, cUTI or HAP/VAP and moderate renal impairment following repeated administration with CAZ-AVI by age group (Module 2.7.2, Table 11)

Age Group	Dose [a] (CAZ/AVI)	cIAI		cUTI		HAP/VAP	
		$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)
Ceftazidime							
12 to <18 yrs	25/6.25 mg/kg q8h	53.7 (26.9)	754 (35.1)	68.5 (27.1)	1000 (35.1)	60.5 (27.4)	911 (35.1)
6 to <12 yrs	25/6.25 mg/kg q8h	61.8 (22.0)	825 (33.8)	78.5 (22.2)	1100 (33.8)	69.4 (22.5)	997 (33.8)
2 to <6 yrs	25/6.25 mg/kg q8h	58.1 (22.7)	727 (33.2)	73.5 (22.8)	967 (33.2)	64.9 (23.2)	879 (33.2)
Adults	1000/250 mg q8h	50.1 (34)	740 (43.1)	64.1 (35.4)	998 (49.7)	56.7 (35.2)	891 (44.2)
Avibactam							
12 to <18 yrs	25/6.25 mg/kg q8h	9.72 (66.3)	131 (54.6)	9.42 (65.7)	131 (54.6)	10.2 (67.1)	105 (71.8)
6 to <12 yrs	25/6.25 mg/kg q8h	11.6 (44.8)	155 (38.5)	11.2 (44.6)	155 (38.5)	12.2 (44.7)	155 (38.5)
2 to <6 yrs	25/6.25 mg/kg q8h	10.6 (51.3)	135 (44)	10.2 (51.4)	135 (44)	11.2 (51.3)	135 (44)
Adults	1000/250 mg q8h	8.55 (86.2)	119 (70.7)	8.02 (68)	122 (72)	8.36 (82)	118 (73.5)

[a] All doses as a 2-hour IV infusion with a maximum dose of 1000 mg ceftazidime and 250 mg avibactam.
Source: CAZ-MS-PED-02 Report Table 40, Table 41, and Table 42

There are insufficient paediatric PK data to recommend a dose adjustment in severe renal impairment. In addition, because renal function in children <2 years was modelled as a function of PMA rather than NCrCL, and because renal impairment categories are not clearly defined in this age range, no dosing recommendations are made for paediatric patients <2 years with renal impairment.

The CHMP considered that, as ceftazidime/avibactam is primarily renally excreted, dosing recommendations in renal impairment is required.

Mild impairment

No adjustment of the dose has been suggested for mild renal impairment in paediatric patients. This is in line with the recommendation for Zavicefta in adults as well as for ceftazidime as monocomponent in children and is considered justified by the Committee.

Moderate to severe impairment in children 2 to <18 years

A 50% reduction of dose is proposed in moderate renal impairment for patients 2 to <18 years, which is similar to the corresponding dosing recommendation in adults.

Initially with this pediatric extension variation, no dosing recommendations was given by the MAH for paediatric patients 2 to <18 years with severe renal impairment (NCrCL <30 mL/min/1.73m^2) due to lack of PK and safety data in this subpopulation. As preexisting renal impairment could be expected also in the target paediatric population, dosing recommendations in these subgroups are desirable. By comparison, dosing recommendations are made for all renal function categories in children aged 2 months to <18 years for CAZ single substance medicinal products, in adults for Zavicefta, and in paediatric (<2 years) and adult populations for the FDA-approved AVYCAZ™ (CAZ-AVI).

Very limited CAZ-AVI PK data are available for paediatric patients with moderate to severe impaired renal function; *i.e.* only one patient with moderate (cohort 4, cUTI) and no patients with severe renal impairment were included in the paediatric phase II studies. Consequently, the recommendation in moderate renal impairment is primarily based on adult PK data. Although not a validated assumption, it is considered reasonable to expect a similar relationship between CrCL and CAZ-AVI clearance in children (aged 2 years and older) and adults when accounting for body weight.). Simulations of exposures and PTA analysis have been provided for patients aged 2 to <18 years with both moderate and severe renal impairment demonstrating a good PTA of >97% at investigated doses (25 mg / 6.25 mg/kg q8h and 18.75 mg / 4.75 mg/kg q12h, respectively).

Dosing recommendations were then proposed for paediatric patients aged 2-<18 years with NCrCL <30 mL/min/1.73m^2:

16 to 30 mL/min/1.73 m2: 18.75/4.75 mg/kg q12h

6 to 15 mL/min/1.73 m2: 18.75/4.75 mg/kg q24h

≤ 5 mL/min/1.73 m2: 18.75/4.75 mg/kg q24h

The dosing recommendation is considered justified based on exposure comparisons and PTA analysis.

Dosing based on NCrCL in paediatric subjects is considered justified. All modelling and simulation work for the CAZ-AVI paediatric programme used NCrCL. Inclusion/exclusion and dosing in the paediatric CAZ-AVI studies were based on the use of the "bedside Schwartz" equation giving estimated creatinine clearance in mL/min/1.73m^2, and for paediatric subjects, GFR is usually expressed as mL/min/1.73m^2. Dosing for drugs that are renally cleared often express paediatric dosing with creatinine clearance expressed in mL/min/1.73m^2 to reflect clinical practice.

More data on CAZ-AVI in paediatric patients with reduced renal function are expected from the two ongoing paediatric studies. The MAH proposed to add pre-existing moderate to severe renal impairment in the paediatric population as additional missing information in the RMP (section 2.7.).

Moderate to severe renal impairment in children 3 months to 2 years

Initially with this pediatric extension variation, no dosing recommendations were proposed by the MAH for paediatric patients <2 years with impaired renal function (≤50 mL/min/1.73m^2). The MAH justified this from the chosen popPK model structure (maturation function on CL instead of NCrCL) and lack of definition of renal impairment categories in this subgroup.

Table 1. Simulation Results (PK and PTA for T4 target and CAZ-AVI MIC of 8 mg/L)) for Paediatric Subjects 3 months to < 2 years with cIAI and the Adult Reference Range (Geometric Mean and CV% for PK)

Age Group	Renal Failure Category	Dosing	CAZ Cmax (mg/L)	CAZ Cmin (mg/L)	CAZ AUC0-24 (mg.h/L)	AVI Cmax (mg/L)	AVI Cmin (mg/L)	AVI AUC0-24 (mg.h/L)	Joint PTA (%)
1 to < 2 years	Mild	50/12.5 mg/kg q8h	88.6 (20.8)	7.11 (122)	912 (32.8)	16.5 (54.4)	1.37 (136)	176 (45.1)	99.6
6 months to < 1 year	Mild	50/12.5 mg/kg q8h	93.8 (21.3)	9.42 (116)	1020 (33.8)	17.1 (54.8)	1.61 (134)	187 (46.2)	99.5
3 to <6 months	Mild	40/10 mg/kg q8h	83.2 (21.1)	12 (97.1)	982 (33.4)	14.8 (54.5)	1.81 (116)	172 (45.7)	99.8
1 to < 2 years	Moderate	25/6.25 mg/kg q8h	58.8 (22)	11.8 (81.4)	752 (34.3)	11.1 (53.5)	2.21 (85.8)	144 (46)	99.8
6 months to < 1 year	Moderate	25/6.25 mg/kg q8h	61.9 (22.2)	14.2 (76.3)	825 (34)	11.4 (53.2)	2.44 (83)	151 (45.7)	99.9
3 to < 6 months	Moderate	20/5 mg/kg q8h	55.4 (23.2)	16.2 (67.9)	797 (34.7)	9.87 (53.1)	2.54 (75.9)	138 (46.6)	99.6
Adults	Normal	2000/500 mg q8h	58.9 (30.4)	5.46 (109)	602 (40.7)	10.5 (81.7)	0.788 (121)	107 (68.8)	94.8
Adults	Mild	2000/500 mg q8h	74.9 (31.9)	14 (88)	917 (42.1)	12.7 (83.8)	1.71 (96.1)	148 (69.7)	98.8
Adults	Moderate	1000/250 mg q8h	50.1 (34)	16.7 (69.8)	740 (43.1)	8.55 (86.2)	2.2 (72.5)	119 (70.7)	98.8

ePharm folder id 2047179; Adult simulations from PMAR-EQDD-C359a-Other-762 *CAZ-MS-PED-02), Table 41

Table 2. Simulation Results (PK and PTA PTA for T4 target and CAZ-AVI MIC of 8 mg/L) for Paediatric Subjects 3 months to < 2 years with cUTI and the Adult Reference Range (Geometric Mean and CV% for PK)

Age Group	Renal Failure Category	Dosing	CAZ Cmax (mg/L)	CAZ Cmin (mg/L)	CAZ AUC0-24 (mg.h/L)	AVI Cmax (mg/L)	AVI Cmin (mg/L)	AVI AUC0-24 (mg.h/L)	Joint PTA (%)
1 to < 2 years	Mild	50/12.5 mg/kg q8h	112 (20.7)	11.9 (104)	1210 (32.8)	15.7 (54.6)	1.61 (130)	176 (45.1)	100
6 months to < 1 year	Mild	50/12.5 mg/kg q8h	118 (21.3)	15.4 (100)	1350 (33.8)	16.3 (54.9)	1.88 (128)	187 (46.2)	100
3 to < 6 months	Mild	40/10 mg/kg q8h	105 (21.2)	19 (85)	1310 (33.4)	14.1 (54.4)	2.08 (110)	172 (45.7)	99.8
1 to < 2 years	Moderate	25/6.25 mg/kg q8h	74.4 (22.3)	17.9 (73)	1000 (34.3)	10.6 (53.3)	2.44 (82.6)	144 (46)	99.9
6 months to < 1 year	Moderate	25/6.25 mg/kg q8h	78.4 (22.5)	21.3 (68.8)	1100 (34)	10.9 (52.9)	2.69 (79.9)	151 (45.7)	99.9
3 to < 6 months	Moderate	20/5 mg/kg q8h	70.4 (23.6)	23.7 (62.3)	1060 (34.7)	9.47 (52.8)	2.76 (73.3)	138 (46.6)	99.6
Adults	Normal	2000/500 mg q8h	74 (29.9)	9.5 (140)	828 (47.8)	9.73 (65.7)	1.15 (191)	113 (69.9)	96.7
Adults	Mild	2000/500 mg q8h	94.3 (32.6)	21.6 (109)	1240 (49.5)	11.8 (66.7)	2.24 (144)	152 (71)	98.6
Adults	Moderate	1000/250 mg q8h	64.1 (35.4)	24.4 (83.3)	998 (49.7)	8.02 (68)	2.7 (105)	122 (72)	98.8

ePharm folder id 2047179; Adult simulations from PMAR-EQDD-C359a-Other-762 *CAZ-MS-PED-02), Table 40

For background, PDCO requested simulations for paediatric subjects <2 years of age with mild and moderate renal impairment as part of the PIP partial compliance check (EMEA-C2-001313-PIP01-12-M08). These simulations were performed based on inclusion of an adjustment factor (AF) for mild and moderate renal impairment (mean [range] AF for AVI: 0.71 [0.55; 0.88] and 0.44 (0.33; 0.55), respectively; mean [range] AF for CAZ: 0.63 [0.49; 0.78] and 0.39 [0.29; 0.49], respectively). Following the request by CHMP the applicant submitted simulations for PK and PTA for paediatric subject <2 years of age with mild renal impairment was performed for the same doses proposed for normal renal function. For patients with cIAI or cUTI and mild renal impairment, Cmax,ss and AUCss,0-24h values for CAZ were similar and for AVI were slightly higher (within 126%) for all age categories <2 years compared to adults with mild renal impairment. Cmin values are similar for AVI but lower for CAZ for paediatric patients with cIAI compared to adults with

mild renal impairment while continuing to achieve a high PTA (>99%). Simulations have not been shown for NP but exposures and joint PTA are expected to be similar to cUTI.

Table 3. Simulation Results for Paediatric Patients 3 months to <2 years with cIAI and Mild, Moderate or Severe Renal Impairment and for Adults as Reference (Geometric Mean and CV%)

Age Group	Renal Failure Category	Dosing	CAZ C_{max} (mg/L)	CAZ C_{min} (mg/L)	CAZ $AUC_{ss,0-24h}$ (mg.h/L)	AVI C_{max} (mg/L)	AVI C_{min} (mg/L)	AVI $AUC_{ss,0-24h}$ (mg.h/L)	Joint PTA (%)a
1 to <2 years	Mild	50/12.5 mg/kg q8h	88.6 (20.8)	7.11 (122)	912 (32.8)	16.5 (54.4)	1.37 (136)	176 (45.1)	99.6
6 months to <1 year	Mild	50/12.5 mg/kg q8h	93.8 (21.3)	9.42 (116)	1020 (33.8)	17.1 (54.8)	1.61 (134)	187 (46.2)	99.5
3 to <6 months	Mild	40/10 mg/kg q8h	83.2 (21.1)	12 (97.1)	982 (33.4)	14.8 (54.5)	1.81 (116)	172 (45.7)	99.8
1 to <2 years	Moderate	25/6.25 mg/kg q8h	58.8 (22)	11.8 (81.4)	752 (34.3)	11.1 (53.5)	2.21 (85.8)	144 (46)	99.8
6 months to <1 year	Moderate	25/6.25 mg/kg q8h	61.9 (22.2)	14.2 (76.3)	825 (34)	11.4 (53.2)	2.44 (83)	151 (45.7)	99.9
3 to <6 months	Moderate	20/5 mg/kg q8h	55.4 (23.2)	16.2 (67.9)	797 (34.7)	9.87 (53.1)	2.54 (75.9)	138 (46.6)	99.6
1 to <2 years	Severe	18.75/4.7 mg/kg q12h	52.5 (22.3)	11.6 (81.9)	673 (36.1)	9.95 (55.9)	2.12 (87.7)	128 (47.5)	98.5
6 months to <1 year	Severe	18.75/4.7 mg/kg q12h	55.3 (23.6)	13.9 (79)	741 (37.8)	10.2 (55.6)	2.35 (86.7)	135 (48.6)	99.3
3 to <6 months	Severe	15/3.75 mg/kg q12h	49 (24.1)	15.5 (67.5)	713 (36.5)	8.77 (56.1)	2.42 (76.7)	123 (49.3)	99.3
Adult	Normal	2000/500 mg q8h	58.9 (30.4)	5.46 (109)	602 (40.7)	10.5 (81.7)	0.788 (121)	107 (68.8)	94.8
Adult	Mild	2000/500 mg q8h	74.9 (31.9)	14 (88)	917 (42.1)	12.7 (83.8)	1.71 (96.1)	148 (69.7)	98.8
Adult	Moderate	1000/250 mg q8h	50.1 (34)	16.7 (69.8)	740 (43.1)	8.55 (86.2)	2.2 (72.5)	119 (70.7)	98.8

AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 hours at steady state; AVI = avibactam; CAZ = ceftazidime; cIAI = complicated intra-abdominal infection; Cmax = maximum plasma drug concentration at steady state; Cmin = minimum plasma drug concentration at steady state; PTA = probability of PK/PD target attainment; q8h = every 8 hours.

[a] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > CT of 1 mg/L for avibactam.

Source: eph:2047179; eph:RA15790272; eph:RA15790273; Adult simulations from PMAR-EQDD-C359a-Other-762 *CAZ-MS-PED-02), Table 41

Table 4. Simulation Results for Paediatric Patients 3 months to <2 years with cUTI and Mild, Moderate or Severe Renal Impairment and for Adults as Reference (Geometric Mean and CV%)

Age Group	Renal Failure Category	Dosing	CAZ C_{max} (mg/L)	CAZ C_{min} (mg/L)	CAZ $AUC_{ss,0-24h}$ (mg.h/L)	AVI C_{max} (mg/L)	AVI C_{min} (mg/L)	AVI $AUC_{ss,0-24h}$ (mg.h/L)	Joint PTA (%)a
1 to <2 years	Mild	50/12.5 mg/kg q8h	112 (20.7)	11.9 (104)	1210 (32.8)	15.7 (54.6)	1.61 (130)	176 (45.1)	100
6 months to <1 year	Mild	50/12.5 mg/kg q8h	118 (21.3)	15.4 (100)	1350 (33.8)	16.3 (54.9)	1.88 (128)	187 (46.2)	100
3 to <6 months	Mild	40/10 mg/kg q8h	105 (21.2)	19 (85)	1310 (33.4)	14.1 (54.4)	2.08 (110)	172 (45.7)	99.8
1 to <2 years	Moderate	25/6.25 mg/kg q8h	74.4 (22.3)	17.9 (73)	1000 (34.3)	10.6 (53.3)	2.44 (82.6)	144 (46)	99.9
6 months to <1 year	Moderate	25/6.25 mg/kg q8h	78.4 (22.5)	21.3 (68.8)	1100 (34)	10.9 (52.9)	2.69 (79.9)	151 (45.7)	99.9
3 to <6 months	Moderate	20/5 mg/kg q8h	70.4 (23.6)	23.7 (62.3)	1060 (34.7)	9.47 (52.8)	2.76 (73.3)	138 (46.6)	99.6
1 to <2 years	Severe	18.75/4.7 mg/kg q12h	66.2 (22.7)	17.3 (73.7)	895 (36.1)	9.46 (55.4)	2.33 (83.9)	128 (47.5)	99.5
6 months to <1 year	Severe	18.75/4.7 mg/kg q12h	69.8 (24.2)	20.6 (71.8)	985 (37.8)	9.76 (55.1)	2.57 (82.9)	135 (48.6)	99.7
3 to <6 months	Severe	15/3.75 mg/kg q12h	62.2 (24.6)	22.5 (62.3)	948 (36.5)	8.38 (55.5)	2.61 (74)	123 (49.3)	99.3
Adult	Normal	2000/500 mg q8h	74 (29.9)	9.5 (140)	828 (47.8)	9.73 (65.7)	1.15 (191)	113 (69.9)	96.7
Adult	Mild	2000/500 mg q8h	94.3 (32.6)	21.6 (109)	1240 (49.5)	11.8 (66.7)	2.24 (144)	152 (71)	98.6
Adult	Moderate	1000/250 mg q8h	64.1 (35.4)	24.4 (83.3)	998 (49.7)	8.02 (68)	2.7 (105)	122 (72)	98.8

AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours at steady state; AVI = avibactam; CAZ = ceftazidime; C_{max} = maximum plasma drug concentration at steady state; C_{min} = minimum plasma drug concentration at steady state; cUTI = complicated urinary tract infection; PTA = probability of PK/PD target attainment; q8h = every 8 hours.

[a] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > CT of 1 mg/L for avibactam.

Source: eph:2047179; eph:RA15790275; eph:RA15790276; Adult simulations from PMAR-EQDD-C359a-Other-762 *CAZ-MS-PED-02), Table 40

As requested by CHMP during assessment of this procedure, potential dosing recommendation in children <2years of age have been explored and model assumptions and uncertainties associated with predictions of exposure in patients <2 years with renal impairment discussed. Addition of NCrCl as a covariate on CL in addition to the Rhodin model of renal maturation did not improve the model fit. This indicates that only maturation processes affected the renal function of the patients <2years included in the study, and that

none (but the one declared) were renally impaired by pathologic means. However, with only one patient <2 years in the data set being renally impaired, the lack of an improvement in model fit when adding NCrCl as a covariate should not be used to conclude that patients <2 years with renal impairment do not need a lower dose. It is agreed that there are uncertainties coming from the lack of data in patients with reduced renal function. However, considering that dosing recommendations are given for ceftazidime as monotherapy in children down to 2mo, that the exposure of avibactam has been shown to be roughly parallel to that of ceftazidime also in this age cohort, and that the conducted simulations support adequate PTAs for the investigated dosing regimens, dosing recommendations should be given for patients below 2years of age with moderate to severe renal impairment. As requested in the second RSI, the applicant has re-discussed the dosing recommendations in children below 2 years with reduced renal function. Section 4.2 of the SmPC have been revised to include dosing recommendations for children 3 months to 2 years of age with CrCL ≥ 16 mL/min/1.73 m^2. Further, it is stated that there is insufficient information to recommend a dosage regimen for paediatric patients < 2 years of age that have a CrCL < 16 mL/min/1.73 m^2. This has been appropriately reflected in the amended Section 4.2 of the SmPC. The revised dosing recommendations are considered appropriate by the CHMP.

2.3.3. Pharmacodynamics

Primary pharmacology

The microbiology profile of CAZ-AVI was extensively described in the original MAA, and is reflected in the approved prescribing information for Zavicefta. The *in vitro* activity of CAZ-AVI against isolates from paediatric patients has been shown to be similar against isolates of the same species in adult patients (INFORM 2017 European Report).

The CHMP acknowledged that CAZ-AVI has demonstrated potent *in vitro* activity against Enterobacteriaceae and *P. aeruginosa* isolates collected globally from paediatric patients in 2012-2017, regardless of infection site.[4]

PK/PD Indices and Targets from Nonclinical Data

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 and are briefly summarised below.

It is well established that the PK/PD index that best describes the antibacterial activity of CAZ is %fT > MIC. Andes and Craig (2002) showed that approximately 30% fT > MIC of CAZ was related to bacteriostasis over 24 hours for Enterobacteriaceae in the neutropenic mouse lung infection model, and a bactericidal effect of 2 to 3 log10 killing was achieved by roughly 50% fT > MIC. For *P. aeruginosa*, stasis was achieved in the neutropenic thigh infection model at about 40% fT > MIC of CAZ. Muller et al analysed clinical study data for a dose of 2 g CAZ administered q8h as a 2-hour infusion in patients with nosocomial pneumonia, including VAP, from whom Gram-negative bacilli, including *P. aeruginosa*, were cultured. The authors concluded that plasma exposures to CAZ predicted clinical and microbiological outcomes and that a %fT > MIC of ≥45% was associated with a favourable outcome. MacVane et al conducted a retrospective E-R analysis of CAZ and cefepime in patients with VAP due to Gram-negative bacilli from previous studies. A similar result was found in that ≥53% fT > MIC of CAZ or cefepime was associated with microbiological eradication or presumed eradication. As 50% fT > MIC for CAZ and other cephalosporins is an established target associated with

[4] Hackel et al. 2019 *In vitro* activity of ceftazidime-avibactam and comparator agents against *Enterobacteriacea*e and *Pseudomonas aeruginosa* collected from paediatric patients as part of the ATLAS Global Surveillance Program 2012-2017. Abstract P1146 29thECCMID, Amsterdam, Netherlands.

efficacy and setting of breakpoints, this was used as the target plasma exposure for CAZ (with AVI). Based on global surveillance studies, the approved breakpoint for CAZ-AVI of ≤8 mg/L includes ≥90% of clinical isolates of Enterobacteriaceae and *P. aeruginosa*.

The relevant PK/PD index for AVI was shown, both *in vitro* using hollow-fiber models and *in vivo* using animal models of infection, to be the %fT > CT. In the hollow-fiber model using CAZ-resistant Enterobacteriaceae, a minimum CT of 0.5 mg/L AVI was shown to be appropriate for estimating PTA for CAZ-AVI. Using the neutropenic mouse thigh infection model with P. aeruginosa, a mean %fT > CT of 40% for a CT of 1 mg/L AVI was associated with bacterial stasis, and a mean %fT > CT of 50% for a CT of 1 mg/L was associated with 1-log kill. Additionally, using the neutropenic mouse lung infection model with P. aeruginosa, the mean %fT > CT values for a CT of 1 mg/L associated with stasis, 1-log kill, and 2-log kill were 20%, 24%, and 30%, respectively.

A conservative target of 1 mg/L (*i.e.* the value determined as the most appropriate for *P. aeruginosa*) was set for the CT of AVI. As the role of AVI is to protect CAZ during the period CAZ is most active, the %fT > CT must be at least the same period of time that the concentration of the β-lactam needs to be above the MIC. Thus, the overall target exposure for CAZ-AVI was simultaneously achieving 50% fT > MIC at an MIC of 8 mg/L for CAZ (with AVI) while maintaining 50% fT > CT of 1 mg/L for AVI as was used in the initial (adult) MAA.

The CHMP noted that no new *in vitro* studies were submitted. There are no expected differences in the mechanism of action of CAZ-AVI based on age as the Gram-negative causative pathogens are similar in adults and children. The conservative joint PKPD target (*i.e.* 50% fT>MIC of 8 mg/L and 50% fT>CT of 1 mg/L), identical to the PKPD target used to assess PTA in adults (cUTI, cIAI and HAP/VAP), have been employed for PTA simulations in children. This was acceptable to the CHMP.

2.3.4. PK/PD modelling

Selection of Phase II dose based on PTA analysis

The popPK model CAZ-MS-06 were updated with data from the phase I study D4280C00014 (described in section 2.3.2). The popPK models of CAZ and AVI were then used to quantify % fT>MIC (CAZ) and % fT>CT (AVI). A joint PK/PD target of 50% time above 8 mg/L for CAZ and 50% time above 1.0 mg/L for AVI, was selected as the primary criterion. This investigation informed the dose selection in the clinical phase II studies. The primary CAZ-AVI dose regimen for paediatric subjects was 50/12.5 mg/kg (capped at 2000/500 mg), given as a 2-hour IV infusion q8h. Two additional dose regimens, 40/10 mg/kg and 30/7.5 mg/kg were also evaluated for Cohorts 2-4 paediatric patients. Three reduced dose regimens were considered for paediatric subjects with moderate renal impairment (*i.e.* 50% of the daily dose administered either q8h or q12h, and 33% of the total daily dose administered q12h).

For Cohort 1 patients with normal renal function receiving 2000/500 mg q8h and Cohort 2-4 patients with normal renal function receiving the 50/12.5 mg/kg q8h regimen capped at 2000/500 mg, predicted PTA rates were >90%. Neither of the alternate lower dose regimens (40/10 mg/kg q8h and 30/7.5 mg/kg q8h) consistently achieved 90% PTA in Cohorts 2-4. For pediatric patients with mild renal impairment, predicted PTA was >97% for all dose regimens and all cohorts. For dose adjustment 1 (50% of daily dose for normal subjects administered q8h) in pediatric patients with moderate renal impairment, predicted PTA was >99% for the highest dose level (1000/250 mg in Cohort 1, 25/6.25 mg/kg in Cohorts 2-4 capped at 1000/250 mg). Exposures for these regimens were predicted to be within 30% of adult cIAI patients with mild renal impairment. Lower PTA, but still exceeding 95%, was predicted for the alternate lower dose levels (20/5

mg/kg, 15/3.75 mg/kg) for Cohorts 2-4. The other investigated dose levels (50%/q12h and 33%/q12h normal dose) achieved PTA >90% for some but not all age cohorts.

Simulation of exposure and PTA analyses following Phase II studies

Individual model-predicted PTA using joint PKPD target (*i.e.* 50%fT > MIC of 8 mg/L and 50%fT > CT of 1 mg/L) in paediatric patients included in the two phase II studies were >94% (CAZ-MS-PED-02, see section 2.3.2). Regardless of the apparent reductions in predicted $C_{min,ss}$ values relative to the adult population, PTA at an MIC of 8 mg/L for CAZ-AVI remained high across age cohorts in studies C3591004 and C3591005. If considered in aggregate, only three paediatric patients out of the 153 included in this analysis failed to achieve joint target attainment, translating to an overall joint attainment rate of 98.0%.

The final popPK models were also used to conduct paediatric and adult simulations (1000 subjects per age group, indication and renal function group) to support paediatric dose recommendations. Sets of PK parameters were simulated with between-subject variability but not parameter uncertainty or residual variability. Between-subject variability was simulated non-parametrically through resampling of individual random effect estimates from the final CAZ and AVI models for adults and for paediatric subjects. Because shrinkage of the random effect has the potential to underestimate between-subject variability, the post-hoc random effect estimates were re-inflated using the shrinkage estimates reported by NONMEM prior to simulation. Simulated plasma concentrations were adjusted to reflect free drug concentrations (85% and 92% for CAZ and AVI, respectively). The following joint PKPD targets were considered to be of principle interest when evaluating the proposed dose regimens, of which, the most stringent target (T4) was considered to be the primary criterion and was also used in adult regulatory filings (CAZ-MS-09) and in the initial paediatric modelling investigations (CAZ-MS-PED-01):

- T1: 40% fT > MIC for CAZ and 40% fT > 0.5 mg/L for AVI
- T2: 50% fT > MIC for CAZ and 50% fT > 0.5 mg/L for AVI
- T3: 40% fT > MIC for CAZ and 40% fT > 1.0 mg/L for AVI
- *T4: 50% fT > MIC for CAZ and 50% fT > 1.0 mg/L for AVI*

Targets T1- T4 were computed for CAZ-AVI MIC values of 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 mg/L.

Normal renal function

PTA from the simulations at an MIC of 8 mg/L, which is the breakpoint for CAZ-AVI for Enterobacteriaceae and *P. aeruginosa*, is shown in the table below by age group and indication for patients with normal renal function receiving the doses used in studies C3591004 and C3591005.

Lower PTAs of 82% for cIAI patients aged 1 to <6 years can be attributed to the following: 1) cIAI patients (adult and paediatric) have 33% increased CAZ CL on average; 2) weight based scaling of CL (E_{max} model) results in higher CAZ CL in younger children; and 3) there were very limited data for cIAI patients ≤6 years in study C3591004 (6 patients >2 to ≤6 years, 0 patients >1 to ≤2 years). Given a PTA of >80% in simulated cIAI patients from 1 to <6 years, and >90% for all other age ranges at an MIC of 8 mg/L, and considering that the PTA for actual cIAI patients <6 years in study C3591004 was 100% at this MIC, the proposed CAZ-AVI dose of 50 / 12.5 mg/kg q8h (2-hour infusion) may still be appropriate. To improve PTA at an MIC of 8 mg/L the infusion time could be extended. A dose of 50 / 12.5 mg/kg q8h administered as a 3- hour infusion is predicted to result in a PTA of 95% for cIAI patients from 1 to <6 years, with the same predicted $AUC_{ss,0-24}$ and 20% less $C_{max,ss}$ compared to the same dose given as a 2-hour infusion for both CAZ and AVI.

Table 23. Percentage of 1000 simulated patients with cIAI, cUTI or HAP/VAP and normal renal function achieving the joint PK/PD target following repeated administration of CAZ-AVI (Module 2.7.2, Table 8)

Age Group	Dose[a] (CAZ-AVI)	Joint PTA at an MIC of 8 mg/L (%)[b]		
		cIAI	cUTI	HAP/VAP
12 to <18 years	50/12.5 mg/kg q8h	96	99	99
6 to <12 years	50/12.5 mg/kg q8h	90	97	97
2 to <6 years	50/12.5 mg/kg q8h	82	94	92
1 to <2 years	50/12.5 mg/kg q8h	82	94	92
6 to <12 months	50/12.5 mg/kg q8h	90	98	97
3 to <6 months	40/10 mg/kg q8h	93	98	98
Adults	2000/500 mg q8h	95	97	95

[a] All doses as a 2-hour IV infusion with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam.
Source: CAZ-MS-PED-02 Report Table 25, Table 26, Table 29, Table 30, Table 33, and Table 34

The simulated joint PTA rates are slightly lower than the predictions in **CAZ-MS-PED-01** because the simulated pediatric subjects in CAZ-MS-PED-01 were not different to healthy adults, whereas the present analysis simulated PK with disease covariates for cUTI, cIAI, and NP patients. The covariate effects of cUTI, cIAI, or NP on CL, which all lead to higher clearance of CAZ and AVI compared to healthy subjects lead to systematically lower joint PTA rates here compared to CAZ-MS-PED-01. The PTA for these doses is predicted to be similar to the PTA for adult patients with cIAI and cUTI, and efficacy from adult patients can therefore be extrapolated to paediatric patients with cIAI and cUTI given the similar prevalence and CAZ-AVI susceptibility of key pathogens in paediatric and adult patients.

The CHMP acknowledged that, for almost all paediatric subgroups, acceptable PTAs of >90% were achieved at the proposed dosing regimens using the same conservative joint PKPD target as employed for simulations in adults (for indications cIAI, cUTI and HAP/VAP), which is reassuring with regards to efficacy. However, lower model-predicted exposures and a PTA of only 82% were observed in cIAI patients aged 1 to <6 years. The Applicant claims that this can be due to the higher CAZ clearance (33%) in cIAI patients (including both paediatric and adult patients) compared to healthy subjects as well as the popPK model structure (*i.e.* weight-based scaling of clearance). Additionally, there are limited PK data based on 6 patients in the cIAI age group 1-6 years. Simulations suggest that PTA could be improved to 95% by prolonging the infusion time to 3 hours with comparable $AUC_{0\text{-}24,ss}$ and a 20% decrease in C_{max} compared to a 2-hour infusion. However, there are no clinical data available with this prolonged infusion time.

As stated by the MAH, PTA for actual cIAI patients <6 years in study C3591004 (n=6) was 100% at the joint target. Additionally, the slightly lower PTA is not considered to be of major concern due to the following: (i) the individual model-predicted PTA was supportive, (ii) the PDT against which PTA was estimated was 1-log kill while stasis might have sufficed for cIAI, and (iii) clinical outcomes of cIAI are strongly driven by adequate surgery. In addition, the proposed dose regimen for this age group is consistent with doses for other indications for CAZ-AVI. Of note, the proposed ceftazidime dose in the CAZ-AVI combination for paediatric patients (including the subgroup of 1-6 years) is also consistent with the approved paediatric posology for CAZ alone, for which there is an extensive experience with the use in children.

Overall, the CHMP considered the proposed dose regimen of 50/12.5 mg CAZ-AVI for patients aged 1-6 years with cIAI to be acceptable.

Renal impairment

PTA from the simulations at an MIC of 8 mg/L for CAZ-AVI is shown in the table below by age group and indication for patients with mild renal impairment receiving the doses used in Studies C3591004 and C3591005. Given the high PTA (≥99%), and similar exposure to adults with mild renal impairment, no

dosage adjustment is considered necessary for paediatric patients with cIAI or cUTI and mild renal impairment. Extended infusion time for cIAI patients 2 to <6 years with mild renal impairment is not necessary to achieve PTA >90%.

Table 24. Percentage of 1000 simulated patients with cIAI, cUTI or HAP/VAP and mild renal impairment achieving the joint PK/PD target following repeated administration of CAZ-AVI (Module 2.7.2, Table 10)

Age Group	Dose[a] (CAZ-AVI)	Joint PTA at an MIC of 8 mg/L (%)[b]		
		cIAI	cUTI	HAP/VAP
12 to <18 years	50/12.5 mg/kg q8h	99	99	99
6 to <12 years	50/12.5 mg/kg q8h	100	100	100
2 to <6 years	50/12.5 mg/kg q8h	100	100	100
Adults	2000/500 mg q8h	99	99	99

[a] All doses as a 2-hour IV infusion with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam.
Source: CAZ-MS-PED-02 Report Table 37, Table 38, and Table 39

PTA from the simulations at an MIC of 8 mg/L is shown in the table below by age group and indication for patients with moderate renal impairment receiving CAZ-AVI 25 / 6.25 mg/kg q8h as a 2-hour infusion (capped at 1000 / 250 mg). Extended infusion time for cIAI patients from 2 to < 6 years with moderate renal impairment is not necessary to achieve PTA >90%.

Table 25. Percentage of 1000 simulated patients with cIAI, cUTI or HAP/VAP and moderate renal impairment achieving the joint PK/PD target following repeated administration of CAZ-AVI (Module 2.7.2, Table 12)

Age Group	Dose[a] (CAZ-AVI)	Joint PTA at an MIC of 8 mg/L (%)[b]		
		cIAI	cUTI	HAP/VAP
12 to <18 years	25/6.25 mg/kg q8h	99	99	99
6 to <12 years	25/6.25 mg/kg q8h	100	100	100
2 to <6 years	25/6.25 mg/kg q8h	100	100	100
Adults	1000/250 mg q8h	99	99	99

[a] All doses as a 2-hour IV infusion with a maximum dose of 1000 mg ceftazidime and 250 mg avibactam.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam.
Source: CAZ-MS-PED-02 Report Table 40, Table 41, and Table 42

The CHMP noted that PTA ≥99% are predicted with the proposed dose recommendations in mild, moderate and severe renal impairment. Dosing recommendations have been given in the SmPC. However, there is insufficient information to recommend a dosage regimen for paediatric patients < 2 years of age that have a CrCL < 16 mL/min/1.73 m^2. This has been appropriately reflected in the amended Section 4.2 of the SmPC. For details, see Section 2.3.2.

Clinical trials

Study **C3591004** (cIAI)

Overall, favourable clinical and microbiological response cure rates of ≥90% were observed for CAZ-AVI + metronidazole (MTZ)-treated CAZ-AVI cIAI patients from the End of 72 Hours Visit through late follow-up (LFU). High favourable microbiological response rates for predominant pathogens (*E. coli* and *P. aeruginosa*) were also observed; although few in number, favourable response rates were also observed in the two patients with CAZ-NS pathogens. These results are consistent with data from adult patients with cIAIs.

Study **C3591005** (cUTI)

Favourable clinical response cure rates of >80% were observed for CAZ-AVI-treated paediatric patients with cUTI from the End of 72 Hours Visit through to the LFU Visit for the majority of the analysis sets. For Enterobacteriaceae, favourable microbiological response rates of approximately 80% or greater were observed for CAZ-AVI through test of cure, which included patients with CAZ-NS pathogens. These results are consistent with data from adult patients with cUTIs.

Overall, in both Study C3591004 and C3591005, the treatment effects in paediatric patients were consistent with the treatment effects observed in the corresponding studies in adult patients with cIAI and cUTI (Studies D4280C0001/5 and D4280C0002/4, respectively). Although the number of patients in some cohorts was small, the microbiological responses were similar amongst the cohorts in either study. Additionally, there were no new safety issues identified in either paediatric study.

Resistance development

Efficacy and safety, as well as microbiological susceptibility in the phase II clinical studies are addressed in sections 2.4 and 2.5.

2.3.5. Discussion on clinical pharmacology

- Pharmacokinetics

With this application, the MAH is extending all four adult indications (cUTI, cIAI, HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options) to children and adolescents ≥3 months to <18 years. The variation application is supported by one phase I (D4280C00014) and two phase II studies (C3591004 and C3591005), as well as PK and PKPD modeling and simulation.

The proposed CAZ-AVI dose in patients aged 6 months to <18 years is 50/12.5 mg/kg q8h (capped at the adult dose of 2 g/0.5 g) as a 2-hour infusion. In patients aged 3 to <6 months, the proposed dose is 40/10 mg/kg q8h as a 2-hour infusion. Dose adjustments are recommended for paediatric patients ≥2 years with impaired renal function (31 to <50 mL/min/1.73m^2) (see below). The proposed paediatric doses were used in the clinical phase II studies (C3591004 and C3591005) in patients with cIAI and cUTI, respectively. Sparse PK sampling was conducted in both studies, also from severely ill cUTI patients. The formulation used for the phase II paediatric studies is identical to the final drug product for commercial use.

The aim of the dose selection was to achieve comparable exposures to those calculated for the phase III studies in adult patients with cIAI, and cUTI and HAP/VAP.

Bioanalytical methods

The analytical methods submitted to support the new phase II clinical studies have been adequately validated in accordance with the EMA bioanalytical guideline (EMEA/CHMP/EWP/192217/2009 Rev. 1). The analysis of PK samples from the phase II studies and phase I study are acceptable.

Population-PK model

To support dosing recommendations in the new target population, popPK models describing CAZ and AVI PK in adults have been modified and updated with available paediatric PK data from the three clinical studies (C3591004, C3591005 and D4280C00014) to predict exposure in both adults and children <18 years old. The preceding models are overall similar to the updated model (CAZ-MS-PED-02) in the structural and co-variate models, (*i.e.* linear two-compartmental models with first order elimination) and with CLCr and body weight as important covariates on CL and V, respectively, for both CAZ and AVI models. Patient population (cIAI and cUTI) was identified as a significant covariate impacting CL and/or Vc of CAZ and AVI,

independent of any demographic differences. Overall, the predictive performance of the updated CAZ-AVI models are supportive of their intended use.

Exposure data and popPK/PTA simulations

- cIAI and cUTI

In general, individually predicted and simulated paediatric exposures do not differ greatly from that of adults. In studies C3591004 and C3591005, model-predicted CAZ geometric mean $C_{max,ss}$ for each age cohort ranged from 97% to 145% and $AUC_{ss,0-24}$ ranged from 76% to 101% of corresponding values for adults. Model-predicted AVI geometric mean $C_{max,ss}$ for each age cohort ranged from 89% to 139% and $AUC_{ss,0-24}$ ranged from 79% to 110% of corresponding values for adults. Mean $C_{min,ss}$ values were lower in all paediatric cohorts than in the corresponding adult reference populations. Simulated geometric mean exposures ($C_{max,ss}$ and $AUC_{ss,0-24}$) ranged from 109% to 124% and from 92% to 110%, respectively, for CAZ. Corresponding values for AVI exposure were 115 to 148% and 104 to 130%.

For almost all paediatric subgroups with cIAI and cUTI, PTAs of >90% were achieved at the proposed doses using the same conservative joint PKPD target as employed in the original MAA for adults, which is reassuring with regards to efficacy. However, lower model-predicted exposures and a PTA of 82% were shown in cIAI patients aged 1 to <6 years. Of note, there is limited data in cIAI subjects ≤6 years (n=6). For both active compounds the predicted exposures show a higher Cmax and lower Cmin (trough) in the paediatric population compared to the adult population, although the total exposure (AUC) appear to be similar. This can be interpreted as the time above MIC is shorter which in turn could be the reason for the lower PTA in the age group 1-6 years. However, the slightly lower PTA is not considered to be of major concern due to the following: (i) the individual model-predicted PTA was supportive, (ii) the PDT against which PTA was estimated was 1-log kill (stasis might have sufficed for cIAI) and (iii) clinical outcomes of cIAI are strongly driven by adequate surgery. In addition, the proposed dose regimen for this age group is consistent with doses for other indications for CAZ-AVI. Of note, the proposed ceftazidime dose in the CAZ-AVI combination is consistent with CAZ alone, for which there is an extensive experience with the use in children.

Taken together, the proposed dose regimens for paediatric patients with cIAI and cUTI are considered acceptable by the CHMP.

- HAP/VAP

No exposure data from paediatric patients with HAP/VAP are available at present. A PK study on NP, HAP/VAP (for children >3 months old to 18 years of age) requested by PDCO as part of the PIP is ongoing. This means that the assessment of this additional indication will be based on extrapolation without a supportive PK bridge. The MAH's extrapolation strategy for HAP/VAP was thus based on popPK/PTA simulations, using adult datasets across all 3 approved indications (cIAI, cUTI, and HAP/VAP) and PK data from paediatric patients with cUTI and cIAI, including children with severe cUTI infections requiring IV treatment. This strategy is considered acceptable since there are paediatric PK data from patients with cIAI and cUTI, including from severely ill patients with cUTI. Of note, the employed extrapolation strategy is in line with the Draft Paediatric Addendum for Antibacterial Agents, in which the following is stated: "*The paediatric pharmacokinetic data may be obtained in patients with one or a limited range of the infectious diseases for which use of the antibacterial agent is proposed, taking into account whether pharmacokinetic differences were observed in adults depending on the site of the infection. It is recommended that pharmacokinetic data are obtained from at least some paediatric patients with evidence of severe systemic illness, if applicable to the indications proposed*".

Based on the updated popPK model (CAZ-MS-PED-02), simulated paediatric exposures ($AUC_{ss,0-24}$ and $C_{max,ss}$) were overall comparable to adult exposures, and a PTA of >90% was achieved in all age-subgroups with HAP/VAP. In the adult patients, the dose regimen of 2/0.5 g q8h was found efficacious for treatment of

all three site-specific infections (cUTI, cIAI and HAP/VAP) based on clinical studies as well as PK/PD data. There were no significant differences in the PK parameters for ceftazidime and avibactam between these patient populations. Considering similarity of PK data for these components in paediatric patients with cIAI and cUTI, it is expected that ceftazidime and avibactam exposures will be similar in paediatric patients with HAP/VAP, as well. It should also be noted that PK characteristics of avibactam were shown to be very similar to ceftazidime in adults in all 3 site specific indications (including patients with HAP/VAP and penetration to ELF).

Taken together, the proposed dose regimens for paediatric patients with HAP/VAP are considered acceptable. It is reassuring that PK data from ongoing HAP/VAP study (to be finalised in December 2020) will be used to confirm the adequacy of the proposed dose regimens for this indication.

- Infections due to aerobic Gram-negative organisms in paediatric patients with limited treatment options

No exposure data has been submitted for this indication. The use of ceftazidime/avibactam for the above-mentioned indication is based on experience with ceftazidime alone and on analyses of the PK-PD relationship for ceftazidime/avibactam in both adults and children.

For cIAI and cUTI indications, CAZ-AVI exposures in paediatric patients from the age of 3 months to >18 years at the proposed doses were demonstrated to be roughly similar to adults. In addition, available data suggest that exposures of both ceftazidime and avibactam were similar between different indications investigated in paediatric studies D4280C00014 (patients with confirmed or suspected infections), C3591004 (cIAI) and C3591005 (cUTI). Therefore, sufficient exposures are expected to be achieved at the proposed CAZ-AVI doses for paediatric patients with limited treatment options as for adults. The proposed dose regimen for this indication is consistent with the doses for site specific infections for children. It should also be noted that, the same dose regimen is recommended for all four approved adult indications.

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 is supported.

Adequacy of the proposed dose regimens in patients with normal renal function

Based on the above-mentioned popPK/PTA simulations, PK parameters were predicted to be comparable in paediatric patients aged 3 month and older across the site specific infections of cUTI, cIAI and HAP/VAP. In addition, PTAs of at least >90% were achieved at the proposed doses using the joint PKPD target for almost all paediatric subgroups with cIAI, cUTI and HAP/VAP.

The above-mentioned data demonstrating similar exposures and target attainments to adults, in conjunction with the consideration that ceftazidime is already approved for use in children, with the same dosing recommendations as the proposed doses for different age categories (including new-borns), allow for concluding that the proposed paediatric dose regimens are appropriate for the applied indications.

Dosing recommendations in children with renal impairment

As ceftazidime and avibactam is primarily renally excreted, dosing recommendations in patients with renal impairment may need to be adjusted. The following recommendations have been made for pediatric patients with different renal function categories (Table 26):

Table 26. Proposed dosing recommendations for Zavicefta compared with the approved dosing recommendation for ceftazidime monotherapy in adults and children with impaired renal function.

Population	Dose Zavicefta	Dose Ceftazidime monotherapy
Target, adult Normal renal function	2g/0.5g every 8h (2h infusion), treatment length depending on the indication	Adults and children above 40kg:

		1-2g every 8h (or 12h for cIAI) 2h infusion or continuous infusion
Mild renal impairment	No adjustment	No adjustment
Moderate-severe renal impairment (mL/min/1.73m^2)	31-50: 1g/0.25g every 8h 16-30: 0.75 g/0.1875 g every 12h 6-15: 0.75 g/0.1875 g every 24h ESRD: 0.75 g/0.1875 g every 48h	31-50: 1g every 12h 16-30: 1g every 24h 6-15: 0.5g every 24h <5: 0.5g every 48h
Subpopulation, children 6mo-18 y Normal renal function	50/12.5mg/kg up to max 2/0.5g every eight hour	2mo – 40kg: 100-150 mg/kg/day divided in 3 doses, maximum 6g/day.
Mild renal impairment	No adjustment	No adjustment
Moderate to severe renal impairment (mL/min/1.73m^2)	2y-18y 31-50: 25/6.25mg/kg to max 1/0.25g every 8h 16-30: 18.75/4.75mg/kg to max 0.75/0.1875g every 12h 6-15: 18.75/4.75mg/kg to max 0.75/0.1875g every 24h ESRD: 18.75/4.75mg/kg to max 0.75/0.1875g every 48h 6mo- <2y 31-50: 25/6.25mg/kg every 8h 16-30: 18.75/4.75mg/kg every 12h 3mo-<6mo 31-50: 20/5mg/kg every 8h 16-30: 15/3.75mg/kg every 12h	2mo – 40kg: 31-50: 25mg/kg every 12h 16-30: 25mg/kg every 24h 6-15: 12.5mg/kg every 24h <5: 12.5mg/kg every 48h
Subpopulation, children 3mo-6mo Normal renal function	40/10mg/kg every 8 h	*As above down to 2mo.*
Reduced renal function	No recommendation	*As above down to 2mo.*
Subpopulation, children <3mo/<2mo	<3mo – not investigated	<2mo 25-60 mg/kg/day divided in 2 doses

Potential dosing recommendation in children <2years of age have been explored and model assumptions and uncertainties associated with predictions of exposure in patients <2 years with renal impairment discussed. There are still uncertainties coming from the lack of data in patients with reduced renal function. However, considering that dosing recommendations are given for ceftazidime as monotherapy in children down to 2mo, that the exposure of avibactam has been shown to be roughly parallel to that of ceftazidime also in this age cohort, and that the conducted simulations support adequate PTAs for the investigated dosing regimens, dosing recommendations have been given for patients below 2years of age with moderate to severe renal impairment. However, there is insufficient information to recommend a dosage regimen for paediatric patients < 2 years of age that have a CrCL < 16 mL/min/1.73 m^2. This has been appropriately reflected in the Section 4.2 of the SmPC.

2.3.6. Conclusions on clinical pharmacology

The totality of the data and the consideration that ceftazidime monotherapy is approved for use in children, with dosing recommendations down to birth, allows for concluding that the proposed dosing recommendations are adequate for both ceftazidime and avibactam, and that the exposures are sufficiently

similar to allow extrapolation of safety and efficacy for cIAI, cUTI and HAP/VAP as well as in aerobic Gram-negative infections in paediatric patients with limited treatment options from adults to children.

2.4. Clinical efficacy in paediatric cIAI

2.4.1. Main study C3591004 (D4280C00015)

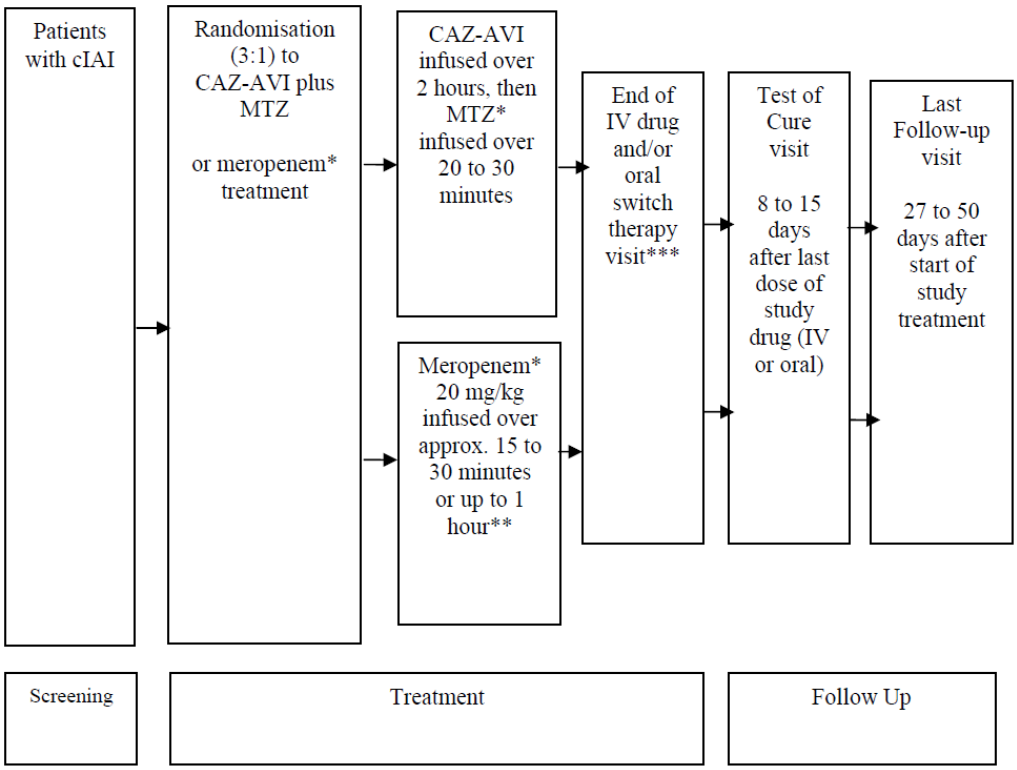
The initial application for authorisation of CAZ-AVI did not include paediatric data from controlled clinical studies. Since completion of the adult studies, a paediatric study in cIAI has been conducted (C3591004 [D4280C00015]). This Phase 2 study was initiated as part of the agreed Paediatric Investigation Plan (PIP).

Study C3591004 (D4280C00015) is designed to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam (CAZ-AVI) + metronidazol, compared with meropenem, in children from 3 months to <18 years of age with complicated intraabdominal infections (cIAIs).

The study was sponsored by AstraZeneca and the sponsorship was transferred to Pfizer, Inc, on 18 September 2017. The study was conducted by investigators contracted by and under the direction of the Sponsor.

Methods

The study was a single-blind, randomised, multi-centre, and actively controlled trial conducted in paediatric patients diagnosed with cIAIs of sufficient severity to require hospitalisation and treatment with intravenous (IV) antibiotics. The study design of study D4280C00015 (C3591004) is illustrated in the Figure below.



Source: Study D4280C00015 protocol, Figure 1 (Section 16.1.1).
CAZ-AVI= ceftazidime avibactam plus metronidazole; cIAI=complicated intra-abdominal infection; IV=intravenous; MTZ=metronidazole.
*Optional switch to oral therapy permitted on or after Study Day 4 (ie, after 72 hours [3 full days, ie, 9 doses] of IV study drug. Assessment should be performed no later than 8 hours after the 72-hour time point. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food:
The patient may continue on IV study drug for the entire duration of the study therapy (7 to 15 days), at the discretion of the Investigator.
** Or infusion duration as per local guidelines. For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours.
*** Visit performed within 24 hours of completion of last infusion or within 48 hours after the last dose of oral switch therapy.

Figure 13. Study design of study C3591004 (D4280C00015)

Study participants

Main inclusion criteria:

1. Must have been ≥3 calendar months to <18 years of age. Patients aged ≥3 calendar months to <1 year must have been born at term (defined as gestational age ≥37 weeks).
2. Must have had clinical evidence of cIAI as follows:

   Pre-operative enrolment inclusion:

   a. Required surgical intervention that was expected to be completed within 24 hours of enrolment-laparotomy, laparoscopy, or percutaneous drainage.

   b. Evidence of a systemic inflammatory response (at least 1): Fever (defined as oral temperature >38.5°C, or equivalent to method used) or hypothermia (with a core body or rectal temperature <35°C, or equivalent to method used); Elevated white blood cells (WBC) (>15000 cells/mm3); C-reactive protein (CRP) levels (>10 mg/L).

c. Physical Findings consistent with intra-abdominal infection, such as: Abdominal pain and/or tenderness, localised or diffuse abdominal wall rigidity, abdominal mass.

Intra-operative/postoperative enrolment inclusion (in cases of postoperative enrolment, must be within 24 hours after the time of incision):

Visual confirmation of intra-abdominal infection associated with peritonitis at laparotomy, laparoscopy or percutaneous drainage (to be confirmed pending feasibility); must have 1 of these diagnoses:

a. Appendiceal perforation or peri-appendiceal abscess;

b. Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall;

c. Acute gastric or duodenal perforations, only if operated on >24 hours after singular perforation occurs;

d. Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs;

e. Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites).

Main exclusion criteria

1. Receipt of non-study systemic antibacterial drug therapy for cIAI, for a continuous duration of more than 24 hours during the 72 hours preceding the first dose of IV drug, except in the case of proven pathogen resistance to the administered antibacterial drug and/or worsening of the clinical condition. More than 2 consecutive doses were not permitted if the individual doses are expected to give >12 hours cover (i.e., giving a total cover of >24 hours). For patients enrolled after a surgical procedure, only 1 dose of non-study antibiotics was permitted postoperatively.
2. Patient was receiving haemodialysis or peritoneal dialysis.
3. Diagnosis of abdominal wall abscess confined to musculature of the abdominal wall or ischaemic bowel disease without perforation, traumatic bowel perforation requiring surgery within 12 hours of perforation, or perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation (these are considered situations of peritoneal soiling before the infection has become established).
4. Simple (uncomplicated), non-perforated appendicitis or gangrenous appendicitis without rupture into the peritoneal cavity identified during a surgical procedure OR presence of primary peritonitis (i.e., spontaneous bacterial peritonitis) or peritonitis associated with cirrhosis or chronic ascites.
5. Presence of any of the following clinically significant laboratory abnormalities:

   (a) Haematocrit <25% or haemoglobin <8 g/dL (<80 g/L, <4.9 mmol/L);

   (b) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the age-specific upper limit of normal (ULN), or total bilirubin >2 × ULN (except known Gilbert's disease).

   For a) and b): unless if these values were acute and directly related to the infectious process being treated.
6. Creatinine clearance (CrCl) <30 mL/min/1.73 m^2 calculated using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula: CrCl (mL/min/1.73m^2) = 0.413 × height (length) (cm)/serum creatinine (mg/dL).

The CHMP considered that, according to the inclusion criteria, it can be concluded that patients with complicated intra-abdominal infections are enrolled as the required infections will lead to infectious processes proceeding beyond the organ that is the source of the infection. Overall, the included types of intra-abdominal infections could be categorised as infections that are neither so limited that just surgery would be curative, nor so complicated that several additional confounding factors would affect curation.

Treatments

Patients received IV treatment for a minimum of 72 hours (3 full days, i.e. 9 doses) before having the option to switch to an oral therapy on Day 4 at the investigator`s discretion, if the patient had good or sufficient response and was tolerating oral fluids or food. CAZ-AVI doses were based on the age and weight of the patient with adjustment according to renal function (see table below). The total period of treatment (i.e. IV drug and oral switch treatment) was to be between 7 and 15 days. Patients could have remained on IV study treatment for the full 7 to 15 days.

Table 27. CAZ-AVI Dose Regimens by Age, Weight and Creatinine Clearance

Cohort	Age range	Body weight	CAZ-AVI dose CrCl ≥50 mL/min	CAZ-AVI dose CrCl ≥30 to <50 mL/min
		CAZ-AVI must be administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes)		
1[a]	12 years to <18 years	≥40 kg	2000 mg CAZ / 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	12 years to <18 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
2[a]	6 years to <12 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	6 years to <12 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
3[a]	2 years to <6 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4a[b]	1 year to <2 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b[b]	6 months to <1 year	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b[b]	3 months to <6 months	All	40 mg/kg CAZ/ 10 mg/kg AVI	20 mg/kg CAZ/ 5 mg/kg AVI

Source: Study D4280C00015 protocol, Table 5 (Section 16.1.1).
CAZ-AVI = ceftazidime- avibactam; CrCl = creatinine clearance.
a. Patients considered for entry into the study were to be within the normal range of BMI for their age, (2 to <18). A healthy weight BMI for this age group falls between the 5th percentile and ≤95th percentile according to height, weight, and age.
b. BMI was not calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

Dosing for Metronidazole (anaerob coverage in the CAZ/AVI treatment group)

The suggested dose regimen of metronidazole is 10 mg/kg IV, administered over 20 to 30 minutes every 8 hours (±30 minutes), or according to local labels. The metronidazole infusion was to be started no later than 30 minutes after completion of the CAZ-AVI infusion.

Dosing for the comparator Meropenem treatment group

The dose regimen of meropenem was to be 20 mg/kg every 8 hours (±1 hour) infused over approximately 15 to 30 minutes or up to 1 hour (or infusion duration as per local guidelines). For patients weighing over 50 kg, the maximum dose of meropenem should not have exceeded 1 g every 8 hours. The Investigator was to follow the package insert for meropenem for dose modifications associated with renal impairment.

Treatment if oral switch after 72 hours IV therapy

Oral amoxicillin/clavulanic acid, oral ciprofloxacin + metronidazole, or pathogen-based therapy (in discussion with the Medical Monitor) were permitted for the oral switch and were administered per local standards of care. Oral amoxicillin/clavulanic acid and oral ciprofloxacin + metronidazole were only used in countries where its use for children is permitted.

Gram positive adjunctive therapy

If Enterococcus species or methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the pathogens suspected or isolated, then open label vancomycin, linezolid, or daptomycin may have been added to either of the study regimens according local label recommendations.

If vancomycin, linezolid, or daptomycin were started empirically to cover MRSA or Enterococcus species, and if final culture results did not isolate MRSA or Enterococcus species, then the Investigator was to discontinue this treatment.

The CHMP considered the choice of meropenem as comparator to be acceptable: it is approved and widely used as treatment for cIAIs and considered the drug of choice for treating infections due to ESBL-producing Gram-negative bacilli.

Metronidazole was added for anaerobic coverage and this is in line with clinical recommendations.

Generally, the treatment options suggested to cover MRSA and Enterococcus, lack activity against Gram-negative pathogens and were therefore not expected to impact efficacy results.

The proposed treatment duration of 7-14 days and the option to switch to oral therapy is generally in line with current IDSA guideline 2010 and World Society of Emergency Surgery (WSES) guidelines 2017 for management of intra-abdominal infections. These guidelines state that patients with cIAI require 4 to 7-day courses of antibiotic therapy, either as oral or parenteral treatment. Switch from parenteral therapy to oral therapy is recommended after at least three days as long as they are clinically improving, according to pre-defined objective criteria. In the current study, clinical improvement at EOIV was defined, and had to be fulfilled before allowing a switch to oral therapy. Thus, the strategy of switching from IV to oral treatment to complete a short course of therapy is considered acceptable by the Committee.

Of note, the Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection, Mazuski 2017 recommend that antimicrobial therapy is restricted to five days in pediatric patients older than one month who have had adequate source control. However, an individualized approach is always mandatory according to the patient's inflammatory response and the severity of the disease. Overall, the total IV and IV/oral treatment duration of 5-14 days proposed in the SmPC is therefore, considered acceptable by the CHMP.

Objectives

Primary Objective:

- To evaluate the safety and tolerability of CAZ-AVI plus metronidazole given at the selected dose regimen versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI.

Secondary Objectives:

- To evaluate the descriptive efficacy of CAZ-AVI plus metronidazole versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI.

- To evaluate the PK of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cIAI.

Outcomes/endpoints

Primary outcome (safety) variables

- Adverse events (AEs) and Serious adverse events (SAEs); Cephalosporin class effects and additional AEs; Vital signs; Physical examination; Laboratory parameters; Electrocardiogram (ECG).

Secondary outcome (efficacy) variables

- Plasma concentrations and PK parameters of CAZ and AVI;
- Clinical response at End of 72 hours' treatment, EOIV, EOT, and TOC;
- Microbiological response at EOIV, EOT, TOC, and LFU;
- Clinical relapse at LFU;
- Emergent infections.

The CHMP noted that, in this study, efficacy was not a primary endpoint. According to Draft guideline EMA/187859/2017 "Addendum to guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements", no appropriately powered efficacy studies are requested in the paediatric population as efficacy can be extrapolated from adults provided that similar exposure is achieved and sufficient safety data have been generated with the intended dose regimen in the paediatric population. Thus, the choice of efficacy as a secondary endpoint is considered acceptable by the Committee.

Table 28. Derivation of Analyses Windows for End of 72 hours, EOIV, EOT, TOC, and LFU Visits

Visit	Protocol-defined Window	Derived Analyses Window
End of 72 hours	After 72 hours of treatment and up to 8 hours later	From completion of the ninth study dose up to 80 hours after start of study drug
End of IV intravenous treatment (EOIV)	Within 24 hours of completion of the last infusion of study drug	On day of last infusion of study drug (or +1 day), and no later than same day as start of oral therapy.
End of Treatment (EOT)	Within 48 hours of completion of the last dose of oral switch therapy for patients who switched, or within 24 hours of the last infusion of study drug for those who did not receive oral switch therapy	On day of last dose of oral therapy (or +2 days) for oral switch patients; on day of last infusion of study drug (or +1 day) for patients who did not switch
Test of cure (TOC)	8 to 15 days after the last dose of any study drug	7 to 19 days after the last dose of study drug
Late follow-up (LFU)	20 to 35 days after the last dose of any study drug	20 to 42 days after the last dose of study drug

Source: Study D4280C00015 SAP, Table 2 (Section 16.1.9.1).

Table 29. Clinical Outcome Assessments at End of 72 Hours

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients who improved but not enough to switch to oral therapy and were still on IV study drug at End of 72 hours and met the following criterion: • Absence of new signs and symptoms, and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign
Clinical Failure	Patients who met any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cIAI that required alternative non-study antimicrobial therapy; • Discontinuation of study drug due to an AE and required alternative non-study antimicrobial therapy for cIAI; • Death in which cIAI is contributory; • Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that required additional antibiotics and/or non-routine wound care. • Patients who were improving but not enough to switch to oral therapy and were still on IV study drug at End of 72 hours and who fail to meet the following criterion: • Absence of new signs and symptoms, and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00015 protocol, Table 7 (Section 16.1.1).

AE = adverse event; cIAI = complicated intra-abdominal infection; CRP = C-reactive protein; IV = intravenous; WBC = white blood cell.

Table 30. Clinical Outcome Assessments at EOIV and EOT (for EOT: ex. def of clinical improvement)

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients 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[a]	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cIAI that requires alternative non-study antimicrobial therapy; • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cIAI; • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00015 protocol, Table 8 (Section 16.1.1).

Table 9 (Section 16.1.1).

[a] A clinical failure at EOIV was carried forward to EOT and TOC.

AE = adverse event; cIAI = complicated intra-abdominal infection; CRP = C-reactive protein; EOIV = end of intravenous treatment; TOC = test of cure; WBC = white blood cell.

Table 31. Clinical Outcome Assessments at TOC

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Failure	Patients who meet either of the following criteria: • Incomplete resolution or worsening of cIAI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy; • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00015 protocol, Table 10 (Section 16.1.1).
cIAI = complicated intra-abdominal infection; TOC = test of cure.

Each patient who was considered clinically cured at TOC was reassessed at LFU for evidence of clinical relapse of cIAI symptoms. A favourable clinical outcome at LFU was a sustained clinical cure.

Microbiological response assessment

Culture and organism identification were (according to protocol) performed at the local or regional laboratory, as applicable. Susceptibility testing was done at the local or regional laboratory to support patient care. All isolates were sent to the central laboratory for organism identification and susceptibility testing.

Table 32. Microbiological Outcome Definitions

Outcome	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Presumed eradication	Source specimen was not available to culture, and the patient was assessed as a clinical cure or sustained clinical cure or (for EOIV only) clinical improvement
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MIC[a]	Source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen
Presumed persistence	Source specimen was not available to culture and the patient was assessed as a clinical failure or clinical relapse
Indeterminate	Source specimen was not available to culture and the patient's clinical outcome was assessed as indeterminate

Source: Study D4280C00015 protocol, Table 12 (Section 16.1.1).
[a] Persistence with increasing MIC is a subset of the Persistence outcome.
EOIV = end of intravenous treatment; MIC = minimum inhibitory concentration.

Table 33. Microbiological Response

Outcome	Definition
Favourable	All baseline pathogens eradicated or presumed eradicated
Unfavourable	Any baseline pathogen with persistence or presumed persistence or persistence with increasing MIC
Indeterminate	Any baseline pathogen indeterminate, and no baseline pathogen persistent

Source: Study D4280C00015 SAP, Table 10 (Section 16.1.9.1).
MIC = minimum inhibitory concentration.

Sample size

A sufficient number of patients were to be randomised for 80 patients to complete at least 72 hours (3 full days, i.e., 9 doses) of study treatment (i.e., evaluable patients; at least 60 patients in the CAZ-AVI plus metronidazole group and at least 20 patients in the meropenem group).

Patients were randomised 3:1 to the CAZ-AVI plus metronidazole or meropenem study treatment groups.

The proposed sample size is based on the probability of observing a 'rare' safety event. The 'rare' term used in this section is not based on the regulatory definition but is instead intended to reflect uncommon events. Safety data from this study and from Study D4280C00016 for complicated urinary tract infection were combined for analysis. As a total of at least 120 patients were treated with CAZ-AVI in both studies combined, when assuming an underlying incidence rate of 3% for a specific 'rare' event, this would ensure that the probability of observing such an event in at least 1 patient treated with CAZ-AVI exceeds 95%.

Randomisation

Patients were allocated to 1 of 4 cohorts based on age. Randomisation was stratified as follows:

- Cohort 1: At least 15:5 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 15:5 evaluable patients aged from 6 years to <12 years;
- Cohort 3: No required minimum of evaluable patients aged from 2 years to <6 years; (as of protocol amendment 2);
- Cohort 4: No required minimum of evaluable patients aged from 3 months to <2 years, (as of protocol amendment 2), comprising Cohorts 4a and 4b as follows:
  - Cohort 4a: Patients aged from 1 year to <2 years
  - Cohort 4b: Patients aged from 3 months to <1 year.

Blinding (masking)

This study was observer-blinded. Each investigational site was required to have a site-specific blinding plan that described the site-specific precautions being taken to ensure that the study was observer-blinded, taking into account the specific patient care procedures, equipment, and information accessibility at that site.

Statistical methods

The study was descriptive in nature, no interim or final inferential analyses were performed for either efficacy or safety. Descriptive summaries was provided for each of the primary and secondary variables. In general, summaries were presented by cohort, treatment group and overall for treatment group across all cohorts. The Safety analysis set was used for summaries and listings. Clinical response outcomes was

summarized by cohort, treatment group and overall for each treatment in the ITT, micro-ITT, CE and ME analysis sets (defined below).

Analysis sets

The Safety analysis set included all randomised patients who received any amount of IV study therapy (ie, CAZ-AVI plus metronidazole or meropenem). For the Safety analysis set, patients were included in all outputs according to the study treatment actually received.

The Safety Evaluable analysis set was the subset of the Safety analysis set that received at least 9 doses of study treatment.

The Pharmacokinetic (PK) analysis set was the subset of the patients in the Safety analysis set who had at least 1 ceftazidime and/or avibactam plasma measurement available.

The Intent-to-Treat (ITT) analysis set included all patients assigned a randomised treatment.

The Microbiological intent-to-treat (micro-ITT) set included all randomised patients who had a baseline pathogen known to cause cIAI.

The Clinically Evaluable (CE) analysis set is defined at the end of 72 hours of study treatment (determined by the 72 hour efficacy assessment visit), and at each of the End of Intravenous Treatment (EOIV), End of Treatment (EOT), Test of Cure (TOC) and Late Follow up (LFU) visits. The CE analysis set will include:

- All randomised patients who receive any amount of IV study drug and have a confirmed diagnosis of cIAI;
- Have received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;
- Have received at least 72 hours of IV study drug, defined as 9 doses, in order to be considered an evaluable clinical cure;
- Have been evaluated at the End of 72 hours assessment and at the specific visits of EOIV, EOT, and TOC with a clinical response of cure or failure (or have been assessed as a clinical failure at or after EOIV and before the planned assessment visit), or for LFU, have been evaluated with a clinical response of sustained cure or relapse;
- Had no important protocol deviations that would affect assessment of efficacy;
- Have not received concomitant antibiotics that would affect assessment of efficacy.

The Microbiologically Evaluable (ME) analysis set will be defined at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC and LFU visits. It includes all patients meeting the following criteria:

- All randomised patients who receive any amount of IV study drug and have a confirmed diagnosis of cIAI;
- Have received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;
- Have received at least 72 hours of IV study drug, defined as 9 doses, in order to be considered an evaluable clinical cure;
- At the specific visit had a microbiological response which was not indeterminate (note; presumed eradication or presumed persistence is acceptable);
- Had no important protocol deviations that would affect assessment of efficacy;
- Have not received concomitant antibiotics that would affect assessment of efficacy.

- Have at least 1 typical intra-abdominal infection (IAI) bacterial pathogen which has been isolated from an adequate microbiological specimen at Baseline that is susceptible to both study agents (CAZ-AVI and meropenem).

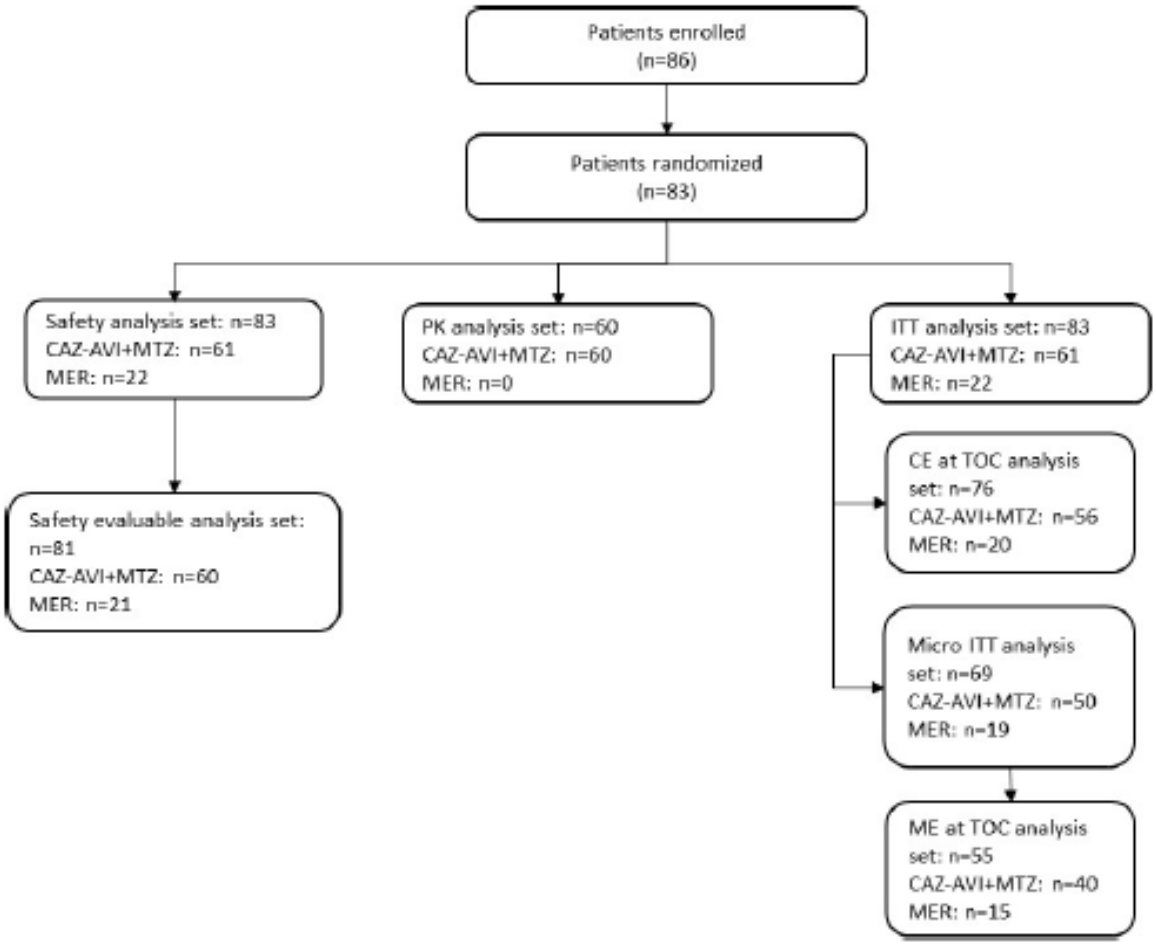
Table 34. Analysis Sets (All Patients)

	CAZ-AVI +MTZ (N = 61) n (%)	MER (N = 22) n (%)	Total (N = 86) n (%)
ITT	61	22	83
Safety	61 (100)	22 (100)	83 (100)
Safety Evaluable	60 (98.4)	21 (95.5)	81 (97.6)
PK	60 (98.4)	0	60 (72.3)
Micro-ITT	50 (82.0)	19 (86.4)	69 (83.1)
CE at End of 72h	49 (80.3)	20 (90.9)	69 (83.1)
CE at EOIV	54 (88.5)	20 (90.9)	74 (89.2)
CE at EOT	52 (85.2)	20 (90.9)	72 (86.7)
CE at TOC	56 (91.8)	20 (90.9)	76 (91.6)
CE at LFU	48 (78.7)	18 (81.8)	66 (79.5)
Micro-ITT	50 (82.0)	19 (86.4)	69 (83.1)
ME at End of 72h	33 (54.1)	15 (68.2)	48 (57.8)
ME at EOIV	40 (65.6)	15 (68.2)	55 (66.3)
ME at EOT	36 (59.0)	15 (68.2)	51 (61.4)
ME at TOC	40 (65.6)	15 (68.2)	55 (66.3)
ME at LFU	37 (60.7)	14 (63.6)	51 (61.4)

Source: Table 14.1.1.1.3.
Percentages use the number of patients in the ITT analysis set within each treatment group as the denominator.
CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; CE = clinically evaluable; EOIV = end of intravenous treatment; EOT = end of treatment; h = hours; ITT = intent-to-treat; LFU = late follow-up; ME = microbiologically evaluable; MER = meropenem; micro-ITT = microbiological ITT; PK = pharmacokinetic; TOC = test of cure.

Results

Participant flow



Source: Tables 14.1.1.1.3 and 16.2.1.7.
CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; CE = clinically evaluable; ITT = intent-to-treat; ME = microbiologically evaluable; MER = meropenem; micro-ITT = microbiological intent-to-treat; PK = pharmacokinetic; TOC = Test of Cure.

Figure 14. Flow Chart of Analysis Sets

Numbers analysed

Table 35. Summary of Clinical Evaluable Analysis Sets at the End of 72 Hours, EOIV, EOT, TOC and LFU

	CAZ-AVI + MTZ (N = 61)	MER (N = 22)	Total (N = 83)[a]
Patients included in the CE at End of 72 hours Analysis Set (%)	49 (80.3)	20 (90.9)	69 (83.1)
Patients excluded from the CE at End of 72 hours Analysis Set (%)	12 (19.7)	2 (9.1)	14 (16.9)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
No valid clinical response within the window	10 (16.4)	1 (4.5)	11 (13.3)
Important protocol deviation that may impact efficacy at end of 72 hours visit	2 (3.3)	0	2 (2.4)
Patients included in the CE at EOIV Analysis Set (%)	54 (88.5)	20 (90.9)	74 (89.2)
Patients excluded from the CE at EOIV Analysis Set (%)	7 (11.5)	2 (9.1)	9 (10.8)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
No valid clinical response within the window	2 (3.3)	0	2 (2.4)
Important protocol deviation that may impact efficacy at EOIV visit	3 (4.9)	0	3 (3.6)
Concomitant medication for reason other than clinical failure up to EOIV	1 (1.6)	1 (4.5)	2 (2.4)
Patients included in the CE at EOT Analysis Set (%)	52 (85.2)	20 (90.9)	72 (86.7)
Patients excluded from the CE at EOT Analysis Set (%)	9 (14.8)	2 (9.1)	11 (13.3)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
No valid clinical response within the window	4 (6.6)	0	4 (4.8)
Important protocol deviation that may impact efficacy at EOT visit	3 (4.9)	0	3 (3.6)
Concomitant medication for reason other than clinical failure up to EOT	1 (1.6)	1 (4.5)	2 (2.4)
Patients included in the CE at TOC Analysis Set (%)	56 (91.8)	20 (90.9)	76 (91.6)
Patients excluded from the CE at TOC Analysis Set (%)	5 (8.2)	2 (9.1)	7 (8.4)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
No valid clinical response within the window	2 (3.3)	0	2 (2.4)
Important protocol deviation that may impact efficacy at TOC visit	1 (1.6)	0	1 (1.2)
Concomitant medication for reason other than clinical failure up to TOC	1 (1.6)	1 (4.5)	2 (2.4)
Patients included in the CE at LFU Analysis Set (%)	48 (78.7)	18 (81.8)	66 (79.5)
Patients excluded from the CE at LFU Analysis Set (%)	13 (21.3)	4 (18.2)	17 (20.5)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
No valid clinical response within the window	7 (11.5)	1 (4.5)	8 (9.6)
Important protocol deviation[a] that may impact efficacy at LFU visit	2 (3.3)	1 (4.5)	3 (3.6)

Table 36. Summary of Microbiological Evaluable Analysis Sets at the End of 72 Hours, EOIV, EOT, TOC and LFU

	CAZ-AVI + MTZ (N = 61)	MER (N = 22)	Total (N = 83)[a]
No Study Qualifying Baseline Pathogen	11 (18.0)	3 (13.6)	14 (16.9)
Important protocol deviation that may impact efficacy at EOT visit	3 (4.9)	0	3 (3.6)
Concomitant medication for reason other than clinical failure up to EOT	1 (1.6)	1 (4.5)	2 (2.4)
Patients included in the ME at TOCAnalysis Set (%)	40 (65.6)	15 (68.2)	55 (66.3)
Patients excluded from the ME at TOC Analysis Set (%)	21 (34.4)	7 (31.8)	28 (33.7)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
Baseline Pathogen was not *Enterobacteriaceae* or *Pseudomonas aeruginosa*	5 (8.2)	3 (13.6)	8 (9.6)
No susceptibility data	3 (4.9)	0	3 (3.6)
No valid microbiological response within the window	12 (19.7)	3 (13.6)	15 (18.1)
No Study Qualifying Baseline Pathogen	11 (18.0)	3 (13.6)	14 (16.9)
Important protocol deviation that may impact efficacy at TOC visit	1 (1.6)	0	1 (1.2)
Concomitant medication for reason other than clinical failure up to TOC	1 (1.6)	1 (4.5)	2 (2.4)
Patients included in the ME at LFU Analysis Set (%)	37 (60.7)	14 (63.6)	51 (61.4)
Patients excluded from the ME at LFU Analysis Set (%)	24 (39.3)	8 (36.4)	32 (38.6)
Patient did not receive 9 doses of study drug	1 (1.6)	1 (4.5)	2 (2.4)
Baseline Pathogen was not *Enterobacteriaceae* or *Pseudomonas aeruginosa*	5 (8.2)	3 (13.6)	8 (9.6)
No susceptibility data	3 (4.9)	0	3 (3.6)
No valid microbiological response within the window	13 (21.3)	3 (13.6)	16 (19.3)
No Study Qualifying Baseline Pathogen	11 (18.0)	3 (13.6)	14 (16.9)
Important protocol deviation that may impact efficacy at LFU visit	2 (3.3)	1 (4.5)	3 (3.6)
Concomitant medication for reason other than clinical failure up to LFU	3 (4.9)	2 (9.1)	5 (6.0)

Source: Table 14.1.1.1.3.

A valid response excludes indeterminate responses. Patients may have more than one reason for exclusion from a given analysis set. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator.

CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; EOIV = end of intravenous treatment; EOT = end of treatment; LFU = late follow-up; ME = microbiologically evaluable; MER = meropenem; TOC = test of cure.

a. Total number of randomised patients. The source table indicates all patients (N=86).

The CHMP noted that, overall, subject disposition was similar between the two treatment groups across the analysis sets. However, an imbalance was observed in CE population at End of 72h analysis set which included 49 [80.3%)] patients in the CAZ/AVI + MTZ group vs. 20 [90.9%] patients in the meropenem group. Similarly, an imbalance was observed in the ME population at End of 72h and EOT with fewer patients included in the CAZ/AVI+MTZ treatment group.

The most common reason for exclusion from the CE population at the End of 72h was "no valid clinical response within the window". It is noted that more patients in the CAZ/AVI+MTZ group (10 [16.4%] patients had no valid response at End of 72h compared to the meropenem treatment group (1 [4.5%]). The reason for this difference is unclear; it could seem as if more patients in the meropenem group achieve a clinical response faster compared to patients in the CAZ/AVI group. However, considering the low number of patients, it could also be random.

At the TOC visit the difference between the two arms was approximately balanced (2 patients, 3.3% in the CAZ/AVI group vs. 0 patients in the meropenem group).

Table 37. Patient Disposition per cohort (All Patients)

	Number (%) of patients Cohort/Treatment Group														
	Cohort 1			Cohort 2			Cohort 3			Cohort 4			All Cohorts		
	CAZ-AVI + MTZ (N = 22)	MER (N = 8)	Total (N = 30)	CAZ-AVI + MTZ (N = 33)	MER (N = 10)	Total (N = 45)	CAZ-AVI + MTZ (N = 6)	MER (N = 3)	Total (N = 10)	CAZ-AVI + MTZ (N = 0)	MER (N = 1)	Total (N = 1)	CAZ-AVI + MTZ (N = 61)	MER (N = 22)	Total (N = 86)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients randomised	22 (100)	8 (100)	30 (100)	33 (100)	10 (100)	43 (95.6)	6 (100)	3 (100)	9 (90.0)	0	1 (100)	1 (100)	61 (100)	22 (100)	83 (96.5)
Patients who received IV study treatment	22 (100)	8 (100)	30 (100)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	61 (100)	22 (100)	83 (100)
Patients who completed the study up to the TOC visit	20 (90.9)	8 (100)	28 (93.3)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	59 (96.7)	22 (100)	81 (97.6)
Patients who completed the study up to the LFU visit	19 (86.4)	8 (100)	27 (90.0)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	58 (95.1)	22 (100)	80 (96.4)
Patients who completed IV study treatment	20 (90.9)	7 (87.5)	27 (90.0)	32 (97.0)	10 (100)	42 (97.7)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	58 (95.1)	21 (95.5)	79 (95.2)
Patients who discontinued IV study treatment	2 (9.1)	1 (12.5)	3 (10.0)	1 (3.0)	0	1 (2.3)	0	0	0	0	0	0	3 (4.9)	1 (4.5)	4 (4.8)
Lack of therapeutic response	1 (4.5)	0	1 (3.3)	0	0	0	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)
Condition under investigation improved/patient recovered	0	1 (12.5)	1 (3.3)	0	0	0	0	0	0	0	0	0	0	1 (4.5)	1 (1.2)
Other	0	0	0	1 (3.0)	0	1 (2.3)	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)
Patients who completed study	20 (90.9)	8 (100)	28 (93.3)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	59 (96.7)	22 (100)	81 (97.6)
Patients prematurely withdrawn from study	2 (9.1)	0	2 (6.7)	0	0	0	0	0	0	0	0	0	2 (3.3)	0	2 (2.4)
Parent/Guardian decision	1 (4.5)	0	1 (3.3)	0	0	0	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)
Investigator determination	1 (4.5)	0	1 (3.3)	0	0	0	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)

Source: Table 14.1.1.1.1.
Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years of age; Cohort 3: ≥2 years to <6 years of age; Cohort 4: ≥3 months to <24 months of age; Percentages for the patients randomised and patients not randomised use all patients in the cohort as the denominator. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator.
CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; IV = intravenous; MER = meropenem; TOC = Test of Cure; LFU = Late Follow-Up.

The CHMP noted that the majority of patients were enrolled in the older age cohorts. No patients less than 2 years of age received CAZ-AVY plus metronidazole and only six patients received CAZ/AVI in the age group 3-6 years. However, in line with CHMP Addendum guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements, efficacy results presented in the initial MA application for the adult in the cIAI indication can be extrapolated to the paediatric population provided similar exposure. In addition, the efficacy results observed in the youngest children with cUTI could be extrapolated to the same age cohorts for children with cIAI as these two infectious diseases are expected to have similar pathophysiology. See also the clinical pharmacology section regarding extrapolation of PK between indications.

Most patients completed IV study treatment (58 [95.1%] patients in the CAZ-AVI plus metronidazole group and 21 [95.5%] patients in the meropenem group). The majority of patients in both treatment groups completed the study through to TOC (81 [97.6%]) and LFU (80 [96.4%]) visits. Four patients (4.8%) discontinued the IV study treatment prematurely, of which one patient in cohort 1 in the CAZ-AVI + MTZ group discontinued due to lack of therapeutic response.

Recruitment

First patient first visit: 01 August 2015, last patient last visit: 01 June 2017.

The study was conducted at 29 centers: 4 in the Czech Republic, 2 in Greece, 5 in Hungary, 1 in Poland, 1 in Romania, 1 in the Russian Federation, 5 in Spain, 3 in Taiwan, 3 in Turkey, and 4 in the US. Medical and

clinical monitoring of this study was conducted by the Sponsor and PRA Health Sciences or its designated representatives.

Conduct of the study

Protocol amendment

The original protocol, approved on 20 January 2015 was amended twice.

Amendment 1 was approved on 22 September 2015 and this modification provided additional doses for Cohort 4 and dose adjustments for patients with moderate to severe renal impairment (CrCL ≤ 50 ml/min.

Amendment 2 was approved 07 March 2017 with endorsement from the European Medicines Agency Paediatric Committee (PDCO) to increase the maximum percentage of patients enrolled with complicated appendicitis from 80% to 90%, remove the requirement for a minimum number of evaluable patients to be enrolled in Cohorts 3 and 4, and remove specific exclusionary criteria related to immunocompromised patients. Amendment 2 also included the addition of two efficacy analysis sets (intent-to-treat [ITT] and microbiological intent-to-treat [micro-ITT]) per agreement with the Food and Drug administration (FDA).

Protocol deviations

Table 38. Important Protocol Deviations (Safety Analysis Set)

Important Protocol Deviation Category	CAZ-AVI + MTZ (N = 61) n (%)	MER (N = 22) n (%)	Total (N = 83) n (%)
Number of patients with at least one protocol deviation	35 (57.4)	10 (45.5)	45 (54.2)
Assessment - Safety	20 (32.8)	4 (18.2)	24 (28.9)
Visit Window	12 (19.7)	3 (13.6)	15 (18.1)
Study Drug	12 (19.7)	2 (9.1)	14 (16.9)
Informed Consent	6 (9.8)	0	6 (7.2)
Other	4 (6.6)	2 (9.1)	6 (7.2)
Lab/Endpoint Data	5 (8.2)	0	5 (6.0)
Overdose/Misuse	0	4 (18.2)	4 (4.8)
Exclusion Criteria	2 (3.3)	0	2 (2.4)
Prohibited Co-medication	2 (3.3)	0	2 (2.4)

Source: Table 14.1.1.1.4.
Important protocol deviations were defined and identified prior to database lock. Patients with multiple deviations in a single category are counted once for each category.
CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; MER = meropenem

The CHMP noted that the US site 5007 (principal investigator J. Blumer) was temporarily suspended and then terminated by the site IRB after one patient was randomised. Termination of this site was based upon findings of non-compliance with IRB policies occurring with other clinical studies. The site IRB performed an investigation and did not identify any adverse effects for the one patient who had been enrolled in this study.

The Sponsor also performed a quality assurance audit at the site. Based on the audit and a review of the safety and efficacy data, the Sponsor concluded there were no data integrity concerns that would preclude the data from being included in any data analysis. This is considered acceptable.

Protocol amendments: Both amendments were implemented after the first subject first visit. Amendment 1 was approved only one month after the first patient was enrolled. This amendment provided dose adjustment for renal impaired patients. However, according to baseline data no patients with moderate to renal impairment (CrCL ≤ 50 ml/min) were included in the study. Regarding Amendment 2: comprised (among other things) increasing the maximum percentage of patients enrolled with complicated appendicitis from 80% to 90%. This proposed change was approved by the PDCO. The PDCO had also noticed that in adult patients with cIAI the efficacy of ceftazidime/avibactam was higher in cases related to appendicitis than in patients with cIAI due to other causes. It is acknowledged that appendicitis is the most commonly diagnosed cIAI in children. Since popPK modelling demonstrates that disease severity has minimal effect on

CAZ-AVI exposure, the high proportion of patients with appendicitis is not considered to affect the applicability of the study results to cIAI patients with non-appendicitis type infections. Consequently, the change to include a proportion of 90% appendicitis is considered acceptable.

The exclusion criterion that prevented immunocompromised patients from being included in the study has been removed. Since immunocompromised patients are more likely to develop infections and therefore constitute an important patient population for parenteral antibiotic therapy in clinical practice, examining efficacy in these patients is very relevant for CAZ-AVI. The MAH was therefore asked in the previous round to submit the number of immunocompromised patients enrolled in the study and provide an overview of the efficacy outcomes observed in these patients compared to patients who were not immunocompromised. The MAH clarified in the response to this request that no patients with significant immunosuppression were enrolled in the cIAI study, most properly due to the late removal of this exclusion criterion of less than 3 months in this study. Please also refer to the assessment for the cUTI indication below.

Protocol deviations: In total, over 50% of the patients had at least one important protocol deviation (35 [57.4%] CAZ-AVI plus metronidazole; 10 [45.5%] meropenem patients). The most common deviations were in the category "Assessment safety" (approx. 30%). A total of 4 patients had important protocol deviations that led to a manual (non-programmatic) exclusion from the CE and ME analysis sets. The MAH argues that most of the deviations in the category "Assessment safety" were related to assessments not being conducted per the study schedule. Although there were 6 patients with important protocol deviations related to informed consent, there were no patients who lacked adequate informed consent. Across all cohorts, only two patients had important protocol deviations related to receipt of prohibited concomitant medications. These few deviations are not considered to have had a significant impact on the final conclusion of the study. Please also refer to section 'Concomitant treatment' below.

Baseline data

Table 39. Demographic Characteristics (Safety Analysis Set)

	CAZ-AVI + MTZ (N = 61)	MER (N = 22)	Total (N = 83)
Age (years)			
n	61	21	82
Mean	10.4	10.1	10.3
SD	3.64	3.63	3.62
Median	11.0	10.0	11.0
Minimum	3	5	3
Maximum	17	16	17
Age (months)			
n	0	1	1
Mean	-	21.0	21.0
SD	-		
Median	-	21.0	21.0
Minimum	-	21	21
Maximum	-	21	21
Sex n (%)			
Female	17 (27.9)	13 (59.1)	30 (36.1)
Male	44 (72.1)	9 (40.9)	53 (63.9)
Race n (%)			
Black or African American	0	0	0
White	53 (86.9)	16 (72.7)	69 (83.1)
Asian	7 (11.5)	4 (18.2)	11 (13.3)
Native Hawaiian or Pacific Islander	0	0	0
American Indian or Alaska Native	1 (1.6)	0	1 (1.2)
Other	0	2 (9.1)	2 (2.4)
Ethnicity n (%)			
Hispanic or Latino	12 (19.7)	1 (4.5)	13 (15.7)
Non-Hispanic or Latino	49 (80.3)	21 (95.5)	70 (84.3)

Source: Table 14.1.2.1.1.
- = not applicable; CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; MER = meropenem; SD = standard deviation.

Table 40. Patient Characteristics at Baseline (Safety Analysis Set)

Characteristic/ Statistic	CAZ-AVI + MTZ (N = 61)	MER (N = 22)	Total (N = 83)
Height (cm) n	60	22	82
Mean	145.8	141.3	144.5
SD	21.97	23.95	22.46
Median	147.0	140.0	144.0
Minimum	102	81	81
Maximum	185	173	185
BMI (kg/m^2) n	60	21	81
Mean	18.1	18.4	18.2
SD	3.35	4.40	3.63
Median	17.6	17.4	17.6
Minimum	13	12	12
Maximum	26	28	28
Creatinine Clearance Category n(%)			
<30mL/min	0	0	0
≥30 to <50 mL/min	0	0	0
≥50 to <8 0mL/min	9 (14.8)	2 (9.1)	11 (13.3)
≥80 mL/min	51 (83.6)	20 (90.9)	71 (85.5)
Type of Procedure n(%)			
Laparoscopy	14 (23.0)	9 (40.9)	23 (27.7)
Laparotomy	8 (13.1)	2 (9.1)	10 (12.0)
Percutaneous Drainage	3 (4.9)	2 (9.1)	5 (6.0)
Appendectomy NOS	36 (59.0)	9 (40.9)	45 (54.2)
Appendicitis at Screening n(%)			
Yes	55 (90.2)	20 (90.9)	75 (90.4)
No	6 (9.8)	2 (9.1)	8 (9.6)
Diagnosis of Intra-Abdominal Infection n(%)			
Appendiceal Perforation or Peri-Appendiceal Abscess	52 (85.2)	20 (90.9)	72 (86.7)
Secondary Peritonitis (But Not Spontaneous Bacterial Peritonitis Associated With Cirrhosis And Chronic Ascites)	8 (13.1)	1 (4.5)	9 (10.8)
Traumatic Perforation Of The Intestines, Only If Operated On >12 Hours After Perforation Occurs	1 (1.6)	1 (4.5)	2 (2.4)

Source: Table 14.1.2.1.2.
BMI was calculated as weight (kg) / (height $(m)^2$. BMI was not calculated for children <24months of age (Cohort 4).
Height and BMI responses are the last non-missing values obtained prior to first administration of study medication.
Creatinine Clearance results as recorded on the CRF using the Schwartz formula.
Percentages are based on the total number of patients in the treatment group/cohort (N).
Appendicitis at screening was recorded on IVRS and procedure type was obtained from either procedures relating to infection CRF page where available, or otherwise surgical history on study day -1 or 1. The text entered from either source is then grouped for this summary.
BMI = body mass index; CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; CRF = case report form; IXRS = Interactive voice/web response system MER = meropenem; NOS = not otherwise specified; SD = standard deviation.

Bacteremia at baseline

Two patients had isolates identified in the blood in the CAZ/AVI + MTZ treatment group at baseline (*E.coli* in 1 patient and *P.aeruginosa* in 1 patient). No patients in the meropenem group had Gram-negative pathogens isolated from blood at baseline.

The CHMP noted that for several of the demographic and baseline characteristics there were imbalances between the two treatment groups. The proportion of males was for instance much higher in the CAZ-AVI plus metronidazole group (72.1%) than in the meropenem group (40.9%).

Overall, the majority of the patients was predominantly white, European, males with a median age of 11 years and had normal renal function. No patients with CrCL < 50 ml/min were included and no dose recommendation is proposed by the MAH in the SmPC for this patient population (Please refer to LoQ for the pharmacology section, OC 14). As noted previously, only six patients of age 2-6 years were included in the study. No patients < 2 years (Cohort 4) were included in the CAZ/AVI arm.

A high proportion in both treatment arms had appendicitis (in total 75 subjects [90.1%]) at screening. This reflects well the actual epidemiological situation in children. The majority were diagnosed as appendiceal perforation or per-appendiceal abscess. However, as previously mentioned, this was accepted by the PDCO (protocol amendment 2). More patients in the CAZ/AVI+ metronidazole group compared to the meropenem group had the operative procedure appendectomy not otherwise specified (NOS) (59.0% vs. 40.9%, respectively).

Baseline microbiology

Table 41. Summary of Baseline Pathogens in ≥ 2 Patients in Either Treatment Group from intra-abdominal site and/or blood (Micro-ITT Analysis Set)

Pathogen Group Pathogen	CAZ-AVI + MTZ (N = 50)	MER (N = 19)	Total (N = 69)
Enterobacteriaceae	**42** **(84.0)**	**14** **(73.7)**	**56** **(81.2)**
Escherichia coli	42 (84.0)	13 (68.4)	55 (79.7)
Klebsiella pneumoniae	2 (4.0)	1 (5.3)	3 (4.3)
Gram-negative other than Enterobacteriaceae	**16** **(32.0)**	**10** **(52.6)**	**26** **(37.7)**
Pseudomonas aeruginosa	14 (28.0)	9 (47.4)	23 (33.3)
Gram-positive	**26** **(52.0)**	**11** **(57.9)**	**37** **(53.6)**
Enterococcus avium	4 (8.0)	1 (5.3)	5 (7.2)
Enterococcus faecium	2 (4.0)	0	2 (2.9)
Streptococcus anginosus group	23 (46.0)	10 (52.6)	33 (47.8)
Anaerobes	**24** **(48.0)**	**12** **(63.2)**	**36** **(52.2)**
Bacteroides caccae	3 (6.0)	0	3 (4.3)
Bacteroides fragilis	14 (28.0)	7 (36.8)	21 (30.4)
Bacteroides fragilis group	2 (4.0)	2 (10.5)	4 (5.8)
Bacteroides ovatus	2 (4.0)	0	2 (2.9)
Bacteroides thetaiotaomicron	3 (6.0)	3 (15.8)	6 (8.7)
Bacteroides vulgatus	2 (4.0)	0	2 (2.9)
Clostridium perfringens	0	2 (10.5)	2 (2.9)
Clostridium ramosum	2 (4.0)	0	2 (2.9)
Eggerthella lenta	2 (4.0)	0	2 (2.9)
Parabacteroides distasonis	2 (4.0)	0	2 (2.9)
Parvimonas micra	4 (8.0)	5 (26.3)	9 (13.0)
Prevotella buccae	2 (4.0)	0	2 (2.9)

Source: Table 14.1.2.1.5.
Pathogens included in this table were collected from intraabdominal site and/or blood.
A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group.
CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; MER = meropenem; micro-ITT = microbiological intent-to-treat.

The CAZ-AVI MIC range for *E. coli* was ≤0.008 to 0.12 mg/L and for *P. aeruginosa* was 0.5 to 8 mg/L. Two patients in the CAZ-AVI plus metronidazole treatment group and none in the meropenem group had ceftazidime-non-susceptible (NS) *E. coli* isolated at baseline. The MICs for these two isolates were 16 mg/L and 32 mg/L, respectively. The meropenem MIC range for *E. coli* was ≤0.008 to 0.03 mg/L and for *P. aeruginosa* it was 0.06 to 4 mg/L. There were no pathogens that were non-susceptible to meropenem.

The CHMP acknowledged that pathogens isolated at baseline reflect the pattern of pathogens most commonly detected for intra-abdominal infections.

The most frequently reported Enterobacteriaceae pathogen reported at baseline was *E. coli* (55 [79.7%] overall; CAZ-AVI plus metronidazole: 42 [84.0%]; meropenem: 13 [68.4%]).

The most frequently reported Gram-negative pathogen other than Enterobacteriaceae was *P. aeruginosa* (23 [33.3%] overall; CAZ-AVI plus metronidazole: 14 [28.0%]; meropenem: 9 [47.4%]). *K. pneumoniae* was reported in 3 (4.3%) patients overall (CAZ-AVI: 2 [4.0%]; meropenem: 1 [5.3%]).

In both treatment groups very few of the pathogens were isolated from blood (2 patients in the CAZ/AVI + MTZ groups vs. none in the meropenem group [micro-ITT population]), reflecting the low number of bacteremic cases. No patients in the ME at TOC analysis set had Gram-negative pathogens identified in the blood at baseline.

Overall, there were no isolates tested that were reported as being non-susceptible to either of the study drugs received.

Two patients in the CAZ-AVI plus metronidazole group had *E. coli* isolates that were non-susceptible to ceftazidime, 1 in cohort 1 and the other in cohort 3.

Over 80% of patients in each treatment group of the safety analysis set belonged to the micro-ITT analysis set, and thus had baseline pathogens identified from intra-abdominal or blood cultures.

Prior Treatments

Systemic antibiotics taken within 2 weeks of the start of study treatment is considered prior treatments, and from randomisation through the LFU visit is considered concomitant treatment.

The proportion of patients who received prior systemic antibiotic medication ranged from 81.8% to 100% across cohorts. The prior systemic antibiotic medication most commonly received by patients was gentamicin, used by 25 (30.1%) patients overall (CAZ-AVI plus metronidazole n = 18 [29.5%] and meropenem n = 7 [31.8%]).

Concomitant treatment

Systemic antibiotics taken from randomisation through the LFU visit is considered concomitant treatment.

Overall, 86.9% of patients in CAZ-AVI plus metronidazole group, and 86.4% in the meropenem group received concomitant systemic antibiotics. The most frequent concomitant systemic antibiotic administered was gentamicin, used by 22 (26.5%) patients overall (CAZ-AVI plus metronidazole n = 16 [26.2%] and meropenem n = 6 [27.3%]). Two (2) patients (1 in each treatment group) were excluded from the CE and ME analysis sets at EOIV, EOT, and TOC and five patients (3 patients in the CAZ-AVI plus metronidazole group and 2 patients in the meropenem group) were excluded from the CE and ME at LFU analysis sets for being in receipt of concomitant medication for a reason other than clinical failure.

For the assessment of prior and concomitant medications, it should be noted that as the start/end time of antibiotic administration was not collected, systemic medications reported with the same start date as study drug administration are captured as both prior and concomitant medications. As a result, the proportions for each summary of prior or concomitant medications may be higher than actual exposures. However, across all cohorts, only two patients had important protocol deviations related to receipt of prohibited concomitant medications.

According to the MAH, the apparent high proportion of patients with concomitant systemic antibiotics (approx. 86% in both treatment groups) could be explained by the fact that the time points for starting/ending points of the dosing of concomitant systemic antibiotics were not collected. The systemic antibiotics taken during Day 1 of IV study medication administration therefore had been reported as both prior and concomitant medications. The CHMP noted that the investigators only reported two cIAI patients who had important protocol deviations related to receipt of prohibited concomitant medications across all cohorts. Lack of data collection on the duration of prior/concomitant treatments is considered a weakness of the conduct of the study. However, considering that the efficacy should be extrapolated from adults this issue was not further pursued with regards to efficacy.

Extent of exposure

For all cohorts combined, the median (minimum-maximum) exposure to IV study drug was 7 (2-13) days for both the CAZ-AVI plus metronidazole and meropenem treatment groups Exposure data are presented separately for CAZ-AVI and metronidazole within the CAZ-AVI + metronidazole group In terms of the individual components, the median (minimum-maximum) exposure was 7 (2-13) days for CAZ-AVI, metronidazole, and meropenem.

Approximately 69% of patients in both treatment groups were switched to oral therapy to complete their study treatment. The median duration of oral drug exposure was 6 and 7 days for patients in the CAZ-AVI plus metronidazole and meropenem treatment groups, respectively. The majority (67/83 [80.7%]) of patients in the study received 8 to 20 days of IV + oral therapy, generally consistent with the protocol recommended treatment duration of 7 to 15 days (IV + oral therapy combined).

Outcomes and estimation

Compliance by study treatment was approximately 100% in all cohorts and treatment groups. The overall mean compliance values for CAZ-AVI plus metronidazole and meropenem ranged from approximately 93% to 105%, with a median of 100%.

Table 42. Favourable Clinical Response by Visit, Treatment Group and Cohort (ITT, Micro-ITT, CE, and ME Analysis Sets by Visit)

		CAZ-AVI + MTZ			MER		
Visit	Analysis Set	N	n	Favorable Response Rate (95% CIa)	N	n	Favorable Response Rate (95% CIa)
End of 72 Hours	ITT	61	57	93.4 (85.2, 97.7)	22	20	90.9 (73.9, 98.1)
	Micro-ITT	50	47	94.0 (84.8, 98.3)	19	18	94.7 (77.9, 99.4)
	CE at 72 hours	49	48	98.0 (90.9, 99.8)	20	19	95.0 (78.9, 99.5)
	ME at 72 hours	33	32	97.0 (86.7, 99.7)	15	15	100.0 (84.8, 100.0)
End of IV Treatment	ITT	61	59	96.7 (89.9, 99.3)	22	22	100.0 (89.3, 100.0)
	Micro-ITT	50	48	96.0 (87.8, 99.2)	19	19	100.0 (87.8, 100.0)
	CE at EOIV	54	53	98.1 (91.7, 99.8)	20	20	100.0 (88.3, 100.0)
	ME at EOIV	40	39	97.5 (88.9, 99.7)	15	15	100.0 (84.8, 100.0)
End of Treatment	ITT	61	56	91.8 (83.0, 96.8)	22	22	100.0 (89.3, 100.0)
	Micro-ITT	50	45	90.0 (79.5, 96.1)	19	19	100.0 (87.8, 100.0)
	CE at EOT	52	49	94.2 (85.4, 98.3)	20	20	100.0 (88.3, 100.0)
	ME at EOT	36	33	91.7 (79.4, 97.6)	15	15	100.0 (84.8, 100.0)
Test of Cure	ITT	61	56	91.8 (83.0, 96.8)	22	21	95.5 (80.7, 99.5)
	Micro-ITT	50	45	90.0 (79.5, 96.1)	19	18	94.7 (77.9, 99.4)
	CE at TOC	56	52	92.9 (83.9, 97.5)	20	19	95.0 (78.9, 99.5)
	ME at TOC	40	36	90.0 (78.0, 96.5)	15	14	93.3 (72.8, 99.3)
Late Follow-up	ITT	61	56	91.8 (83.0, 96.8)	22	21	95.5 (80.7, 99.5)
	Micro-ITT	50	45	90.0 (79.5, 96.1)	19	18	94.7 (77.9, 99.4)
	CE at LFU	48	48	100.0 (94.9, 100.0)	18	18	100.0 (87.1, 100.0)
	ME at LFU	37	33	89.2 (76.3, 96.2)	14	13	92.9 (71.2, 99.2)

Source: Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, and 14.2.1.4.
The denominator for percentages is the total number of patients in the respective Analysis Set at the given visit, denoted by N within each section. A favourable clinical outcome (for which the count is indicated by n) was defined as clinical cure, sustained clinical cure, or clinical improvement. See SAP Section 3.3.1 for rules regarding clinical outcome definitions.
CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; CE = clinically evaluable; CI = confidence interval; EOIV = End of Intravenous treatment; EOT = End of treatment; ITT = intent-to-treat; IV = intravenous; LFU = Late Follow-up; ME = Microbiologically Evaluable. MER = meropenem; micro-ITT = microbiological intent-to treat; SAP = statisticial analysis plan; TOC = Test of Cure.
[a]. Jeffrey's method was used to calculate the two-sided 95% confidence intervals.

Table 43. Clinical response at TOC by visit, treatment group and cohort (ITT Analysis Set)

		Cohort/Treatment Group			
		Cohort 1		Cohort 2	
Nominal Visit	Clinical Outcome	CAZ-AVI	MER	CAZ-AVI	MER
TOC	ITT Analysis Set	N=22	N=8	N=33	N=10
	Favourable Outcome n (%)	17 (77.3)	8 (100)	33 (100)	9 (90.0)
	95% CI of Favourable Outcome [a]	(57.1, 90.8)	(73.8, 100)	(92.7, 100)	(61.9, 98.9)
	Clinical Cure n (%)	17 (77.3)	8 (100)	33 (100)	9 (90.0)
	Clinical Failure n (%)	4 (18.2)	0	0	1 (10.0)
	Indeterminate n (%)	1 (4.5)	0	0	0

CAZ-AVI ceftazidime-avibactam plus metronidazole; MER meropenem; EOIV End of Intravenous treatment; EOT End of treatment; TOC Test of Cure; LFU Late Follow-up; CI Confidence Interval;
Cohort 1: >=12 years to <18 years of age; Cohort 2: >=6 years to <12 years of age; Cohort 3: >=2 years to <6 years of age; Cohort 4: >=3 months to <24 months of age;
[a] A two-sided 95% CI computed using Jeffreys method.
The denominator for percentages is the total number of patients in the ITT Analysis Set, denoted by N within each section.
A favourable clinical outcome is defined as clinical cure or clinical improvement for the end of 72 hour and EOIV visits, clinical cure for the EOT and TOC visits, and sustained clinical cure for the LFU visit.
See section 3.3.1 of the SAP for rules regarding clinical outcome definitions.
Source Data: Tables 16.2.6.4 & 16.2.1.7

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The CHMP considered that, in general, across all analysis sets, favourable clinical response rates of ≥90% were observed at the End of 72 hour visit and were sustained through the LFU visit for both treatment groups. In the CE population at TOC, 56 patients (91.8%) in the CAZ-AVI plus metronidazole group and 21 patients (95.5%) in the meropenem group had a favourable clinical response. However, the study was not statistically powered to conclude on efficacy.

The clinical response rates in the individual cohorts were in general consistent with those observed in the overall study population, except for cohort 1 (12-18 years of age).

Table 44. Favourable Clinical Response at TOC, by Baseline Pathogen in ≥ 2 Patients and Treatment Group (Micro-ITT and ME Analysis Sets)

	Pathogen Group	Baseline Pathogen	CAZ-AVI + MTZ	MER
Micro-ITT	*Enterobacteriaceae*	Overall n/N*	38/42 (90.5)	13/14 (92.9)
		Escherichia coli	38/42 (90.5)	12/13 (92.3)
		Klebsiella pneumoniae	2/2 (100)	1/1 (100)
	Gram-negative other than *Enterobacteriaceae*	Overall n/N*	14/16 (87.5)	9/10 (90.0)
		Pseudomonas aeruginosa	12/14 (85.7)	8/9 (88.9)
ME	*Enterobacteriaceae*	Overall n/N*	34/38 (89.5)	12/13 (92.3)
		Escherichia coli	34/38 (89.5)	11/12 (91.7)
	Gram-negative other than *Enterobacteriaceae*	Overall n/N*	13/14 (92.9)	8/9 (88.9)
		Pseudomonas aeruginosa	12/13 (92.3)	8/9 (88.9)

Source: Tables 14.2.1.10 and 14.2.1.11.
The denominator for percentages is the total number of patients in the analysis set with a baseline pathogen (or pathogen group) indicated in each row, denoted by N*. The number of patients with a favourable clinical outcome at TOC (ie clinical cure) is represented by n. A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group.
CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; ME = microbiologically evaluable; MER = meropenem; micro-ITT = microbiological intent-to-treat; TOC = Test of Cure.

Favourable clinical outcomes were reported at all visits for both patients in the CAZ-AVI plus metronidazole group infected with ceftazidime non-susceptible (CAZ-NS) *E.Coli* at baseline.

Table 45. Per Patient Favourable Microbiological Response by Visit and Treatment Group (Micro-ITT Analysis Set)

	Favourable Response; n (%)	
Visit	CAZ-AVI +MTZ N = 50	MER N = 19
EOIV	48 (96.0)	19 (100)
EOT	45 (90.0)	19 (100)
TOC	45 (90.0)	18 (94.7)
LFU	45 (90.0)	18 (94.7)

Source: Table 14.2.1.12.
The denominator for percentages is the number of patients in the Micro ITT analysis set within each treatment group and cohort.
favourable clinical outcome is defined as clinical cure, sustained clinical cure, or clinical improvement.
CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; EOIV = End of Intravenous treatment; EOT = End of treatment; LFU = Late Follow-up; MER = meropenem; micro-ITT = microbiological intent-to-treat; TOC = Test of Cure.

Table 46. Per-Pathogen Favourable Microbiological Response Rate in ≥ 2 Patients in Either Treatment Group at TOC by Pathogen and Treatment Group (Micro-ITT Analysis Set)

Baseline Pathogen Group Baseline Pathogen	Number (%) of patients CAZ-AVI + MTZ	 MER
	N = 50	N = 19
Enterobacteriaceae	**38/42 (90.5)**	**13/14 (92.9)**
Escherichia coli	38/42 (90.5)	12/13 (92.3)
Klebsiella pneumoniae	2/2 (100)	1/1 (100)
Gram-negative other than *Enterobacteriaceae*	**14/16 (87.5)**	**9/10 (90.0)**
Pseudomonas aeruginosa	12/14 (85.7)	8/9 (88.9)
Gram-positive	**24/26 (92.3)**	**11/11 (100)**
Enterococcus avium	4/4 (100)	1/1 (100)
Enterococcus faecium	2/2 (100)	0
Streptococcus anginosus group	21/23 (91.3)	10/10 (100)
Anaerobes	**22/24 (91.7)**	**11/12 (91.7)**
Bacteroides fragilis	13/14 (92.9)	7/7 (100)
Bacteroides fragilis group	2/2 (100)	2/2 (100)
Bacteroides ovatus	2/2 (100)	0
Bacteroides thetaiotaomicron	3/3 (100)	3/3 (100)
Bacteroides vulgatus	2/2 (100)	0
Clostridium perfringens	0	2/2 (100)
Parabacteroides distasonis	2/2 (100)	0
Parvimonas micra	4/4 (100)	5/5 (100)
Prevotella buccae	2/2 (100)	0

Source: Table 14.2.1.14.
The denominator for percentages is the total number of patients in the micro-ITT Analysis Set (TOC) at the given visit with that baseline pathogen.
CAZ-AVI +MTZ = ceftazidime-avibactam plus metronidazole; ME = microbiologically evaluable; MER = meropenem; TOC = Test of Cure.

The MIC distributions for each baseline pathogen were presented based on ceftazidime, CAZ-AVI and meropenem MICs. Additionally, for pathogens for which the number was 10 or more, the MIC to inhibit the growth of 50% (MIC50), and for which the number is 10 or more the MIC to inhibit the growth of 90% of organisms (MIC90) were reported.

Susceptibility testing methods and interpretive results were based upon CLSI criteria for meropenem and ceftazidime while the interpretation for CAZ-AVI was according to the FDA label.

Two patients in the CAZ-AVI plus metronidazole group had *E. coli* isolates that were non-susceptible to ceftazidime, 1 in cohort 1 and the other in cohort 3.

Overall, there were no isolates tested that were reported as being non-susceptible to study drug received.

For CAZ-AVI, the MIC range for *E. coli* was ≥0.008-0.12 mg/L and MIC90 was 0.12 mg/L for the CAZ-AVI plus metronidazole group and the corresponding data was 0.03-0.12 mg/L and MIC90 was 0.12 mg/L for the meropenem group. The MIC range for *P. aeruginosa* was 0.5-4 mg/L and the MIC90 was 4.0 mg/L for the CAZ-AVI plus metronidazole group. The corresponding data for the meropenem group were 1-8 mg/L and the MIC90 was not reported, due to <10 isolates.

In CAZ/AVI + MTZ group, there were no reported cases of persistence showing an increase in CAZ/AVI MIC.

According to the MAH, review of per-pathogen responses by MIC did not identify any trends. For predominant pathogens, such as *E. coli* and *P. aeruginosa*, there was no indication that increasing MICs were associated with a lower favourable response rate in either treatment group.

The CHMP noted that most microbiological outcomes were presumed eradicated based on clinical response; showing a similar pattern to the per-patient clinical response for the pathogens isolated. For cIAI, it is not unexpected that the microbiological eradication rates are mostly based on presumptions.

Due to the high number of presumed eradications, the per-pathogen clinical response and per-pathogen microbiological response were comparable.

In general, the per-pathogen microbiological response rates were similar between the Micro-ITT and the ME populations.

Since CAZ-AVI was administered with MTZ throughout the treatment period, the relevant comparison of response rates by pathogen should exclude the anaerobes.

Treatment emergent infections

There were no treatment emergent infections reported in either treatment group.

2.5. Clinical efficacy in paediatric cUTI

2.5.1. Main study C3591005 (D4280C00016)

The initial MAA application for authorisation of CAZ-AVI did not include paediatric data from controlled clinical studies. Since completion of the adult studies, a paediatric study in cUTI has been conducted (C3591005 [D4280C00016]). This Phase 2 study was initiated as part of the agreed Paediatric Investigation Plan (PIP).

Study C3591005 (D4280C00016) is designed to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam (CAZ-AVI), compared with cefepime (CEF), in children from 3 months to <18 years of age with complicated urinary tract infections (cUTIs).

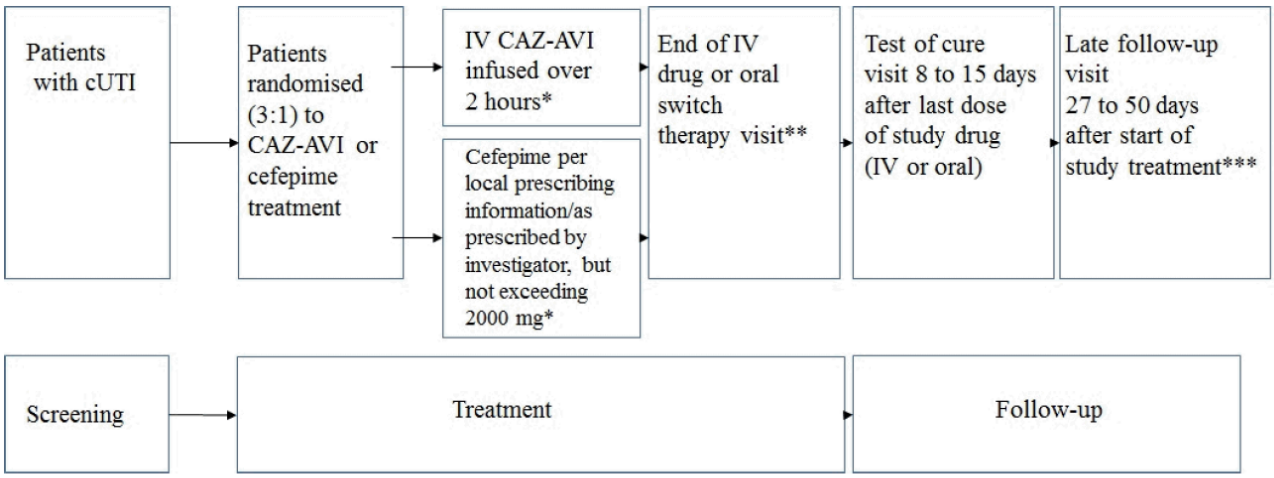
The study was sponsored by AstraZeneca and the sponsorship was transferred to Pfizer, Inc, on 18 September 2017. The study was conducted by investigators contracted by and under the direction of the Sponsor.

Methods

The efficacy of CAZ-AVI for the extended paediatric indication of cUTIs was evaluated in one single-blind, randomised, multi-centre, and actively controlled trial conducted in hospitalised paediatric patients with cUTIs requiring treatment with intravenous (IV) antibiotics. Patients aged from 3 months to <18 years with cUTIs were randomised in a 3:1 ratio to receive CAZ-AVI or CEF. Patients aged from 3 months to <1 year were to have been born at term (defined as gestational age ≥37 weeks).

The duration of each patient's participation in the study was to be a minimum of 27 days to a maximum of 50 days from the start of study treatment, at which time a late follow-up (LFU) assessment visit was performed (20 to 36 days from the last dose of study drug).

The study design of study C3591005 (D4280C00016) is illustrated in Figure 15 below.



CAZ-AVI = ceftazidime-avibactam; cUTI = complicated urinary tract infections; IV = intravenous.

*Optional switch to oral therapy was permitted on or after Study Day 4 (ie, after 72 hours [3 full days, ie, 9 doses if given 3 times daily, or 6 doses if given twice daily] of IV study drug). Assessment should be performed no later than 8 hours after the 72-hour time point. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food: oral ciprofloxacin (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or oral cefixime (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or oral amoxicillin/clavulanic acid (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or oral sulfamethoxazole/trimethoprim (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or pathogen-based therapy (in discussion with the Medical Monitor). The patient may continue on IV study drug for the entire duration of the study therapy (7 to 14 days), at the discretion of the Investigator.
**Visit performed within 24 hours of completion of last infusion or within 48 hours after the last dose of oral switch therapy.
***And 20 to 36 days from the last dose of study drug.

Figure 15. Study design of study C3591005 (D4280C00016)

Study participants

Main inclusion criteria:

1. Must have been ≥3 calendar months to <18 years of age. Patients aged ≥3 calendar months to <1 year must have been born at term (defined as gestational age ≥37 weeks).
2. For females who had reached menarche or had reached Tanner stage 3 development (even if not having reached menarche) the patient was authorised to participate in this clinical study if no indications of pregnancy were apparent and if the acceptable contraception was used.
3. Clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis as judged by the investigator to be serious and require hospitalisation for treatment with IV therapy.
4. Pyuria determined as follows:
    a. Cohorts 1 to 3: by a midstream clean catch or clean urethral catheterisation urine specimen with ≥10 white blood cells (WBCs) per high-power field on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine
    b. Cohorts 4a and 4b: by a midstream clean catch or clean urethral catheterisation urine specimen, or urine specimen obtained using urine collection pads (or supra-pubic collection if standard procedure in the assigned sites) ≥5 WBCs per high-power field on standard examination of urine sediment or ≥5 WBCs/mm^3 in unspun urine.
5. Positive urine culture: 1 midstream clean catch or clean urethral catheterisation urine specimen taken within 48 hours of randomisation containing ≥10^5 colony-forming units (CFU)/mL of a recognised uropathogen known to be susceptible to IV study therapy (CAZ-AVI and CEF).

Note: If patients met all of the entry criteria except for positive urine culture as outlined above, the patients may have been enrolled before urine culture results were available if the results were likely (based on urinalysis and clinical findings) to be positive and study drugs were considered appropriate empiric therapy. If a patient's urine culture was negative after 24 or 48 hours of treatment but the patient was improving, the Investigator could keep the patient on treatment. If the urine culture was negative and the patient was not improving, study treatment was to be stopped, and the patient was to be followed for the rest of the study including undergoing all safety assessments until LFU.

6. Demonstrated either acute pyelonephritis or complicated lower UTI as defined by the following:
    a. Qualifying criteria requiring that patients must have had at least one of the following signs/symptoms with onset or worsening within 7 days of enrolment in addition to pyuria:
        i. Dysuria (including perceived dysuria as referred by parent/caregiver);
        ii. Urgency;
        iii. Frequency;
        iv. Abdominal pain;
        v. Fever defined as oral temperature >38.5°C (or equivalent by other methods) with or without patient symptoms of rigor, chills, warmth;
        vi. Nausea;
        vii. Vomiting;
        viii. Irritability;
        ix. Loss of appetite;
        x. Flank pain.
    b. Or patients considered to have cUTI as indicated by 2 of the previous qualifying signs/symptoms in (a) plus at least 1 complicating factor from the following:
        i. Recurrent UTI (2 or more within 12 months period);
        ii. Obstructive uropathy that is scheduled to be surgically relieved during IV study therapy and before the end of treatment (EOT);
        iii. Functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder;
        iv. Vesicoureteral reflux;
        v. Use of intermittent bladder catheterisation or presence of an indwelling bladder catheter for >48 hours prior to the diagnosis of cUTI;
        vi. Urogenital procedure (e.g., cystoscopy or urogenital surgery) within the 7 days prior to study entry.

<u>Main exclusion criteria</u>

7. Participation in another clinical study with an IP during the last 30 days before the first dose of IV study drug or have previously participated in the current study or in another study of CAZ-AVI (in which an active agent was received).
8. History of hypersensitivity reactions to carbapenems, cephalosporins, penicillins or other β-lactam antibiotics.
9. Concurrent infection, including, but not limited to, central nervous system infection requiring systemic antibiotics in addition to the IV study drug therapy at the time of randomisation.
10. Receipt of more than 24 hours of any systemic antibiotics after culture and before study drug therapy.

11. Receipt of systemic antibiotics within 24 hours before obtaining the study-qualifying pre-treatment baseline urine sample and before study drug therapy.
12. Suspected or documented infection caused by organisms resistant to the prophylactic antibiotics.
13. A permanent indwelling bladder catheter or instrumentation including nephrostomy or current urinary catheter that would not be removed or anticipation of urinary catheter placement that would not be removed during the course of IV study drug therapy administration.
14. Suspected or known complete obstruction of any portion of the urinary tract, perinephric abscess, or ileal loops.
15. Trauma to the pelvis or urinary tract.
16. Previous renal transplantation.
17. Condition or history of any illness that, in the opinion of the investigator, would have made the patient unsuitable for the study (e.g., may have confounded the results of the study or posed additional risk in administering the study therapy to the patient).
18. Considered unlikely to survive the 6 to 8 week study period or rapidly progressive illness, including septic shock associated with a high risk of mortality.
19. Known to have a cUTI caused by pathogens resistant to the antimicrobials that were planned to be used in the study at the time of randomisation.
20. Presence of any of the following clinically significant laboratory abnormalities:
    a. Haematocrit <25% or haemoglobin <8 g/dL (<80 g/L, <4.9 mmol/L);
    b. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the age-specific upper limit of normal (ULN), or total bilirubin >2 × ULN (except known Gilbert's disease).

    For a) and b): unless if these values were acute and directly related to the infectious process being treated.
21. Creatinine clearance (CrCL) <30 mL/min/1.73 m^2 calculated using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula (Schwartz et al. 2009): CrCl (mL/min/1.73 m^2) = 0.413 × height (length) (cm)/serum creatinine (mg/dL).
22. History of seizures, excluding documented febrile seizure of childhood.
23. Currently pregnant or breast-feeding female.

The CHMP considered that the selection criteria reflect a patient population with ongoing acute infections of the urinary tract, including acute pyelonephritis (AP), evaluated as being complicated, serious and require hospitalisation for treatment with IV therapy. The selected criteria are largely considered acceptable and in accordance with the patient criteria specified for UTI in the CHMP's "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013)".

The MAH has planned to perform analyses of the clinical responses in the enrolled patients based on the diagnosis of cUTI with or without AP at screening in the CE, ME, micro-ITT, and ITT analysis sets. Since patients with AP do not always require parenteral treatment, this is considered useful by the CHMP for the evaluation of the efficacy results of CAZ-AVI.

Treatments

The dosing of CAZ-AVI was dependent on the age and weight of the enrolled patients with adjustments according to renal function in line with the dosing applied in the paediatric cIAI study C3591004 (D4280C00015). Please refer to the "Treatments" section for this cIAI study above for more information.

Dosing of Cefepime (CEF)

The dose, schedule and infusion duration of CEF have been dosed and adjusted for according to the local prescribing information or as prescribed by the investigator. Cefepime 50 mg/kg were administered IV every 8 or 12 hours. The maximum dose of CEF in any single infusion should not have exceeded 2000 mg.

For both treatment groups (CAZ-AVI or CEF) patients were to have received a minimum of 9 doses (if given 3 times daily, or 6 doses if given twice daily) of IV study drug, representing 3 full days (72 hours) of dosing prior to the optional switch to oral therapy. At any time after a minimum of 72 hours of IV study treatment with CAZ-AVI or CEF had been received, there was the option to switch to an oral therapy or continue IV therapy. The decision to switch to oral therapy was entirely at the investigator's discretion, if the patient had good or sufficient clinical response, and the patient was tolerating oral fluids or food.

Treatment options if oral switch after 72 hours IV therapy

- Oral ciprofloxacin (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or
- Oral cefixime (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or
- Oral amoxicillin/clavulanic acid (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or
- Oral sulfamethoxazole/trimethoprim (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or
- Pathogen-based therapy (in discussion with the medical monitor). The choice of oral antibacterial agent for pathogen-based therapy was driven by the results of a susceptibility test, which was provided to the investigator by either the local or central laboratory. Initiation of pathogen-based therapy was at the investigator's discretion. Before administering pathogen-based therapy, the investigator was to discuss the results of the susceptibility test and the selected antibacterial drug (which should be approved for use in children) with the medical monitor.

The CHMP noted that the MAH chose cefepime (CEF) as comparator because it has been widely used for treating pyelonephritis and cUTIs in children. According to the European Association of Urology (EAU), hospitalized patients with symptomatic cUTI, including AP, should initially be treated with an antimicrobial regimen. The choice of CEF as comparator in this paediatric cUTI study is considered acceptable. CEF is a fourth-generation cephalosporin antibiotic approved as monotherapy for the treatment of cUTI, including pyelonephritis, caused by *E. coli*, *K. pneumoniae*, or *Proteus mirabilis*, including cases associated with concurrent bacteraemia with these microorganisms. The chosen dose and dosing frequencies of CEF used in this study is within the dose range recommended for treatment of infants from 2 months of age, children and adolescents with cUTI.

Regarding the timing of oral switch and duration of overall treatment, the EAU/ European Society for Paediatric Urology (ESPU) guidelines for UTI in children recommend that parenteral antibiotic therapy should be given until the child is afebrile, before switching to and continuing on oral antibiotics for additional 7-14 days (Stein et al. 2015). In the majority of patients with UTI, normalisation of body temperature can be expected within 24-48 hours after start of therapy. Hence, both the timing of the optional switch from

parenteral to oral antibiotics from the fourth day after treatment initiation, and the recommended total duration of IV and oral treatment of 7-14 days, are considered acceptable by the Committee. However, the recommended duration of treatment for adult patients with cUTI is 5-10 days according to the approved SmPC. It is noted that 55.2% of patients in the paediatric cUTI study received treatment for 11 or more days. This is a duration of 5 days longer than the one proposed for treating adults. Furthermore, the proposed amended SmPC specifies an overall treatment duration of 5-14 days for paediatric patients with cUTI. Thus, the MAH was asked to explain why the dosing recommendation should be different between children and adult patients with cUTI, and revise the SmPC if considered necessary to reflect the treatment duration applied in the clinical paediatric study C3591005 (D4280C00016). The MAH explained that the majority of patients in the paediatric cUTI study received longer duration of treatment for up to 14 days, since these patients had more serious infections such as bacteremia. The MAH further clarified that patients in the adult study typically received CAZ-AVI for 10 days if they did not have bacteremia and for 14 days if they had bacteremia. The MAH therefore proposed to harmonies the adult and paediatric sections of the SmPC by adding a footnote suggesting longer total duration of treatment for adult cUTI patients in cases where patients have bacteremia. The explanation provided by the MAH regarding durations of treatment for both the paediatric and adult populations was acceptable.

The oral treatment options for switching are all frequently used oral antibacterial agents known to be effective for treatment of paediatric UTIs. Nevertheless, ciprofloxacin, amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, are not considered suitable agents for treatment of AP or all types of cUTIs because of the current resistance percentages observed to these antibiotics.

Prior and Concomitant treatments

No other oral, intramuscular, or IV concomitant antibacterial treatments were permitted while receiving study therapy at any time up to the LFU visit. A patient requiring such antibacterial treatments other than the allowed study therapy for the treatment of the cUTI was considered a treatment failure. Other medication, which was considered necessary for the patient's safety and well-being, could have been given at the discretion of the investigator. If analgesic medications were needed for pain, the use of analgesic medication without antipyretic properties was preferred. All concomitant medication(s) taken during the trial were to be recorded with indication, daily dose, and start and stop dates of administration.

Objectives

Primary Objective:

- To evaluate the safety and tolerability of CAZ-AVI given at the selected dose regimen versus CEF in paediatric patients aged ≥3 months to <18 years with cUTI.

Secondary Objectives:

- To evaluate the descriptive efficacy of CAZ-AVI versus CEF in paediatric patients aged ≥3 months to <18 years with cUTI.
- To evaluate the PK of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cUTI.

Outcomes/endpoints

Primary (safety) outcome variables

- AEs and SAEs;
- Cephalosporin class effects and additional AEs of special interest for CAZ and CAZ-AVI, such as liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorder, and renal disorder);
- Vital signs (pulse, blood pressure, respiratory rate, temperature);
- Physical examination;
- Electrocardiogram (ECG).
- Laboratory parameters, including CrCl.

Secondary (efficacy) outcome variables

- Plasma concentrations and PK parameters of CAZ and AVI;
- Clinical response at End of 72 hours treatment, end of intravenous treatment (EOIV), end of treatment (EOT), and test of cure (TOC);
- Microbiological response at EOIV, EOT, TOC, and late follow-up (LFU);
- Clinical relapse at LFU;
- Emergent infections;
- Combined response.

As this study was descriptive in nature, it was not powered for inferential testing and was intended to provide descriptive statistics only. Based on the 3:1 randomisation, meaningful interpretation of direct comparisons is not possible.

The CHMP noted that efficacy measures were defined as secondary endpoints in this paediatric cUTI study and evaluation of efficacy was based on descriptive statistics. According to the Draft guideline EMA/CHMP/187859/2017 "Addendum to guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements", it is considered appropriate to extrapolate efficacy observed in adults to paediatric patients with cUTI provided similar exposure is achieved in the paediatric population across different age subgroups. In addition, sufficient safety data with the intended dose regimen have to be collected in the paediatric population, which is defined as a primary endpoint in the study. Thus, the primary and secondary endpoints of the paediatric cUTI study were considered acceptable by the Committee.

Table 47. Derivation of Analyses Windows for End of 72 hours, EOIV, EOT, TOC, and LFU Visits

Visit	Protocol-Defined Window	Derived Analyses Window
End of 72 hours	After 72 hours of treatment and up to 8 hours later	From completion of the ninth study dose of CAZ-AVI or sixth dose of cefepime to 80 hours after start of study drug
End of IV intravenous treatment (EOIV)	Within 24 hours of completion of the last infusion of study drug	On day of last infusion of study drug (or +1 day), and no later than same day as start of oral therapy.
End of Treatment (EOT)	Within 48 hours of completion of the last dose of oral switch therapy for patients who switched, or within 24 hours of the last infusion of study drug for those who did not receive oral switch therapy	On day of last dose of oral therapy (or +2 days) for oral switch patients; on day of last infusion of study drug (or +1 day) for patients who did not switch
Test of cure (TOC)	8 to 15 days after the last dose of any study drug	7 to 19 days after the last dose of study drug
Late follow-up (LFU)	20 to 36 days after the last dose of any study drug	20 to 43 days after the last dose of study drug

Source: Study D4280C00016 SAP, Table 2 (Section 16.1.9.1).
CAZ-AVI = ceftazidime-avibactam.

Table 48. Clinical Outcome Assessments at EOIV and EOT (for EOT: ex. def of clinical improvement)

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients 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[a]	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cUTI that requires alternative non-study antimicrobial therapy; • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cUTI; • Death in which cUTI is contributory.
Outcome	**Definition**
Indeterminate[b]	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00016 protocol, Table 8 (Section 16.1.1).
a. A clinical failure at EOIV was carried forward to EOT and TOC.
b. Any prophylactic systemic antibiotic medication use after first dose until the EOIV assessment would have resulted in a clinical outcome of Indeterminate.
AE = adverse event; CRP = C-reactive protein; cUTI = complicated urinary tract infection; EOIV = end of intravenous treatment; EOT =end of treatment; TOC = test of cure; WBC = white blood cell.

Table 49. Clinical Outcome Assessments at TOC

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Failure	Patients who meet either of the following criteria: • Incomplete resolution or worsening of cUTI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy; • Death in which cUTI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00016 protocol, Table 10 (Section 16.1.1).
cUTI = complicated urinary tract infection; EOT = end of treatment; TOC = test of cure.
Prophylactic systemic antibiotic medication initiated after the EOT assessment did not impact clinical outcome at TOC.

Each patient who was considered clinically cured at TOC was reassessed at LFU for evidence of clinical relapse of cUTI symptoms. The clinical outcome categories at LFU are defined in Table 50. A favourable clinical outcome at LFU was a sustained clinical cure.

Table 50. Clinical Outcome Assessments at LFU

Outcome	Definition
Sustained Clinical Cure	Continued favourable response, defined as resolution of all acute signs and symptoms of cUTI and no further antimicrobial therapy is required
Clinical Relapse	Patients who meet either of the following criteria: • Reappearance or worsening of signs and symptoms of cUTI that requires further antimicrobial therapy and/or surgery • Death after TOC in which cUTI is contributory
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory; • Extenuating circumstances precluding classification as sustained clinical cure or clinical relapse (eg, patient lost to follow-up).

Source: Study D4280C00016 protocol, Table 11 (Section 16.1.1).
Note: Clinical outcome at LFU were only assessed in patients who were considered clinically cured at TOC.
cUTI = complicated urinary tract infection; EOT = end of treatment; LFU = late follow-up; TOC = test of cure.
Prophylactic systemic antibiotic medication initiated after the EOT assessment did not impact clinical outcome at LFU.

Microbiological response assessments

Culture and organism identification were to be performed at the local or regional laboratory, as applicable, and susceptibility testing was to have been done at the local or regional laboratory to support patient care. All isolates were to be sent to the central laboratory for organism identification and susceptibility testing.

Urine samples were to be obtained for culture and routine quantitative analysis (including microscopic examination) at baseline (before any antibiotics were administered) and at EOIV, EOT, TOC, and LFU. Cultures were to be repeated per standard of care upon knowledge of a positive result until sterilisation is confirmed. In addition, if clinically indicated, blood samples may have been obtained for culture and routine analysis (including microscopic examination) at baseline (before any antibiotics are administered) and at any time until LFU.

Table 51. Microbiological Outcome Definitions

Outcome	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MIC[a]	Source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥ 4-fold larger than that observed for the baseline pathogen
Indeterminate	Source specimen was not available to culture

Source: Study D4280C00016 protocol, Table 12 (Section 16.1.1). a Persistence with increasing MIC is a subset of the Persistence outcome. MIC = minimum inhibitory concentration.

Emergent Infections

Pathogens first isolated after baseline are categorised as "emergent infections" until the LFU in patients with a baseline pathogen are:

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

Combined Response

At the EOIV and TOC assessments, the clinical and per-patient microbiological responses were to be used to create a combined response. If either clinical or microbiological response was unfavourable, then the combined response was unfavourable. Otherwise, in the absence of unfavourable responses, if either clinical or microbiological response was indeterminate or missing, then the response was indeterminate. Finally, if both clinical and microbiological responses were favourable, then the outcome was favourable. Indeterminate responses include missing assessments and assessments which were not performed.

Table 52. Outcomes definitions

	Clinical outcome		
Microbiologic outcome	**Favourable**	**Indeterminate**	**Unfavorable**
Favorable	Favorable	Indeterminate	Unfavorable
Indeterminate	Indeterminate	Indeterminate	Unfavorable
Unfavorable	Unfavorable	Unfavorable	Unfavorable

Sample size

The planned sample size for this paediatric cUTI study was 80 evaluable patients comprised of a minimum of 60 and 20 patients, respectively, from the CAZ-AVI and CEF groups. For the purpose of this study, an evaluable patient was defined as having completed at least 72 hours (3 full days, i.e., 9 doses if given 3 times daily, or 6 doses if given twice daily) of study treatment.

The planned sample size was based on the probability of observing a 'rare' safety event. The 'rare' term used in this section is not based on the regulatory definition but is instead intended to reflect uncommon events. Safety data from this study and from study C3591004 (D4280C00015) in paediatric patients with cIAI was

to be integrated, analysed, and reported separately. As a total of at least 120 patients were to be treated with CAZ-AVI in both studies combined, when assuming an underlying incidence rate of 3% for a specific 'rare' event, this was to ensure that the probability of observing such an event in at least 1 patient treated with CAZ-AVI exceeds 95%.

Randomisation

Patients were randomised to CAZ-AVI versus CEF in a 3:1 ratio, and allocated to 1 of 4 cohorts based on age. Randomisation was stratified as follows:

- Cohort 1: At least 6:2 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 6:2 evaluable patients aged from 6 years to <12 years;
- Cohort 3: At least 9:3 evaluable patients aged from 2 years to <6 years;
- Cohort 4: At least 18:6 evaluable patients aged from 3 months to <2 years, sub-divided into Cohorts 4a and 4b as follows:
    - Cohort 4a: At least 9:3 evaluable patients aged from 1 year to <2 years
    - Cohort 4b: At least 6:2 evaluable patients aged from 3 months to <1 year, with a minimum of 3 patients with at least 1 PK sample aged from 3 months to <6 months treated with CAZ-AVI.

The inclusion of more patients in the younger age cohorts (Cohorts 3, 4a, and 4b) compared to Cohorts 1 and 2 was based on epidemiological data. Considering patients over all cohorts combined, at least 10% of evaluable patients with urological abnormalities in the urinary tract were to be included.

Block randomisation using an interactive voice/web response system (IXRS) was used to assign patients in a ratio of 3:1 to the study treatment groups of CAZ-AVI or CEF, respectively, in each of the cohorts for the age groups. A representative of AstraZeneca, under the supervision of AstraZeneca statistical personnel, performed the randomisation. Patients who were randomised and ended IV treatment with <72 hours of study treatment did not meet the criteria for the safety evaluable population as decided by medical review and were eligible for enrolment replacement. Data from the replaced patients was included in the safety analysis set (and not the safety evaluable analysis set). The replacement process ensured that the next patient randomised in the same stratum was automatically assigned to the same treatment group as the non-evaluable patient who was replaced.

Blinding (masking)

This study was observer-blinded. Each investigational site was required to have a site-specific blinding plan that described the site-specific precautions being taken to ensure that the study was observer-blinded, taking into account the specific patient care procedures, equipment, and information accessibility at that site.

At each investigational site, at least 1 blinded investigator, referred to as Blinded Observer, who was not to know the patient's treatment assignment conducted the clinical assessments related to safety and efficacy. The Blinded Observer was allowed to see the patient during times when the study drug was not being administered, and when possible was to complete all clinical assessments and perform causality assessments for AEs and SAEs. A DSMB reviewed unblinded safety data at regular intervals during the study. In addition, the main programming and statistical teams were blinded from study treatment during the course of development of reporting materials.

Statistical methods

The study was descriptive in nature, no interim or final inferential analyses were performed for either efficacy or safety. Descriptive summaries were provided for each of the primary and secondary variables. In general, summaries were presented by cohort, treatment group and overall for treatment group across all cohorts. The Safety analysis set was used for summaries and listings. Clinical response outcomes was summarized by cohort, treatment group and overall for each treatment in the ITT, micro-ITT, CE and ME analysis sets (defined below).

Analysis sets

The Safety analysis set included all randomised patients who received any amount of IV study therapy (ie, CAZ-AVI or cefepime), categorized according to the study treatment actually received.

The safety evaluable analysis set was the subset of the patients in the Safety analysis set that received at least 9 doses of study treatment for patients on the CAZ-AVI arm, or 6 doses for patients on the cefepime arm.

The Pharmacokinetic (PK) analysis set was the subset of the patients in the Safety analysis set who had at least 1 ceftazidime and/or avibactam plasma measurement available.

The Intent-to-Treat (ITT) analysis set included all patients assigned a randomised treatment.

The Microbiological intent-to-treat (micro-ITT) analysis set included all randomised patients who had at least 1 Gram-negative typical pathogen (in the urine) at baseline known to cause cUTI and no Gram-positive pathogen (in the urine) at baseline.

The Clinically evaluable (CE) analysis set was defined separately at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC and LFU visits. It included all patients meeting the following criteria:

a) Patients in the micro-ITT analysis set who have received IV study therapy and had a confirmed diagnosis of cUTI;
b) Had received at least 48 hours of IV study drug, unless discontinued due to a treatment-limiting AE;
c) At the specific visit had
   a clinical response of cure, improvement or failure (or had been assessed as a clinical failure before the planned assessment visit),
   or for LFU, had been evaluated with a clinical response of sustained cure or relapse.
d) Had no important protocol deviations that would affect assessment of efficacy;
e) Did not take any concomitant antibiotics that would affect assessment of efficacy. This does not include antibiotic therapy taken for the treatment of cUTI by patients who are considered clinical failures.

The Microbiologically evaluable (ME) analysis set was defined separately at each of the EOIV, EOT, TOC and LFU visits. It included all patients meeting the following criteria:

a) Patients in the micro-ITT analysis set who have received IV study therapy and had a confirmed diagnosis of cUTI;
b) Had received at least 48 hours of IV study drug, unless discontinued due to a treatment-limiting AE;
c) At the specific visit had a (per-patient) microbiological response which was not indeterminate;
d) Had no important protocol deviations that would affect assessment of the microbiological responses;
e) Did not take any concomitant antibiotics that would affect assessment of the microbiological responses.
f) Had at least 1 Gram-negative typical UTI bacterial pathogen which has been isolated from an adequate microbiological specimen (in the urine) at Baseline that was susceptible to both study agents (CAZ-AVI and cefepime).

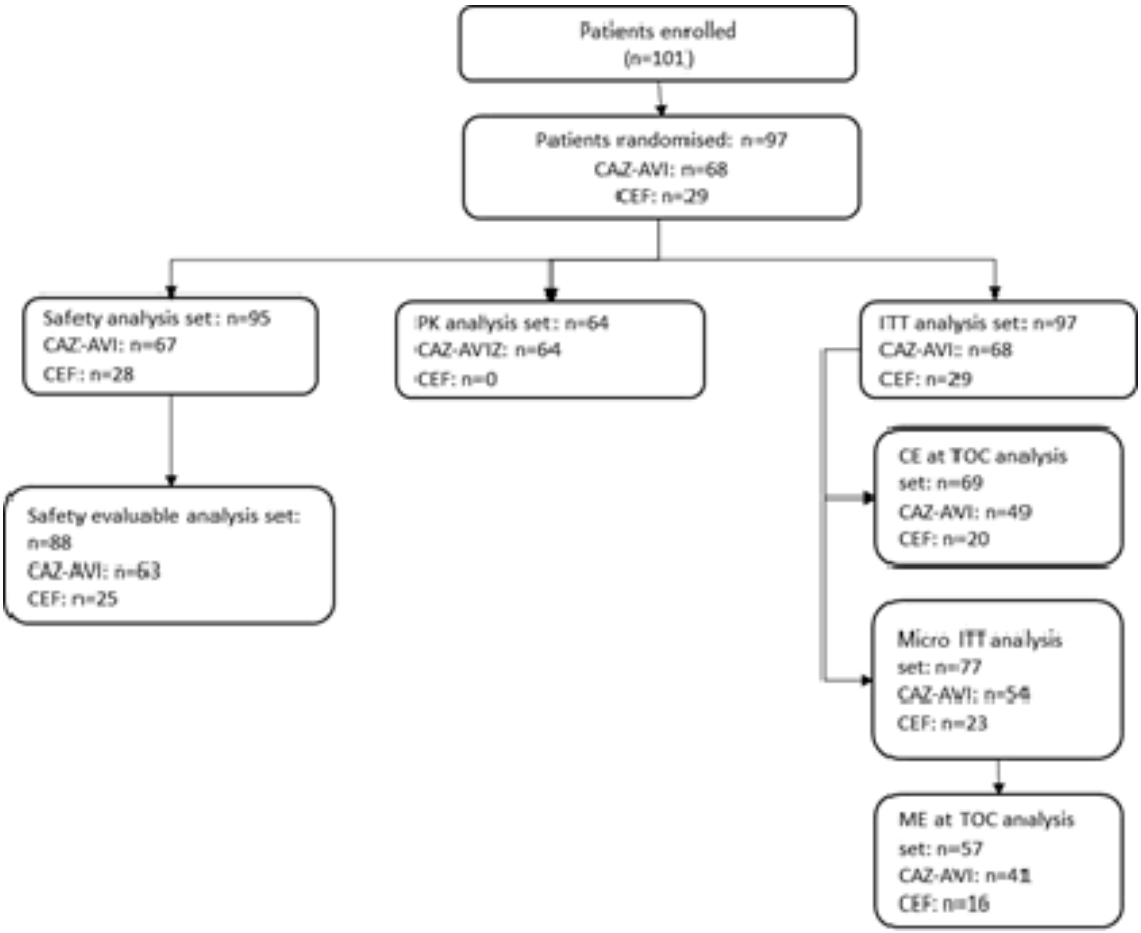
Table 53. Analysis Sets (All Patients)

	CAZ-AVI (N = 68) n (%)	CEF (N = 29) n (%)	Total (N = 101) n (%)
ITT	68	29	97
Safety	67 (98.5)	28 (96.6)	95 (97.9)
Safety Evaluable	63 (92.6)	25 (86.2)	88 (90.7)
PK	64 (94.1)	0	64 (66.0)
micro-ITT	54 (79.4)	23 (79.3)	77 (79.4)
CE at End of 72 h	47 (69.1)	21 (72.4)	68 (70.1)
CE at EOIV	52 (76.5)	22 (75.9)	74 (76.3)
CE at EOT	49 (72.1)	19 (65.5)	68 (70.1)
CE at TOC	49 (72.1)	20 (69.0)	69 (71.1)
CE at LFU	44 (64.7)	15 (51.7)	59 (60.8)
ME at EOIV	35 (51.5)	16 (55.2)	51 (52.6)
ME at EOT	39 (57.4)	14 (48.3)	53 (54.6)
ME at TOC	41 (60.3)	16 (55.2)	57 (58.8)
ME at LFU	16 (23.5)	9 (31.0)	25 (25.8)

Source: Table 14.1.1.1.3.
Percentages use the number of patients in the ITT analysis set within each treatment group as the denominator.
CAZ-AVI = ceftazidime avibactam; CE = clinically evaluable; CEF = cefepime; EOIV = end of intravenous treatment; EOT = end of treatment; h = hours; ITT = intent-to-treat; LFU = late follow-up;
ME = microbiologically evaluable; micro-ITT = microbiological ITT; N/n = number of patients;
PK = pharmacokinetic; TOC = test of cure.

Results

Participant flow



Source: Tables 14.1.1.1.3.
CAZ-AVI = ceftazidime-avibactam; CE = clinically evaluable; CEF = cefepime; ITT = intent-to-treat; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; PK = pharmacokinetic; TOC = test of cure.

Figure 16. Flow Chart of Analysis Sets

Table 54. Patient Disposition (All Patients)

	Number (%) of patients														
	Cohort/Treatment Group														
	Cohort 1			Cohort 2			Cohort 3			Cohort 4			All Cohorts		
	CAZ-AVI (N = 13)	CEF (N = 6)	Total (N = 19)	CAZ-AVI (N = 17)	CEF (N = 5)	Total (N = 22)	CAZ-AVI (N = 11)	CEF (N = 7)	Total (N = 22)	CAZ-AVI (N = 27)	CEF (N = 11)	Total (N = 38)	CAZ-AVI (N = 68)	CEF (N = 29)	Total (N = 101)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients randomised	13	6	19 (100)	17	5	22 (100)	11	7	18 (81.8)	27	11	38 (100)	68	29	97 (96.0)
Patients who were not randomised			0			0			4 (18.2)			0			4 (4.0)
Patients who received IV study treatment	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	11 (100)	7 (100)	18 (100)	26 (96.3)	10 (90.9)	36 (94.7)	67 (98.5)	28 (96.6)	95 (97.9)
Patients who were randomised but did not receive IV study treatment	0	0	0	0	0	0	0	0	0	1 (3.7)	1 (9.1)	2 (5.3)	1 (1.5)	1 (3.4)	2 (2.1)
Patients who completed the study up to the TOC visit	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	10 (90.9)	6 (85.7)	16 (88.9)	24 (88.9)	9 (81.8)	33 (86.8)	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed the study up to the LFU visit	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	10 (90.9)	6 (85.7)	16 (88.9)	24 (88.9)	9 (81.8)	33 (86.8)	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed IV study treatment	11 (84.6)	5 (83.3)	16 (84.2)	16 (94.1)	5 (100)	21 (95.5)	11 (100)	5 (71.4)	16 (88.9)	25 (92.6)	10 (90.9)	35 (92.1)	63 (92.6)	25 (86.2)	88 (90.7)
Patients who discontinued IV study treatment	2 (15.4)	1 (16.7)	3 (15.8)	1 (5.9)	0	1 (4.5)	0	2 (28.6)	2 (11.1)	1 (3.7)	0	1 (2.6)	4 (5.9)	3 (10.3)	7 (7.2)
Patient/parent/legal representative decision	0	0	0	0	0	0	0	0	0	1 (3.7)	0	1 (2.6)	1 (1.5)	0	1 (1.0)
Adverse event	2 (15.4)	0	2 (10.5)	1 (5.9)	0	1 (4.5)	0	0	0	0	0	0	3 (4.4)	0	3 (3.1)
Condition under investigation improved/patient recovered	0	1 (16.7)	1 (5.3)	0	0	0	0	0	0	0	0	0	0	1 (3.4)	1 (1.0)
Based on enrolment culture or susceptibility results	0	0	0	0	0	0	0	2 (28.6)	2 (11.1)	0	0	0	0	2 (6.9)	2 (2.1)
Patients who completed study	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	10 (90.9)	6 (85.7)	16 (88.9)	24 (88.9)	9 (81.8)	33 (86.8)	64 (94.1)	26 (89.7)	90 (92.8)
Patients prematurely withdrawn from study	0	0	0	0	0	0	1 (9.1)	1 (14.3)	2 (11.1)	3 (11.1)	2 (18.2)	5 (13.2)	4 (5.9)	3 (10.3)	7 (7.2)
Parent/Guardian decision	0	0	0	0	0	0	0	0	0	2 (7.4)	0	2 (5.3)	2 (2.9)	0	2 (2.1)
Lack of therapeutic response	0	0	0	0	0	0	0	1 (14.3)	1 (5.6)	0	0	0	0	1 (3.4)	1 (1.0)
Patient lost to follow-up	0	0	0	0	0	0	1 (9.1)	0	1 (5.6)	0	1 (9.1)	1 (2.6)	1 (1.5)	1 (3.4)	2 (2.1)
Other	0	0	0	0	0	0	0	0	0	1 (3.7)	1 (9.1)	2 (5.3)	1 (1.5)	1 (3.4)	2 (2.1)

Source: Table 14.1.1.1.1.

Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years of age; Cohort 3: ≥2 years to <6 years of age; Cohort 4: ≥3 months to <24 months of age; Percentages for the patients randomised and patients not randomised use all patients in the cohort as the denominator. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator.

CAZ-AVI = ceftazidime avibactam; CEF = cefepime; IV = intravenous; ITT = intent-to-treat; TOC = test of cure; LFU = late follow-up; N/n = number of patients.

The CHMP noted that, in total, 68 patients were randomised to the CAZ-AVI group and 29 patients to the CEF group. The enrolment was considered by the Committee to be well balanced between the age cohorts.

The majority of patients completed IV study treatment (92.6% in the CAZ-AVI group and 86.2% in the CEF group) and completed the study through to TOC and LFU visits (92.8% overall). Approximately 80% of the patients in each treatment group belonged to the micro-ITT analysis set with a baseline pathogen, and approximately 70% in each treatment group were considered clinically evaluable at the TOC visit.

Seven patients (7.2%) discontinued from IV study treatment prematurely, of which four patients in the CAZ-AVI arm due to adverse events (n=3) and legal representative decision (n=1). Three patients in the CEF group discontinued from IV study treatment due to condition under investigation improving/patient recovering (n=1) and enrolment culture or susceptibility results (n=2).

Numbers analysed

Table 55. Summary of Clinical Evaluable Analysis Sets at the End of 72 Hours, EOIV, EOT, TOC, and LFU

	CAZ-AVI (N = 68)	CEF (N = 29)	Total (N = 97)[a]
Patients included in the CE at End of 72 hours Analysis Set (%)	47 (69.1)	21 (72.4)	68 (70.1)
Patients excluded from the CE at End of 72 hours Analysis Set (%)	21 (30.9)	8 (27.6)	29 (29.9)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid clinical response within the window	6 (8.8)	1 (3.4)	7 (7.2)
Important protocol deviation that may impact efficacy at End of 72 hours visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to End of 72 hours	0	1 (3.4)	1 (1.0)
Patients included in the CE at EOIV Analysis Set (%)	52 (76.5)	22 (75.9)	74 (76.3)
Patients excluded from the CE at EOIV Analysis Set (%)	16 (23.5)	7 (24.1)	23 (23.7)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid clinical response within the window	1 (1.5)	0	1 (1.0)
Important protocol deviation that may impact efficacy at EOIV visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to EOIV	0	1 (3.4)	1 (1.0)
Patients included in the CE at EOT Analysis Set (%)	49 (72.1)	19 (65.5)	68 (70.1)
Patients excluded from the CE at EOT Analysis Set (%)	19 (27.9)	10 (34.5)	29 (29.9)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid clinical response within the window	5 (7.4)	3 (10.3)	8 (8.2)
Important protocol deviation that may impact efficacy at EOT visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to EOT	0	1 (3.4)	1 (1.0)
Patients included in the CE at TOC Analysis Set (%)	49 (72.1)	20 (69.0)	69 (71.1)
Patients excluded from the CE at TOC Analysis Set (%)	19 (27.9)	9 (31.0)	28 (28.9)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid clinical response within the window	5 (7.4)	1 (3.4)	6 (6.2)
Important protocol deviation that may impact efficacy at TOC visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to TOC	1 (1.5)	2 (6.9)	3 (3.1)
Patients included in the CE at LFU Analysis Set (%)	44 (64.7)	15 (51.7)	59 (60.8)
Patients excluded from the CE at LFU Analysis Set (%)	24 (35.3)	14 (48.3)	38 (39.2)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid clinical response within the window	8 (11.8)	6 (20.7)	14 (14.4)
Important protocol deviation that may impact efficacy at LFU visit	2 (2.9)	1 (3.4)	3 (3.1)
Concomitant medication for reason other than clinical failure up to LFU	4 (5.9)	2 (6.9)	6 (6.2)

Source: Table 14.1.1.1.3. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator. A valid response excludes indeterminate responses. Patients may have more than one reason for exclusion from a given analysis set. CAZ-AVI = ceftazidime avibactam CE = clinically evaluable; CEF = cefepime; EOIV = end of intravenous treatment; EOT = end of treatment; ITT = intent-to-treat; IV = intravenous; LFU = late follow-up; micro- ITT = microbiological intent-to-treat; N/n = number of patients; TOC = test of cure.
a. Total number of randomised patients.

Table 56. Summary of Microbiological Evaluable Analysis Sets at the EOIV, EOT, TOC, and LFU

	CAZ-AVI (N = 68)	CEF (N = 29)	Total (N = 97)a
Patients included in the ME at EOIV Analysis Set (%)	35 (51.5)	16 (55.2)	51 (52.6)
Patients excluded from the ME at EOIV Analysis Set (%)	33 (48.5)	13 (44.8)	46 (47.4)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid microbiological response within the window	12 (17.6)	5 (17.2)	17 (17.5)
No susceptibility data	5 (7.4)	3 (10.3)	8 (8.2)
Important protocol deviation that may impact efficacy at EOIV visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to EOIV	2 (2.9)	1 (3.4)	3 (3.1)
Patients included in the ME at EOT Analysis Set (%)	39 (57.4)	14 (48.3)	53 (54.6)
Patients excluded from the ME at EOT Analysis Set (%)	29 (42.6)	15 (51.7)	44 (45.4)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid microbiological response within the window	11 (16.2)	8 (27.6)	19 (19.6)
No susceptibility data	5 (7.4)	3 (10.3)	8 (8.2)
Important protocol deviation that may impact efficacy at EOT visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to EOT	2 (2.9)	1 (3.4)	3 (3.1)
Patients included in the ME at TOC Analysis Set (%)	41 (60.3)	16 (55.2)	57 (58.8)
Patients excluded from the ME at TOC Analysis Set (%)	27 (39.7)	13 (44.8)	40 (41.2)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid microbiological response within the window	7 (10.3)	4 (13.8)	11 (11.3)
No susceptibility data	5 (7.4)	3 (10.3)	8 (8.2)
Important protocol deviation that may impact efficacy at TOC visit	1 (1.5)	1 (3.4)	2 (2.1)
Concomitant medication for reason other than clinical failure up to TOC	3 (4.4)	2 (6.9)	5 (5.2)
Patients included in the ME at LFU Analysis Set (%)	16 (23.5)	9 (31.0)	25 (25.8)
Patients excluded from the ME at LFU Analysis Set (%)	52 (76.5)	20 (69.0)	72 (74.2)
Patient did not receive IV study therapy	1 (1.5)	1 (3.4)	2 (2.1)
Patient not in micro-ITT analysis set	13 (19.1)	5 (17.2)	18 (18.6)
No valid microbiological response within the window	31 (45.6)	14 (48.3)	45(46.4)
No susceptibility data	5 (7.4)	3 (10.3)	8 (8.2)
Important protocol deviation that may impact efficacy at LFU visit	2 (2.9)	1 (3.4)	3 (3.1)
Concomitant medication for reason other than clinical failure up to LFU	7 (10.3)	2 (6.9)	9 (9.3)

Source: Table 14.1.1.1.3. A valid response excludes indeterminate responses. Patients may have more than one reason for exclusion from a given analysis set. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator.
CAZ-AVI = ceftazidime avibactam; CEF = cefepime; EOIV = end of intravenous treatment; EOT = end of treatment; ITT = intent-to-treat; IV = intravenous; LFU = late follow-up; ME = microbiologically evaluable; micro-ITT = microbiologically intent-to-treat; N/n = number of patients; TOC = test of cure. a. Total number of randomised patients. The source table indicates all patients (N = 101).

In general, the CHMP noted that subject disposition was similar between the two treatment groups across the analysis sets. However, an imbalance was observed in the CE population at LFU with 64.7% vs. 51.7% in the CAZ-AVI and CEF groups, respectively. The main reason for this difference was a higher proportion of patients in the CAZ group that had "no valid clinical response within the window" compared to the CAZ-AVI-group (20.7% vs 11.8%). Similarly, an imbalance was observed in the ME population at EOT with a lower proportion included in the CEF group (48.3% vs. 57.4% in the CAZ-AVI group). This was also mainly due to a higher proportion of patients in the CEF group that had "no valid microbiological response within the window" (27.6% vs 16.2% in the CAZ-AVI group). The opposite was observed in the ME population at LFU,

with a lower proportion included in the CAZ-AVI group compared to the CEF group (23.5% vs. 31.0%, respectively). This could partly be due to exclusion of patients who received "concomitant medication for reason other than clinical failure up to LFU" form the ME population, with a slightly higher proportion of patients observed in the CAZ-AVI group (10.3% vs. 6.9% in the CEF group).

Similarly to the cIAI study, the highest number of patients in this paediatric cUTI study were excluded from the efficacy analysis sets in the investigated treatment group because of lack of valid clinical responses within the window or due to protocol deviations. The main reason for patients being excluded from the analysis was lack of valid microbiological response within the window. This persisted until the LFU visit. Based on PK/PD modelling, this was not unexpected.

Recruitment

First patient first visit: 24 September 2015, last patient last visit: 15 September 2017.

The study was conducted at 25 centres in 9 different countries: 3 in the Czech Republic, 4 in Greece, 4 in Hungary, 2 in Poland, 1 in Romania, 2 in the Russian Federation, 4 in Taiwan, 2 in Turkey, and 3 in the US.

Medical and clinical monitoring of this paediatric cUTI study was conducted by the Sponsor and PRA Health Sciences or its designated representatives.

Conduct of the study

Protocol amendment

The original protocol, approved on 14 January 2015 was amended three times.

Amendment 1 was approved on 22 September 2015. This modification divided Cohort 4 into 4a and 4b, added the requirement that patients in Cohort 4b were to have gestational age ≥37 weeks, added a time window of 8 hours for conducting assessments after 72 hours of treatment, added flank pain as a symptom of cUTI, allowed inclusion of patients with moderate renal impairment, added specific exclusion criteria related to immunocompromised patients, required that creatinine clearance was to be calculated at time points when serum creatinine was being assessed as part of the clinical chemistry panel, revised timelines for urine culture, and made changes to wording and terminology.

Amendment 2 was approved 07 March 2017 with endorsement from the EMA Paediatric Committee (PDCO) to remove specific exclusion criteria related to immunocompromised patients that had been added at amendment 1. Further, the amendment clarified several aspects of analysis set definitions and added the two efficacy analysis sets ITT and micro-ITT, and a combined responder outcome including clinical and microbiological response, all these changes per agreement with FDA. In addition, Amendment 2 clarified the definitions for minimum treatment duration, and added other minor changes.

Amendment 3 was approved 17 July 2017 and contained mainly administrative changes. The amendment was partly implemented due to the switch of the sponsor from AstraZeneca to Pfizer. In addition, a change of the definition of the end of the trial from Q3 2017 to Q3 2018 was implemented, due to challenges in patient enrolment.

Protocol deviations

Table 57. Important Protocol Deviations (Safety Analysis Set)

Important Protocol Deviation Category	CAZ-AVI (N = 67) n (%)	CEF (N = 28) n (%)	Total (N = 95) n (%)
Number of patients with at least one protocol deviation	41 (61.2)	19 (67.9)	60 (63.2)
Lab/Endpoint Data	11 (16.4)	9 (32.1)	20 (21.1)
Assessment Safety	9 (13.4)	10 (35.7)	19 (20.0)
Study Drug	16 (23.9)	2 (7.1)	18 (18.9)
Visit Window	6 (9.0)	4 (14.3)	10 (10.5)
Informed Consent	6 (9.0)	2 (7.1)	8 (8.4)
Other	4 (6.0)	1 (3.6)	5 (5.3)
Exclusion Criteria	2 (3.0)	1 (3.6)	3 (3.2)
Inclusion Criteria	1 (1.5)	1 (3.6)	2 (2.1)
Overdose/Misuse	1 (1.5)	0	1 (1.1)
Prohibited Co-Medication	1 (1.5)	0	1 (1.1)

Source: Table 14.1.1.1.4.
Important protocol deviations were defined and identified prior to database lock. Patients with multiple deviations in a single category are counted once for each category.
CAZ-AVI = ceftazidime avibactam; CEF = cefepime; N/n = number of patients.

With regard to Protocol amendments, the CHMP noted that Amendment 1 was implemented 2 days before the first subject first visit. This amendment is not suspected to have had an impact on the study results. Amendment 2 was approved approximately 1.5 years after the first patient was enrolled and 6 months before last patient last visit. The changes introduced in the amendment were largely agreed by PDCO or FDA and is therefore considered acceptable. Of note, one of the main changes in this amendment was removal of a specific exclusion criteria related to immunocompromised patients. Since immunocompromised patients are more likely to develop infections and therefore constitute a relevant patient population intended for parenteral antibiotic therapy in clinical practice, efficacy in these patients is relevant for the evaluation of the efficacy outcomes of CAZ-AVI. The MAH was therefore asked in the previous round to provide the exact number of immunocompromised patients enrolled in the study together with an overview of the efficacy outcomes observed in these patients compared to patients who were not immunocompromised. The MAH clarified in the response to this request that only one patient enrolled in the cUTI study potentially could have been immunocompromised. The apparent lack of enrolment of immunocompromised patients could be expected as these patients initially were excluded from being enrolled and removal of this exclusion criterion was implemented relatively late and approximately 6 months prior to LSLV for the cUTI study. Please also refer to the assessment for the cIAI indication above.

Amendment 3 was mainly for administrative purposes and transfer of sponsor from AstraZeneca to Pfizer.

With regards to Protocol deviations, the CHMP noted that over 60% of the patients had at least one protocol deviation. The most common deviations were "Lab/Endpoint Data" (21.1% of subjects) and "Assessment Safety" (20.0% of all subjects) with a higher proportion reported in the CEF group. The MAH argues that most deviations within these two categories were related to assessments not being conducted as per the study schedule of activities. Another common category of recorded protocol deviation was "Study Drug" (18.9% of all subjects), with a higher frequency in the CAZ-AVI group. The MAH states that most of the deviations for this category were related to minor variations in the expected timing of CAZ-AVI infusions (expected every 8 hours +/-30 minutes). Additional types of protocol deviations were relatively infrequent.

Although multiple deviations to the study protocol were reported, these are not considered to have had a significant impact on the study results or the integrity of the study. However, one patient in the CAZ-AVI group was randomised to Cohort 4b of the study although the patient was premature (born at 30 weeks gestation). In addition, another patient in the CAZ-AVI group received a higher dose than specified in the

protocol for the first 3 doses, corresponding to 50 mg/kg CAZ and 12.5 mg/kg AVI instead of 40 mg/kg CAZ and 10 mg/kg AVI. This patient experienced a non-serious AE of mild dermatitis diaper on Day 2 that was related to study treatment, and an SAE of severe pyelonephritis acute on Day 46 that was considered unrelated to study treatment.

The pre-specified ratio for allocating patients to treatment groups was 3:1. However, the actual disposition of patients was more towards a ratio of 2:1 (given there were 67 patients in CAZ-AVI group and 28 in CEF group).

Baseline data

Table 58. Demographic Characteristics (Safety Analysis Set)

	CAZ-AVI (N = 67)	CEF (N = 28)	Total (N = 95)
Age (years)			
n	67	28	95
Mean	6.08	6.19	6.12
SD	5.647	6.072	5.743
Median	4.22	3.20	3.87
Minimum	0.3	0.3	0.3
Maximum	17.7	17.9	17.9
Sex n (%)			
Female	56 (83.6)	21 (75.0)	77 (81.1)
Male	11 (16.4)	7 (25.0)	18 (18.9)
Race n (%)			
Black or African American	0	0	0
White	49 (73.1)	23 (82.1)	72 (75.8)
Asian	12 (17.9)	5 (17.9)	17 (17.9)
Native Hawaiian or Pacific Islander	0	0	0
American Indian or Alaska Native	1 (1.5)	0	1 (1.1)
Other	5 (7.5)	0	5 (5.3)
Ethnicity n (%)			
Hispanic or Latino	1 (1.5)	0	1 (1.1)
Non-Hispanic or Latino	66 (98.5)	28 (100)	94 (98.9)

Source: Table 14.1.2.1.1.

The median age was 4.2 years (range: 0.3 to 17.7 years) in the CAZ-AVI group and 3.2 years (range: 0.3 to 17.9 years) in the CEF group. For Cohort 4, the median age was 11.4 months (range: 3.5 to 22.4 months) in the CAZ-AVI group and 9.5 months (range: 3.1 to 22.5 months) in the CEF group. Most of the patients (75.8%) were White. The distribution of racial origin reflects the countries that participated in the study.

Table 59. Patient Characteristics at Baseline (Safety Analysis Set)

Characteristic/ Statistic	CAZ-AVI (N = 67)	CEF (N = 28)	Total (N = 95)
Height (cm)			
n	**67**	**28**	**95**
Mean	108.7	108.9	108.7
SD	34.40	37.16	35.03
Median	99.5	97.5	99.5
Minimum	53	60	53
Maximum	170	177	177
BMI (kg/m^2) n	41	18	59
Mean	18.6	18.5	18.6
SD	4.47	4.56	4.46
Median	17.2	18.9	17.7
Minimum	13	11	11
Maximum	34	27	34
Creatinine Clearance Category n (%)			
<30 mL/min/1.73 m^2	0	0	0
≥ 30 to <50 mL/min/1.73 m^2	1 (1.5)	1 (3.6)	2 (2.1)
≥ 50 to <80 mL/min/1.73 m^2	23 (34.3)	7 (25.0)	30 (31.6)
≥ 80 mL/min/1.73 m^2	43 (64.2)	20 (71.4)	63 (66.3)
Diagnosis n (%)			
cUTI without pyelonephritis	12 (17.9)	4 (14.3)	16 (16.8)
Acute pyelonephritis	55 (82.1)	24 (85.7)	79 (83.2)
No complicating factors present	53 (79.1)	21 (75.0)	74 (77.9)
With at least 1 complicating factor	2 (3.0)	3 (10.7)	5 (5.3)
Complicating Factors n (%)			
No complicating factors present	53 (79.1)	21 (75.0)	74 (77.9)
With at least 1 complicating factor	14 (20.9)	7 (25.0)	21 (22.1)
Recurrent UTI	7 (10.4)	1 (3.6)	8 (8.4)
Functional or anatomical abnormality of the urogenital tract	6 (9.0)	5 (17.9)	11 (11.6)
Vesicoureteral reflux	5 (7.5)	4 (14.3)	9 (9.5)
Intermittent bladder catheterization	0	1 (3.6)	1 (1.1)
Urological Abnormalities n (%)			
No	58 (86.6)	22 (78.6)	80 (84.2)
Yes	9 (13.4)	6 (21.4)	15 (15.8)

Source: Table 14.1.2.1.2.
BMI was calculated as weight (kg)/(height $(m)^2$. BMI was not calculated for children <24 months of age (Cohort 4). Height and BMI responses are the last non missing values obtained prior to first administration of study medication.
Creatinine Clearance results as recorded on the CRF using the Schwartz formula. Percentages are based on the total number of patients in the treatment group/cohort (N). The Urological Abnormalities data were collected in IXRS.
Patients may have been counted in more than one complicating factor category for type of infection. Patients with multiple complicating factors that fell into one complicating factor category were counted once for that complicating factor category.

The CHMP considered the demographic and baseline characteristics to be relatively well balanced between the treatment groups. However, a higher proportion of patients in the CEF group had functional or anatomical abnormality of the urogenital tract (17.9% vs. 9.0%), vesicoureteral reflux (14.3% vs. 7.5%), and urological abnormalities (21.4% vs. 13.4%) compared to the CAZ-AVI group. On the contrary, more patients in the CAZ-AVI group had recurrent UTI than in the CEF group (10.4% vs 3.6%). A high proportion in both treatment arms had AP at screening, i.e. 82.1% in the CAZ-AVI group and 85.7% in the CEF group.

The median age of all enrolled patients was 3.87 years. The majority of patients were female, White, enrolled in European, and 66.3% had CrCl values in the normal range of ≥ 80 ml/min/1.73 m^2. Most of the patents did not have any complicating factors of the urinary tract infections beyond the requirements from the inclusion criteria (77.9% overall) and the majority had no urological abnormalities (84.2% overall).

Baseline microbiology

Table 60. Summary of Baseline Aerobic Gram-Negative Uropathogens (Micro-ITT Analysis Set)

Pathogen Group **Pathogen**	**CAZ-AVI (N = 54)**	**CEF (N=23)**	**Total (N = 77)**
Enterobacteriaceae	54 (100)	23 (100)	77 (100)
Citrobacter freundii complex	0	1 (4.3)	1 (1.3)
Enterobacter cloacae	1 (1.9)	0	1 (1.3)
Escherichia coli	49 (90.7)	22 (95.7)	71 (92.2)
Klebsiella pneumoniae	2 (3.7)	0	2 (2.6)
Proteus mirabilis	2 (3.7)	0	2 (2.6)
Gram-negative other than *Enterobacteriaceae*	0	0	0

Source: Table 14.1.2.1.5. A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group. CAZ-AVI = ceftazidime avibactam; CEF = cefepime; micro-ITT = microbiological intent-to-treat; N/n = number of patients.

The CAZ-AVI MIC range for *Enterobacteriaceae* was ≤0.015 to 0.5 mg/L with all being confirmed to be susceptible to CAZ-AVI (MIC ≤0.5 mg/L). E. coli was the most common pathogen and the MIC range was ≤0.015 to 0.25 mg/L. The CAZ MIC range for *Enterobacteriaceae* was ≤0.06 to 64.0 mg/L. E. coli was the most common pathogen and the MIC range was ≤0.06 to 64 mg/L. The CEF MIC range for Enterobacteriaceae was ≤0.015 to >16.0 mg/L. E. coli was the most common pathogen and the MIC range was ≤0.015 to >16.0 mg/L.

Two patients in the CAZ-AVI group (both in Cohort 2) and one patient in the CEF group (in Cohort 3) had E. coli isolates that were non-susceptible to CAZ (based on an interpretive criterion of an MIC >4 mg/L) and CEF (based on an interpretive criterion of an MIC >8 mg/L) at baseline.

The CHMP noted that, in total, 79% of the randomised patients in each treatment group had baseline pathogens identified from the urine cultures, thereby encompassing the micro-ITT population. None of the patients in the micro-ITT analysis set was infected with Gram-negative pathogens other than Enterobacteriaceae. The majority of patients in both treatment groups (>90%) who had microbiologically confirmed disease were infected by *E.coli*, which is the most common infectious cause to UTI, particular if it is a first infection. Additionally, three patients in the CAZ-AVI group had pathogen isolates at baseline of *Enterobacter cloacae* (n=1) and *K. pneumoniae* (n=2), which are more common the first year of life.

Overall, no isolates that were tested were reported to be non-susceptible in vitro to CAZ-AVI, but two patients in the CAZ-AVI group and one patient in the CEF group were reported to have *E. coli* isolates non-susceptible to both CEF- and CAZ monotherapy. Since most patients in the study had isolates that were susceptible in vitro to both study drugs, resistance is not suspected to have had any impact on the efficacy results.

Prior and Concomitant treatments

For the assessment of prior and concomitant medications, it should be noted that as the start/end time of antibiotic administration was not collected, systemic medications reported with the same start date as study drug administration are captured as both prior and concomitant medications. As a result, the proportions for each summary of prior or concomitant medications may be higher than actual exposures.

Approximately 60% of the patients across both treatment groups had no prior systemic antibiotic medication, i.e. taken within 2 weeks of the start of study treatment. In total, 25 (37.3%) patients in the CAZ-AVI group and 15 (53.6%) patients in the CEF group, received concomitant antibiotics and 40 (42.1%) patients overall received concomitant systemic antibiotics. Both the prior systemic antibiotic medication most frequently received and concomitant systemic antibiotic administered was cefuroxime sodium, used by 8 (8.4%) patients overall (CAZ-AVI n = 6 [9.0%] and CEF n = 2 [7.1%]). In addition, 86 (90.5%) patients received concomitant medications other than systemic antibiotics.

Across all cohorts, 10.3% (7 patients) in the CAZ-AVI group and 6.9% (2 patients) in the CEF group had important protocol deviations, which were related to receipt of concomitant medications for reasons other than clinical failure up to LFU, that may have had an impact on the efficacy outcome at LFU visit (Table 14.1.1.1.3). However, only 1 patients in Cohort 4 of the CAZ-AVI group received concomitant treatment that was prohibited in the study protocol (Table 57).

The CHMP noted that, in total, 42.1% of the patients received concomitant antibiotics. The MAH explained that this apparent high proportion might reflect the fact that the start/end points of dosing were not collected in the study, and systemic antibiotics taken during Day 1 of IV study medication administration therefore were reported as both prior and concomitant medications. Hence, the reported proportions of prior and concomitant treatments might be higher than what were actually administered, according to the MAH. Although this assumption might be plausible, lack of data collection on the duration of prior/concomitant treatments is considered a weakness of the conduct of the study. However, considering that the efficacy should be extrapolated from adults this issue was not be further pursued by the Committee with regards to efficacy. Please also refer to the clinical pharmacology section.

In addition, there is a marked difference between the two treatment groups with a higher proportion of concomitant antibiotics used in the CEF group compared to the CAZ-AVI group (53.6% vs. 37.3%). This could potentially also have influenced both the type and frequencies of AEs reported within the two treatment groups.

The most frequent systemic antibiotic administered was cefuroxime sodium, used by 9.0% in the CAZ-AVI group and 7.1% in the CEF group (8.4% of the patients overall).

Extent of exposure

Of the 101 enrolled patients, 97 were randomised and 95 received treatment (67 were treated in the CAZ-AVI group and 28 were treated within in the CEF group). For all cohorts combined, the median (minimum-maximum) exposure to IV study drug was 4 (1-11) days for the CAZ-AVI group and 4 (2-11) days for the CEF group (Table 61). The exposure results for the safety evaluable analysis set were consistent with the safety analysis set (data not shown).

Table 61. Summary of IV study drug exposure by treatment group and cohort (Safety Analysis Set)

		Cohort/Treatment Group											
		Cohort 1		Cohort 2		Cohort 3		Cohort 4				All Cohorts	
								Cohort 4a		Cohort 4b			
	Statistic	CAZ-AVI (N=13)	CEF (N=6)	CAZ-AVI (N=17)	CEF (N=5)	CAZ-AVI (N=11)	CEF (N=7)	CAZ-AVI (N=12)	CEF (N=5)	CAZ-AVI (N=14)	CEF (N=5)	CAZ-AVI (N=67)	CEF (N=28)
Exposure (in days) categorised													
1-4 days	n (%)	7 (53.8)	5 (83.3)	8 (47.1)	1 (20.0)	7 (63.6)	5 (71.4)	8 (66.7)	3 (60.0)	13 (92.9)	3 (60.0)	43 (64.2)	17 (60.7)
5-7 days	n (%)	6 (46.2)	1 (16.7)	7 (41.2)	2 (40.0)	4 (36.4)	2 (28.6)	3 (25.0)	2 (40.0)	1 (7.1)	2 (40.0)	21 (31.3)	9 (32.1)
8-10 days	n (%)	0	0	1 (5.9)	1 (20.0)	0	0	1 (8.3)	0	0	0	2 (3.0)	1 (3.6)
11-15 days	n (%)	0	0	1 (5.9)	1 (20.0)	0	0	0	0	0	0	1 (1.5)	1 (3.6)
>15 days	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Exposure (in days)	n	13	6	17	5	11	7	12	5	14	5	67	28
	Mean	4.5	4.0	5.2	6.6	4.5	4.0	5.0	4.6	3.7	4.6	4.6	4.7
	SD	1.61	1.67	2.43	2.88	1.44	1.29	2.00	0.89	0.83	0.89	1.82	1.81
	Median	4.0	4.0	5.0	5.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
	Minimum	2	2	1	4	3	2	3	4	3	4	1	2
	Maximum	7	7	11	11	7	6	10	6	6	6	11	11
Average daily infusions	n	13	6	17	5	11	7	12	5	14	5	67	28
	Mean	2.85	2.13	2.82	2.16	2.83	2.20	2.87	2.00	2.90	1.95	2.86	2.10
	SD	0.297	0.440	0.488	0.477	0.224	0.451	0.162	0.000	0.214	0.112	0.309	0.355
	Median	3.00	2.00	3.00	2.00	3.00	2.00	2.95	2.00	3.00	2.00	3.00	2.00
	Minimum	2.0	1.8	1.0	1.8	2.5	1.8	2.5	2.0	2.3	1.8	1.0	1.8
	Maximum	3.0	3.0	3.0	3.0	3.0	3.0	3.0	2.0	3.0	2.0	3.0	3.0
Total number of IV infusions	n	13	6	17	5	11	7	12	5	14	5	67	28
	Mean	13.2	8.5	15.1	15.2	12.6	8.9	14.4	9.2	10.8	9.0	13.3	10.0
	SD	5.16	3.78	7.43	10.43	4.52	3.58	6.04	1.79	2.46	2.00	5.58	5.37
	Median	12.0	7.5	15.0	10.0	10.0	8.0	12.0	8.0	11.0	8.0	12.0	8.0
	Minimum	4	4	1	8	9	4	9	8	7	7	1	4
	Maximum	21	14	32	33	21	15	29	12	17	12	32	33

CAZ-AVI ceftazidime-avibactam; CEF cefepime; SD standard deviation; IV intravenous;
Cohort 1: >=12 years to <18 years of age; Cohort 2: >=6 years to <12 years of age; Cohort 3: >=2 years to <6 years of age; Cohort 4: >=3 months to <24 months of age; Cohort 4a: >=1 year to <2 years; Cohort 4b: >=3 months to <12 months;
Exposure (in days) to the study therapy for ceftazidime-avibactam and cefepime is calculated as the difference between the last study therapy date and time and the first study therapy date and time converted to days, plus 1 day.
Average daily infusions is calculated by dividing total number of infusions by days of exposure.
Total number of infusions is calculated by summing all the number of infusions together.
Source Data: Table 16.2.5.1

Around 90% of patients in both treatment groups were switched to oral therapy to complete their study treatment, and most of these switched between either 3-5 or 6-9 days after initiation of study treatment. The median duration of oral drug exposure was 7 days for both treatment groups. The majority (84/95 [88.4%]) of patients received IV + oral therapy for 8-15 days, consistent with the protocol recommended treatment duration of 7 to 14 days (IV + oral therapy combined).

Outcomes and estimation

Treatment compliance over the entire treatment period was defined as the number of infusions over all doses received, divided by the number of infusions over all doses expected during the treatment period, then multiplied by 100. The mean compliance for IV treatment was 100% across all cohorts, treatment groups, and overall, with a median of 100% across both treatment groups.

Table 62. Favourable Clinical Response by Visit and Treatment Group (ITT, micro-ITT, CE, and ME Analysis Sets by Visit)

Visit	Analysis Set	CAZ-AVI			CEF		
		N	n	Favorable Response Rate (95% CI[a])	N	n	Favorable Response Rate (95% CI[a])
End of 72 Hours	ITT	68	60	88.2 (79.0, 94.3)	29	25	86.2 (70.5, 95.2)
	micro-ITT	54	49	90.7 (80.9, 96.4)	23	22	95.7 (81.4, 99.5)
	CE at 72 hours	47	47	100 (94.8, 100)	21	20	95.2 (79.8, 99.5)
End of IV Treatment	ITT	68	62	91.2 (82.7, 96.2)	29	26	89.7 (74.9, 97.0)
	micro-ITT	54	52	96.3 (88.6, 99.2)	23	22	95.7 (81.4, 99.5)
	CE at EOIV	52	51	98.1 (91.4, 99.8)	22	21	95.5 (80.7, 99.5)
	ME at EOIV	35	35	100 (93.1, 100)	16	16	100 (85.7, 100)
End of Treatment	ITT	68	60	88.2 (79.0, 94.3)	29	26	89.7 (74.9, 97.0)
	micro-ITT	54	49	90.7 (80.9, 96.4)	23	22	95.7 (81.4, 99.5)
	CE at EOT	49	48	98.0 (90.9, 99.8)	19	18	94.7 (77.9, 99.4)
	ME at EOT	39	39	100 (93.8, 100)	14	14	100 (83.8, 100)
Test of Cure	ITT	68	59	86.8 (77.2, 93.2)	29	24	82.8 (66.3, 93.1)
	micro-ITT	54	48	88.9 (78.5, 95.2)	23	19	82.6 (63.8, 93.8)
	CE at TOC	49	46	93.9 (84.6, 98.2)	20	17	85.0 (65.1, 95.6)
	ME at TOC	41	38	92.7 (81.7, 97.9)	16	14	87.5 (65.6, 97.3)
Late Follow-up	ITT	68	55	80.9 (70.4, 88.8)	29	24	82.8 (66.3, 93.1)
	micro-ITT	54	44	81.5 (69.6, 90.1)	23	19	82.6 (63.8, 93.8)
	CE at LFU	44	41	93.2 (82.9, 98.0)	15	15	100 (84.8, 100)
	ME at LFU	16	12	75.0 (50.9, 90.9)	9	6	66.7 (34.8, 89.6)

Source: Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, and 14.2.1.4.
The denominator for percentages is the total number of patients in the respective Analysis Set at the given visit, denoted by N within each section. A favourable clinical outcome (for which the count is indicated by n) was defined as clinical cure, sustained clinical cure, or clinical improvement. See SAP Section 3.3.1 for rules regarding clinical outcome definitions.
CAZ-AVI = ceftazidime-avibactam; CE = clinically evaluable; CEF = cefepime; CI = confidence interval; EOIV = end of intravenous treatment; EOT = End of treatment; ITT = intent-to-treat; IV = intravenous; LFU = late follow-up; ME = microbiologically evaluable; micro-ITT = microbiological intent-to treat; N/n = number of patients; SAP = statistical analysis plan; TOC = test of cure.
[a] Jeffrey's method was used to calculate the two-sided 95% confidence intervals.

Four patients (5.9%) in the CAZ-AVI treatment group of the ITT analysis set had a clinical response of clinical failure at the TOC visit, three of which were carried forward from EOIV and were due to a treatment-limiting AE. The fourth patient was a clinical failure due to "additional infections" at the TOC visit. This patient had a microbiological response of eradication at the TOC visit, and eradication at LFU.

Three patients (10.3%) in the CEF group of the ITT analysis set had a clinical response of clinical failure at the TOC visit, one of which was carried forward from EOIV and had E. coli at baseline that was found to be non-susceptible to CEF. Study medication for this patient was discontinued at the EOIV visit. The two other patients were assessed as clinical failures due to additional infections. Both patients also had a reported microbiological response of persistence at the TOC visit.

Table 63. Clinical, Microbiological, and Combined Response at EOIV and at TOC by Treatment Group (micro-ITT Analysis Set)

Visit	Per-Patient Response	Outcome	CAZ-AVI (N = 54)		CEF (N = 23)	
			N (%)	95% CI[a]	N (%)	95% CI[a]
End of IV Treatment	Combined Response[b]	Favourable	43 (79.6)	[67.5, 88.7]	18 (78.3)	[58.7, 91.2]
		Unfavourable	3 (5.6)		1 (4.3)	
		Indeterminate	8 (14.8)		4 (17.4)	
	Clinical Response	Favourable	52 (96.3)	[88.6, 99.2]	22 (95.7)	[81.4, 99.5]
		Unfavourable	2 (3.7)		1 (4.3)	
		Indeterminate	0		0	
	Microbiological Response	Favourable	44 (81.5)	[69.6, 90.1]	18 (78.3)	[58.7, 91.2]
		Unfavourable	1 (1.9)		0	
		Indeterminate	9 (16.7)		5 (21.7)	
Test of Cure	Combined Response[b]	Favourable	39 (72.2)	[59.3, 82.8]	14 (60.9)	[40.6, 78.6]
		Unfavourable	8 (14.8)		6 (26.1)	
		Indeterminate	7 (13.0)		3 (13.0)	
	Clinical Response	Favourable	48 (88.9)	[78.5, 95.2]	19 (82.6)	[63.8, 93.8]
		Unfavourable	3 (5.6)		3 (13.0)	
		Indeterminate	3 (5.6)		1 (4.3)	
	Microbiological Response	Favourable	43 (79.6)	[67.5, 88.7]	14 (60.9)	[40.6, 78.6]
		Unfavourable	5 (9.3)		5 (21.7)	
		Indeterminate	6 (11.1)		4 (17.4)	

Source: Table 14.2.1.24.
The denominator for percentages is the total number of patients with a favourable, unfavourable or indeterminate outcome at the given visit.
CAZ-AVI = ceftazidime avibactam; CEF = cefepime; CI = confidence interval; EOIV = end of intravenous treatment; IV = intravenous; micro-ITT = microbiological intent-to-treat; N = number of patients; TOC = test of cure.
[a]. A two sided 95% CI computed using Jeffrey's method.
[b]. If either clinical or microbiological response was unfavourable, then the combined response was unfavourable. Otherwise, in the absence of unfavourable responses, then if either clinical or microbiological response was indeterminate or missing, then the response was indeterminate. Finally if both clinical and microbiological responses were favourable, then the outcome was favourable.

In general, the CHMP considered that favourable clinical response rates were high across all analysis sets in both treatment groups and the rates were sustained from the end of the 72 hours visit through to the EOT visit, with responses remaining ≥ 80% at LFU for the ITT, micro-ITT, and CE analysis sets of both treatment groups. At the TOC visit, 86.8% and 82.6% in the ITT population of the CAZ-AVI and CEF groups, respectively, had a favourable clinical response. No numerical trends pointed to any specific efficacy concern for CAZ-AVI.

The per-patient microbiological success rates in the micro-ITT analysis set at both the EOIV and TOC visits were lower than the clinical response rates in both treatment groups. The eradication rates at the TOC visit were 79.6% for the CAZ-AVI group compared to 60.9% for the CEF group, indicating that the pathogens were more susceptible to CAZ-AVI. Moreover, favourable combined response rates at the EOIV visit for the micro-ITT analysis set were 79.6% in the CAZ-AVI group and 78.3% in the CEF group. The combined success rates were numerical lower at the TOC visit, i.e. 72.2% for the CAZ-AVI group and 60.9% for the CEF group. Hence, the combined clinical and microbiological success rates observed in the micro-ITT population at the TOC visit points to a numerical trend of better efficacy of CAZ-AVI compared to CEF. Of note, between 13-17% of the patients in both treatment groups had a combined response defined as indeterminate at both the EOIV and TOC visits.

The clinical response rates in the individual cohorts were consistent with those observed in the overall study population; there were no notable trends observed within the cohorts in terms of clinical response in any of the analysis sets.

Table 64. Favourable Clinical Response at TOC by Pyelonephritis Diagnosis and Treatment Group (ITT, micro-ITT, CE, and ME Analysis Sets)

Pyelonephritis Diagnosis at Screening	Analysis Set	CAZ-AVI N	CAZ-AVI n	CAZ-AVI Favourable Response Rate (95% CI)[a]	CEF N	CEF n	CEF Favourable Response Rate (95% CI)[a]
Yes	ITT	55	49	89.1 (78.9, 95.3)	25	21	84.0 (66.3, 94.3)
	micro-ITT	45	40	88.9 (77.3, 95.6)	20	17	85.0 (65.1, 95.6)
	CE at TOC	40	38	95.0 (84.9, 98.9)	17	15	88.2 (67.3, 97.5)
	ME at TOC	34	32	94.1 (82.4, 98.8)	15	13	86.7 (63.7, 97.1)
No	ITT	13	10	76.9 (50.3, 93.0)	4	3	75.0 (28.4, 97.2)
	micro-ITT	9	8	88.9 (58.6, 98.8)	3	2	66.7 (17.7, 96.1)
	CE at TOC	9	8	88.9 (58.6, 98.8)	3	2	66.7 (17.7, 96.1)
	ME at TOC	7	6	85.7 (49.9, 98.4)	1	1	100 (14.7, 100)

Source: Tables 14.2.1.5, 14.2.1.6, 14.2.1.7, and 14.2.1.8.
The denominator for percentages is the total number of patients in the respective analysis set at the given visit, denoted by N within each section. A favourable clinical outcome is defined as clinical cure, or clinical improvement. See SAP Section 3.3.1 for rules regarding clinical outcome definitions.
CAZ-AVI = ceftazidime avibactam; CE = clinically evaluable; CEF = cefepime; CI = confidence interval; ITT = intent-to-treat; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; N/n = number of patients; SAP = statistical analysis plan; TOC = test of cure.
[a] A two-sided 95% CI computed using Jeffrey's method.

In the micro-ITT analysis set, favourable clinical responses by pathogen at TOC for infections due to *E. coli* was >81% for both treatment groups (87.8% for the CAZ-AVI group and 81.8% for the CEF group). The results for the ME analysis set were similar to the results for the micro-ITT population; most patients had favorable clinical responses by pathogen at TOC for infections due to *E. coli* (91.9% for the CAZ-AVI group and 86.7% for the CEF group).

Table 65. Per-Patient Favourable Microbiological Response by Visit and Treatment Group (micro-ITT Analysis Set)

Visit	Favorable Response; n (%)	
	CAZ-AVI N = 54 n (%)	CEF N = 23 n (%)
EOIV	44 (81.5)	18 (78.3)
EOT	45 (83.3)	17 (73.9)
TOC	43 (79.6)	14 (60.9)
LFU	16 (29.6)	4 (17.4)

Source: Table 14.2.1.12. The denominator for percentages is the number of patients in the micro-ITT analysis set. Per patient favourable microbiological response is defined as the eradication of all pathogens. CAZ-AVI = ceftazidime avibactam; CEF = cefepime; EOIV = End of Intravenous treatment; EOT = end of treatment; LFU = late follow-up; micro-ITT = microbiological intent-to-treat; N/n = number of patients; TOC = test of cure.

Favourable microbiological response rates were lower at the LFU visit for both treatment groups than at the preceding visits. This was primarily due to a high percentage of indeterminate responses (i.e., source specimen was not available to culture) at the LFU visit (CAZ-AVI: n = 32 [59.3%]; CEF: n = 14 [60.9%]). Since the LFU visit could have been performed via telephone for any patient who had not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC, a urine culture was not required at this visit and was therefore not collected in a large proportion of the patients.

Clinical Relapse at LFU

A total of 4 (5.9%) patients in the CAZ-AVI group were reported to have clinical relapse in the ITT and 4 (7.4%) patients in the micro-ITT analysis sets. This number was 3 patients (6.8%) in the CE analysis set and 2 (12.5%) patients in the ME analysis set. Of the 4 patients, 3 had underlying urological abnormalities and complicating factors reported at baseline. No patients had clinical relapse at LFU in the CEF group in any of the four efficacy analysis sets.

Table 66. Per-Pathogen Favourable Microbiological Response Rate in >2 Isolates in Either Treatment Group at TOC by Pathogen and Treatment Group (micro-ITT and ME Analysis Sets)

Baseline Pathogen Group Baseline Pathogen	Number (%) of patients	
	CAZ-AVI	CEF
micro-ITT Analysis Set	N = 54	N = 23
Enterobacteriaceae n (%)	43/54 (79.6)	14/23 (60.9)
Escherichia coli n (%)	39/49 (79.6)	13/22 (59.1)
ME Analysis Set	N = 41	N = 16
Enterobacteriaceae n (%)	36/41 (87.8)	11/16 (68.8)
Escherichia coli n (%)	32/37 (86.5)	10/15 (66.7)

Source: Tables 14.2.1.14 and 14.2.1.15. The denominator for percentages is the total number of pathogens in the specified analysis set (at TOC) at the given visit with that baseline pathogen. A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group. CAZ-AVI = ceftazidime-avibactam; CEF=cefepime; ME=microbiologically evaluable; micro-ITT=microbiological intent-to-treat; N/n=number of patients; TOC=test of cure.

No uropathogens were identified in the blood in the micro-ITT and ME at TOC analysis sets.

The CHMP noted that the total proportion of patients with a baseline diagnosis of AP was >80% and the relative frequency was comparable between the two treatment groups, i.e. 81% (55/68) in the CAZ-AVI group and 86% (25/29) in the CEF group. The clinical success rates at the TOC visit remained high for patients treated with CAZ-AVI regardless of the diagnosis of AP and was consistent with the overall clinical response. For patient treated with CEF, a higher proportion of patients with AP in the micro-ITT analysis set at TOC had a favourable clinical response compared to those without AP. The opposite was seen for patients treated with CEF in the ME at TOC analysis set. However, caution should be taken when interpreting these results, as only a limited number of patients without AP have been included in the separate analysis sets.

Apparently, the microbiological eradication rates were low at the LFU visit in both treatment groups, i.e. 29.6% in the CAZ-AVI group and 17.4% in the CEF group. According to the MAH, this was mainly due to indeterminate responses for around 60% of the patients in each treatment group because the visit could have been done via phone, and thus only more complicated cases were at the hospital, where sampling and culture was done. Consistent with the explanation given by the MAH, the proportions of clinical evaluable patients with a favourable clinical response at LFU were high in both treatment groups, i.e. 93.2% and 100% in the CAZ-AVI and CEF groups, respectively, implying that most of the patients had a sustained response to the study treatment. It is noted, though, that there were four patients who had a relapse in the CAZ-AVI group. Three of these patients had underlying urological abnormalities and complicating factors and two of them had E.coli as baseline pathogen. It is acknowledged that no incidences of pathogens with increasing MIC with any of the study drug were observed, despite clinical relapses in four of the patients treated with CAZ-AVI. However, none of the patients in the CAZ group had relapse, and in general, patient's baseline characteristics were balanced between the treatment groups. Considering uncertain adequacy of CAZ-AVI exposure, this is not unexpected.

The eradication rates of infections due to *E. coli* in the micro-ITT analysis set at the TOC visit were 79.6% in the CAZ-AVI group and 59.1% in the CEF group, and 86.5% and 66.7%, respectively, in the ME analysis set.

Pathogen susceptibility, MIC and persistence

The MIC distributions for each baseline pathogen were presented based on CAZ, CAZ-AVI and CEF MICs. Additionally, for pathogens for which the number was 10 or more, the MIC to inhibit the growth of 50% (MIC_{50}), and the MIC to inhibit the growth of 90% of organisms (MIC_{90}) were reported.

Susceptibility testing methods and interpretive results were based upon CLSI (Clinical and laboratory standards institute) criteria for CEF and CAZ, while the interpretation for CAZ-AVI was according to the FDA label.

For the 46 *E. coli* isolates in the CAZ-AVI group, the CAZ-AVI MIC range was ≤0.015-0.25 mg/L and the MIC_{90} was 0.12 mg/L. For the 20 *E. coli* isolates in the CEF group, the CAZ-AVI MIC range was 0.06-0.25 mg/L and the MIC_{90} was 0.12 mg/L.

For the 46 *E. coli* isolates in the CAZ-AVI group, the CAZ MIC range was ≤0.06-0.64 mg/L and MIC_{90} was 0.0.25 mg/L. For the 20 *E. coli* isolates in the CEF group, the CAZ MIC range was 0.12-16.0 mg/L and MIC_{90} was 0.0.25 mg/L.

For the 46 *E. coli* isolates in the CAZ-AVI group, the CEF MIC range was ≤0.015->16.0 mg/L and MIC_{90} was 0.06 mg/L. For the 20 *E. coli* isolates in the CEF group, the CEF MIC range was ≤0.015->16.0 mg/L and MIC_{90} was 0.25 mg/L.

Overall, there were no isolates tested that were reported as being non-susceptible to CAZ-AVI. There were 2 patients (both in Cohort 2) in the CAZ-AVI group infected with ceftazidime non-susceptible (CAZ-NS) *E. coli*; one patient had *E. coli* at baseline that was resistant to ceftazidime (MIC = 32 µg/mL) and had favourable clinical responses at all time points; one patient had *E. coli* at baseline that was resistant to ceftazidime (MIC = 64 µg/mL) and had favourable clinical responses at all time points except for the EOT visit, at which the response was indeterminate. The one patient in the CEF group (in Cohort 3) infected with CAZ-NS *E. coli* had an isolate that was also resistant to CEF at baseline (MIC = >16 µg/mL) and was a clinical failure.

There were 5 patients in each treatment group (CAZ-AVI: 5/54 [9.3%] and CEF: 5/23 [21.7%]) at TOC with persistent Enterobacteriaceae infections. At LFU, there were 6/54 patients with persistent pathogens (11.1%) in the CAZ-AVI group and 5/23 (21.7%) in the CEF group. All patients who had a microbiological response of persistence (EOIV, EOT, TOC and/or LFU) in the micro-ITT analysis set had *E. coli* as a baseline pathogen. The microbiological outcome of persistence at a particular visit was carried forward to subsequent visits. There were no reported cases of pathogens with reported persistence with increasing MIC in either treatment group.

Review of per-pathogen responses by MIC did not identify any notable trends. For the predominant pathogen (E. coli), there was no indication that increasing MIC was associated with a lower favourable response rate in either treatment group.

Treatment emergent infections

A total of 3 patients (7.3%) in the CAZ-AVI group had treatment emergent infections, whereas none were occurring in the CEF group as assessed by the ECMA review committee. Of the three new infections, two patients were reported to have both underlying urological abnormalities and complicating factors.

In addition to those emergent infections as assessed by the ECMA review committee, there were five cases of new infection reported . These 5 cases were reviewed by the study team and determined not to be new infections. None of the 5 cases met the definition in the study SAP: "*A urine culture identified pathogen other than a baseline pathogen at any time after study treatment has finished along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy*."

The CHMP noted that, at TOC and LFU, a high proportion of patients in the micro-ITT population for both treatment groups had persistent Enterobacteriaceae infections, i.e. 9.3% (5/54) and 11.1% (6/54; 1 additional patient), respectively, in the CAZ-AVI group, and 21.7% (5/23) for both visits in the CEF group. All patients who had a microbiological response of persistence had an infection caused by *E. coli*. Considering uncertain adequacy of CAZ-AVI exposure, this is not unexpected.

No new infections occurred during the study in the CEF treatment group, whereas three patients (7.3%) had treatment emergent infections in the CAZ-AVI group. Two of these patients had both complicating factors and underlying urological abnormalities.

Summary of main studies

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

Table 67. Summary of Efficacy for trial C3591004 (D4280C00015) cIAIs

Title: A Single Blind, Randomized, Multi-centre, Active Controlled, Trial to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam When Given in Combination With Metronidazole, Compared With Meropenem, in Children From 3 Months to Less Than 18 Years of Age With Complicated Intra-Abdominal Infections (cIAIs)			
Study identifier	C3591004 (D4280C00015)		
Design	A Single Blind, Randomized, Multi-centre, Active Controlled study. Enrolled patients were divided to four Cohorts, according to their age and stratified according to renal function and weight. Patients received CAZ-AVI+MTZ in the treatment group and MER in the comparator group.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years not applicable not applicable	
Hypothesis	Exploratory: To evaluate the safety and tolerability of ceftazidime and avibactam (CAZ-AVI) plus metronidazole given at the selected dose regimen versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI		
Treatments groups	CAZ-AVI+MTZ		<u>CrCl ≥50 mL/min</u> 6 years to <18 years, ≥40 kg: **2000 mg CAZ /500 mg AVI** 6 years to <18 years, <40 kg: **50 mg/kg CAZ/12.5 mg/kg AVI** 6 months to <6 years, all weight: **50 mg/kg CAZ/12.5 mg/kg AVI** 3 months to <6 months, all weight: **40 mg/kg CAZ/ 10 mg/kg AVI** <u>CrCl ≥30 to <50 mL/min</u> 6 years to <18 years, ≥40 kg: **1000 mg CAZ/ 250 mg AVI** 6 years to <18 years, <40 kg: **25 mg/kg CAZ/ 6.25 mg/kg AVI** 6 months to <6 years, all weight: **25 mg/kg CAZ/ 6.25 mg/kg AVI** 3 months to <6 months, all weight: **20 mg/kg CAZ/ 5 mg/kg AVI** MTZ: suggested regimen 10 mg/kg IV q8 n = 60 Median treatment duration in all cohorts was 12.0 days, min 2, max 17.
	MER		20 mg/kg q8 Median treatment duration in all cohorts was 13.0 days, min 6, max 20. n = 21
Endpoints and definitions	Primary endpoint	Safety	Adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), physical examination, and laboratory safety tests

	Secondary endpoints	Efficacy	Clinical response at End of 72 hours' treatment, End of Intravenous Treatment (EOIV), End of Treatment (EOT), and Test of Cure (TOC)
		Efficacy	Microbiological response at EOIV, EOT, TOC, and Late Follow-up (LFU)
		Efficacy	Clinical relapse at LFU
		Efficacy	Emergent infections
Database lock	Data not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy analysis of data in this study was based on 4 analysis sets of patients (intent-to-treat [ITT], microbiological ITT [micro-ITT], clinically evaluable [CE], and microbiologically evaluable [ME] analysis sets). The data in the table is presented for the ITT set.		
Descriptive statistics and estimate variability	Treatment group	CAZ-AVI+MTZ	MER
	Number of subjects	60	21
	Clinical response End of 72 hours % of patients	93.4	90.9
	(95% CI)	85.2, 97.7	73.9, 98.1
	Clinical response at the End of IV treatment % of patients	96.7	100.0
	(95% CI)	89.9, 99.3	89.3, 100.0
	Clinical response at End of treatment % of patients (95% CI)	91.8 83.0, 96.8	100.0 89.3, 100.0
	Clinical response at Test of Cure % of patients (95% CI)	91.8 83.0, 96.8	95.5 80.7, 99.5
	Clinical response at Late Follow Up % of patients (95% CI)	91.8 83.0, 96.8	95.5 80.7, 99.5
Notes	Efficacy was not the primary endpoints for this study.		

Table 68. Summary of Efficacy for trial C3591005 (D4280C00016) cUTI

Title: A Single Blind, Randomized, Multi-Centre, Active Controlled, Trial to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam Compared with Cefepime in Children From 3 Months to Less Than 18 Years of Age With Complicated Urinary Tract Infections (cUTIs)		
Study identifier	C3591005 (D4280C00016)	
Design	A Single Blind, Randomized, Multi-Centre, Active Controlled clinical trial. Enrolled patients were divided to four Cohorts, according to their age and stratified according to renal function and weight. Patients received CAZ-AVI in the treatment group and CEF in the comparator group.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years not applicable not applicable
Hypothesis	Exploratory: To evaluate the safety and tolerability of ceftazidime and avibactam (CAZ-AVI) given at the selected dose regimen versus cefepime in paediatric patients aged ≥ 3 months to <18 years with cUTI.	

Treatments groups	CAZ-AVI+MTZ		CrCl ≥50 mL/min 6 years to <18 years, ≥40 kg: **2000 mg CAZ /500 mg AVI** 6 years to <18 years, <40 kg: **50 mg/kg CAZ/12.5 mg/kg AVI** 6 months to <6 years, all weight: **50 mg/kg CAZ/12.5 mg/kg AVI** 3 months to <6 months, all weight: **40 mg/kg CAZ/ 10 mg/kg AVI** CrCl ≥30 to <50 mL/min 6 years to <18 years, ≥40 kg: **1000 mg CAZ/ 250 mg AVI** 6 years to <18 years, <40 kg: **25 mg/kg CAZ/ 6.25 mg/kg AVI** 6 months to <6 years, all weight: **25 mg/kg CAZ/ 6.25 mg/kg AVI** 3 months to <6 months, all weight: **20 mg/kg CAZ/ 5 mg/kg AVI** MTZ: suggested regimen 10 mg/kg IV q8 n = 67 Median treatment duration in all cohorts was 11.0 days, min 1, max 17.
	CEF		1000 mg and 2000 mg to 50 mg/kg IV q12 h Median treatment duration in all cohorts was 11.5 days, min 2, max 27. n = 28
Endpoints and definitions	Primary endpoint	Safety	Adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), physical examination, and laboratory safety tests
	Secondary endpoints	Efficacy	Clinical response at End of 72 hours' treatment, End of Intravenous Treatment (EOIV), End of Treatment (EOT), and Test of Cure (TOC)
		Efficacy	Microbiological response at EOIV, EOT, TOC, and Late Follow-up (LFU)
		Efficacy	Clinical relapse at LFU
		Efficacy	Emergent infections
Database lock	Data not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy analysis of data in this study was based on 4 analysis sets of patients (intent-to-treat [ITT], microbiological ITT [micro-ITT], clinically evaluable [CE], and microbiologically evaluable [ME] analysis sets). The data in the table is presented for the ITT set.		
Descriptive statistics and estimate variability	Treatment group	CAZ-AVI	CEF
	Number of subjects	68	29
	Clinical response End of 72 hours % of patients	88.2	86.2
	(95% CI)	79.0, 94.3	70.5, 95.2
	Clinical response at the End of IV treatment % of patients	91.2	89.7
	(95% CI)	82.7, 96.2	74.9, 97.0
	Clinical response at End of treatment % of patients (95% CI)	88.2 79.0, 94.3	89.7 74.9, 97.0
	Clinical response at Test of Cure % of patients (95% CI)	86.8 77.2, 93.2	82.8 66.3, 93.1

	Clinical response at Late Follow Up % of patients (95% CI)	80.9 70.4, 88.8	82.8 66.3, 93.1
Notes	Efficacy was not the primary endpoints for this study.		

Ancillary analyses

N/A

2.5.2. Discussion on clinical efficacy

This variation application is intended to broaden the approved indication for CAZ-AVI to include paediatric population 3 months to <18 years of age with complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI).

Design and conduct of clinical studies

The MAH conducted two phase 2 studies that aimed to include children from 3 months to less than 18 years of age with cIAI (c3591004) and cUTI (study C3591005). The phase 2 studies were open label, observer-blinded, randomised, active-controlled studies, in which efficacy was defined as a secondary objective, and hence was not powered to determine efficacy. According to draft "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/187859/2017)", no appropriately powered efficacy study is requested in the paediatric population. Efficacy can be extrapolated from data in adults provided that similar exposure of CAZ-AVI is achieved and a sufficiently amount of safety data is collected in the paediatric age groups. Thus, the efficacy data in this submission are only descriptive and this is considered acceptable.

The MAH chose meropenem as comparator in the cIAI study and cefepime (CEF) in the cUTI study. Both antibacterial agents are approved and widely used for treating paediatric patients with cIAI and cUTI, including pyelonephritis, respectively.

A high proportion of patients in both studies received concomitant systemic antibiotics (86% overall in the cIAI study and 42% in the cUTI study). The MAH enlightens that this was due to the fact that the time points for starting/ending the dosing of concomitant systemic antibiotics were not collected. Systemic antibiotics taken during Day 1 of IV study medication administration therefore had been reported as both prior and concomitant medications. In addition, there is a marked difference between the two treatment groups with a higher proportion of concomitant antibiotics used in the CEF group compared to the CAZ-AVI group (53.6% vs. 37.3%). This could potentially have influenced both the type and frequencies of AEs reported within the two treatment groups. Furthermore, it is noted that the investigators have only reported two cIAI patients and one cUTI patient who had important protocol deviations related to receipt of prohibited concomitant medications across all cohorts. Lack of data collection on the duration of prior/concomitant treatments is considered a weakness of the conduct of the study. However, considering that the efficacy should be extrapolated from adults this issue will not be further pursued with regards to efficacy. Please refer to the clinical pharmacology section for more information regarding the extrapolation.

One of the main changes in amendment 2 of the protocol for both studies were removal of a specific exclusion criterion related to immunocompromised patients (enacted in amendment 2). Since immunocompromised patients are more likely to develop infections and therefore constitute an important patient population intended for parenteral antibiotic therapy in clinical practice, efficacy in these patients is

relevant for the evaluation of the efficacy outcomes of CAZ-AVI. The MAH was therefore asked in the previous round to submit an overview of the number of immunocompromised patients enrolled in the two studies, and provide an overview of the overall efficacy outcomes related to the baseline pathogens in these patients compared to other patients who were not immunocompromised. The MAH clarified in the response to this request that only one patient enrolled in the cUTI study potentially could have been immunocompromised. This apparent lack of enrolment of immunocompromised patients in the two clinical studies could be expected, since these patients initially were excluded from being enrolled and the two amendments, which allowed enrolment of immunocompromised patients, were implemented relative late prior to LSLV in both studies. The MAH informs that the remaining paediatric studies that are being conducted as part of a PIP (Decision P/0062/2017), which include study C3591024 in neonates and study C3591024 in patients with HAP/VAP (single-dose PK), will allow for enrolment of immunocompromised patients.

Complicated intra-abdominal infection

Initially, the protocol was approved by the PDCO based on inclusion of 80% of patient with focus of infection in the appendix. However, the protocol was later amended to allow for inclusion of a higher proportion of patients (90%) with infection originating from appendix. It is acknowledged that appendicitis is the most commonly diagnosed cIAI in children. Furthermore, since the population pharmacokinetics (PK) modelling demonstrates that disease severity has minimal effect on CAZ-AVI exposure, the high proportion of patients with appendicitis is not considered to affect the applicability of the study results to cIAI patients with non-appendicitis type infections. Therefore, the change to include 90% appendicitis is considered acceptable.

Efficacy data and additional analyses

See below in the section regarding assessment of paediatric data on clinical efficacy.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

Complicated intra-abdominal infection

In total 61 subjects were included to receive CAZ-AVI + MTZ in the study compared to 22 subjects in the meropenem group. The demographic and baseline characteristics were balanced between the two groups. European subjects were adequately represented; 64% male with median age 11.0 years in the CAZ-AVI plus MTZ group.

Most patients (90%) in both treatment groups in the ITT and CE population had appendix as primary focus of infection and was diagnosed as appendiceal perforation or peri-appendiceal abscess. Recruitment in the lowest age group (3 to < 6 years) was low (n=6) and no children below the age of 2 years were included to receive CAZ-AVI + MTZ. Although very few or no patients were included in the youngest age cohorts, the efficacy results presented in the initial MA application for the adult cIAI indication can be extrapolated to the paediatric population provided similar exposure of CAZ-AVI. In addition, efficacy observed in the youngest cUTI children could be extrapolated to the same age cohorts for the cIAI patients as these two infectious diseases are expected to have similar pathophysiology.

The microbiological intent-to treat (micro-ITT) population, which included all patients who had at least one baseline intra-abdominal pathogen, consisted of 69 patients (CAZ-AVY + MTZ, n=50; meropenem, n=19). The predominant baseline pathogens were *E. coli* (79.7%) and *P. aeruginosa* (33.3%).

A high proportion of patients completed the trial (98%), with no major imbalances between treatment groups. Premature discontinuations were few and evenly distributed between treatment groups.

In general, across all analysis sets, favourable clinical response rates of $\geq$ 90% were observed at the End of 72 hours IV visit and were sustained through the LFU visit for both treatment groups. The clinical response rates in the individual cohorts were in general consistent with those observed in the overall study population, except for cohort 1 (12-18 years of age). In this cohort, it seems to be numerical lower clinical cure rates across all analysis populations at TOC. Although efficacy in the paediatric population could be extrapolated from adults, it should be noted that it was only in cohort 1 all clinical failures were identified of CAZ-AVI in this specific age group. The MAH is therefore asked to clarify the dose and duration of IV therapy received, as well as the duration and type of oral treatment given to the four patients who had a clinical failure, and the one who was indeterminate.

In the micro-ITT population, clinical response rates at TOC for the predominant pathogens, *E.coli* and *P.aeruginosa* were >90% and >85%, respectively for patients treated with CAZ-AVI + MTZ, and >92% and >88%, respectively for patients treated with meropenem. Approximately the same results were observed for the ME population. Most microbiological outcomes were presumed eradicated based on clinical response; showing a similar pattern to the per-patient clinical response for the pathogens isolated. It is not unexpected for an indication like cIAI that the majority of the microbiological results were based on presumed eradication. Review of per-pathogen responses by MIC did not identify any trends. For predominant pathogens, such as *E. coli* and *P. aeruginosa*, there was no indication that increasing MICs were associated with a lower favourable response rate in either treatment group.

Complicated urinary tract infections (UTIs)

Of the 101 enrolled cUTI patients, 97 were randomised in a 3:1 ratio to receive CAZ-AVI or CEF and 95 received treatment (67 were treated in the CAZ-AVI group and 28 were treated in the CEF group). The paediatric age groups who received CAZ-AVI were as follows: 12 to <18 years (n=13), 6 to < 12 years (n=17), 3 to < 6 years (n=11), and i3 months of age to <2 years (n=27). The inclusion of patients was well balanced between the four different age cohorts.

The demographic and baseline characteristics appear relatively well balanced between the treatment groups. The majority of cUTI patients were diagnosed with acute pyelonephritis at screening, i.e. 82.1% and 85.7% in the CAZ-AVI and CEF groups, respectively. The median age of the enrolled patients was 3.87 years. The majority were female, White, enrolled in European, and 66.3% had normal renal function (i.e. CrCl ≥ 80 ml/min/1.73 m2). Most of the patents did not have any complicating factors of the urinary tract infections beyond the requirements from the inclusion criteria (77.9% overall) or had any urological abnormalities (84.2% overall).

The intent-to-treat (ITT) population consisted of 95 patients (CAZ-AVI, n=67, CEF, n= 28) who were randomised and received treatment. A comparable exposure was observed across the different age cohorts within the two treatment groups.

Approximately 80% of the patients in each treatment group belonged to the micro-ITT analysis set with a baseline pathogen, and approximately 70% in each treatment group were considered clinically evaluable at the TOC visit. None of the patients in the micro-ITT analysis set was infected with Gram-negative pathogens other than *Enterobacteriaceae*. The majority of patients in both treatment groups (>90%) who had microbiologically confirmed disease were infected by *E.coli*, which is the most common infectious cause to UTI, particular if it is a first infection.

In general, favourable clinical response rates were high across all analysis sets in both treatment groups and the rates were sustained from the end of the 72 hours visit through to the EOT visit, with responses remaining ≥ 80% at LFU for the ITT, micro-ITT, and CE analysis sets of both treatment groups. At the TOC visit, 86.8% and 82.6% in the ITT population of the CAZ-AVI and CEF groups, respectively, had a favourable clinical response. No numerical trends pointed to any specific efficacy concern for CAZ-AVI.

The per-patient microbiological success rates in the micro-ITT analysis set at both the EOIV and TOC visits were lower than the clinical response rates in both treatment groups. The eradication rates at the TOC visit were 79.6% for the CAZ-AVI group compared to 60.9% for the CEF group, indicating that the pathogens were more susceptible to CAZ-AVI. Moreover, favourable combined response rates at the EOIV visit for the micro-ITT analysis set were 79.6% in the CAZ-AVI group and 78.3% in the CEF group. The combined success rates were numerical lower at the TOC visit, i.e. 72.2% for the CAZ-AVI group and 60.9% for the CEF group. Hence, the combined clinical and microbiological success rates observed in the micro-ITT population at the TOC visit points to a numerical trend of better efficacy of CAZ-AVI compared to CEF. However, the study was not statistically powered to demonstrate efficacy.

The total proportion of patients with a baseline diagnosis of AP was >80% and the relative frequency was comparable between the two treatment groups, i.e. 81% (55/68) in the CAZ-AVI group and 86% (25/29) in the CEF group. The clinical success rates at the TOC visit remained high for patients treated with CAZ-AVI regardless of the diagnosis of AP and was consistent with the overall clinical response. For patient treated with CEF, a higher proportion of patients with AP in the micro-ITT analysis set at TOC had a favourable clinical response compared to those without AP. The opposite was seen for patients treated with CEF in the ME at TOC analysis set. However, caution should be taken when interpreting the results as only a limited number of patients without AP have been included in the separate analysis sets.

The eradication rates of infections due to *E.coli* in the micro-ITT analysis set at the TOC visit were 79.6% in the CAZ-AVI group and 59.1% in the CEF group, and 86.5% and 66.7%, respectively, in the ME analysis set. The microbiological eradication rates appeared to be low at the LFU visit in both treatment groups, i.e. 29.6% in the CAZ-AVI group and 17.4% in the CEF group. According to the MAH, this was mainly due to indeterminate responses for around 60% of the patients in each treatment group. In addition, the proportions of clinical evaluable patients with a favourable clinical response at LFU were high in both treatment groups, i.e. 93.2% and 100% in the CAZ-AVI and CEF groups, respectively, implying that most of the patients had a sustained clinical response to the study treatment.

A higher proportion of patients in the micro-ITT population at the TOC and LFU visits who were treated with CEF compared to CAZ-AVI had persistent *Enterobacteriaceae* infections, i.e. 21.7% for both visits in the CEF group, and 9.3% and 11.1% (1 additional patient) in the CAZ-AVI group, respectively. All patients who had a microbiological response of persistence had an infection caused by *E. coli*. Although the number of patients in each treatment group is low, the clinical responses observed at TOC and LFU indicate a numerical trend in favour of CAZ-AVI.

No new infections occurred during the study in the CEF treatment group, whereas three patients (7.3%) had treatment emergent infections in the CAZ-AVI group. Two of these patients had both underlying urological abnormalities and complicating factors rendering them more susceptible for a new infection.

2.5.3. Conclusions on the clinical efficacy

The CHMP considered the submitted efficacy data to support the extension of indication for CAZ-AVI to include treatment of the paediatric population from age 3 months to 18 years with cUTI and cIAI.

2.6. 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, *Clostridium difficile*-associated diarrhoea, renal impairment, concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products, and direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia.

An overview is given on the important identified and potential risks in adults in the initial RMP submission and which were approved in the initial MAA in 2016.

Table 69. Listing of Important Identified and Potential Risks in the Initial RMP Submission

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

The assessment of safety in children with cIAIs and cUTis is based on data from two phase 2 paediatric studies and the population PK modelling/simulation analyses that are submitted to support the current extension of the indication.

The present application for extension of indication to include children presents a summary of pooled safety data from these two Phase 2 paediatric studies:

- Study C3591004 (Paediatric Investigation Plan (PIP) Study 4, previously referred to as Study D4280C00015 by AstraZeneca): A Single Blind, Randomised, Multi-centre, Active Controlled, Trial to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam When given in Combination with Metronidazole, Compared with Meropenem, in Children from 3 months to Less Than 18 years of Age with Complicated Intra-Abdominal Infections (cIAIs).
- Study C3591005 (PIP Study 5, previously referred to as Study D4280C00016 by AstraZeneca): A Single Blind, Randomised, Multi-centre, Active Controlled, Trial to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam Compared With Cefepime In Children From 3 Months to Less Than 18 Years of Age With Complicated Urinary Tract Infections (cUTIs).

These studies were conducted as part of the agreed European Union (EU) Paediatric Investigation Plan (PIP). Both studies were initially sponsored by AstraZeneca. Sponsorship for Study D4280C00015 was transferred to Pfizer, Inc, on 17 July 2017, and for Study D4280C00016 was transferred on 18 September 2017. For the purposes of this submission, Studies D4280C00015 and D4280C00016, are referred to by the Pfizer study numbers of C3591004 and C3591005, respectively.

A PDCO/EMA compliance report was adopted on 01 February 2019 in scope of procedure EMEA-C2-001313-PIP01-12-M08.

The paediatric data were analysed in comparison with the known safety profile of ceftazidime monotherapy in children, as presented in the United Kingdom (UK) Summary of Product Characteristics (SmPC) and the United States Prescribing Information (USPI), and with the observed safety profile of CAZ-AVI from the pooled Phase 2/3 adult studies.

There are 2 planned clinical studies in paediatric patients: a 2 part, single- and multiple dose study in neonates (Study D4280C00017, also known as C3591024, or PIP study 6) and a single dose PK study in paediatric patients with HAP/VAP (Study D4280C00028, also known as C3591025, or PIP study 8) (Table on clinical studies given in Section 3).

According to Draft guideline EMA/187859/2017 "Addendum to guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements", no appropriately powered efficacy studies are requested in the paediatric population as efficacy can be extrapolated from adults provided that similar exposure is achieved in the paediatric population. Furthermore, sufficient safety data have to be generated with the intended dose regimen in the paediatric population. In both paediatric studies submitted to support the indication extensions, safety and tolerability are primary endpoint, while pharmacokinetic and efficacy variables are secondary.

The extension of indication to include paediatric patients aged 3 months to less than 18 years for Zavicefta was suggested by the CHMP to be further extended to include the other approved Zavicefta indications HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options, in addition to cIAI and cUTI.

The CHMP noted that this safety assessment is based on the two phase 2 single-blind, randomized, multicenter active-controlled studies of paediatric patients aged ≥3 months to 18 years. This safety evaluation presents a summary of the safety data and emphasises the pooled safety data from the two paediatric studies. Details from the individual studies are presented when applicable.

No clinical study results have yet been reported for children with the indication of HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options. These two indications are based on extrapolation from adult indication.

Patient exposure

The first study of CAZ-AVI in paediatric patients (Study D4280C00014) was a Phase 1, single-dose, pharmacokinetic (PK), and safety study in 32 paediatric patients with ages ranging from 3 months to <18 years, with suspected or confirmed bacterial infection for which they were receiving other systemic antibiotic therapy. Data from this study were used in PK/pharmacodynamic (PD) modeling and simulations to support dose selection for the subsequent Phase 2 Studies C3591004 and C3591005. Studies C3591004 and C3591005 were initiated in 2015 and both studies have now been completed, along with population PK (popPK) and PK/PD target attainment analyses to support paediatric dose regimens (CAZ-MS-PED-02).

The safety assessment is based on a total of 128 children exposed in the 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 D4280C00015 [C3591004]) and cUTI (Study D4280C00016 [C3591005]). In both studies, patients were allocated to 1 of 4 cohorts based on age. Randomisation was stratified as follows:

- Cohort 1: Patients aged from 12 years to <18 years;

- Cohort 2: Patients aged from 6 years to <12 years;
- Cohort 3: Patients aged from 2 years to <6 years;
- Cohort 4: Patients aged from 3 months to <2 years, comprising Cohorts 4a and 4b as follows:
- Cohort 4a: Patients aged from 1 year to <2 years;
- Cohort 4b: Patients aged from 3 months to <1 year.

Patients were randomised 3:1 to the CAZ-AVI ± metronidazole or comparator treatment groups. The proposed sample size for each study was 80 evaluable patients comprised of a minimum of 60 and 20 patients, respectively, from the CAZ-AVI ± metronidazole and comparator groups. An evaluable patient was defined as a subject having completed at least 72 hours of treatment (3 full days). The sample size was based on the probability of observing a 'rare' safety event. The 'rare' term used in this section is not based on the regulatory definition but is instead intended to reflect uncommon events with an underlying incidence rate of 3%. A total of at least 120 patients were to be treated with CAZ-AVI in both studies combined, when assuming an underlying incidence rate of 3% for a specific 'rare' event, to ensure that the probability of observing such an event in at least 1 patient treated with CAZ-AVI exceeded 95%.

A description of both Phase 2 studies is provided in Table 70.

Table 70. Description of Phase 2 Studies Pertinent to the Analysis of Safety in Children*

Study ID Study Title	Comparator Dosage Regimen	CAZ-AVI Dosage Regimen	Total Safety Population*	Safety Results
Study C3591004 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 children 3 months to less than 18 years of age with cIAI.	Meropenem: 20 mg/kg every 8 hours (±1 hour) infused over approximately 15 to 30 minutes or up to 1 hour (or infusion duration as per local guidelines)	Multiple doses of CAZ AVI (ceftazidime 50 mg/kg + avibactam 12.5 mg/kg for patients aged 6 months to <18 years up to a maximum of 2000 mg + avibactam 500 mg based on weight ≥40 kg; 2 hour IV infusion) followed by MTZ 500 mg (1 hour IV infusion) q8h for a minimum of 72 hours (3 full days) before having the option to switch to an oral therapy on Day 4.	83 total patients 61 CAZ-AVI plus MTZ/ 22 meropenem Cohort 1: 30 total patients 22 CAZ-AVI + MTZ/8 meropenem Cohort 2: 43 total patients 33 CAZ-AVI + MTZ 10 meropenem Cohort 3: 9 total patients 6 CAZ-AVI + MTZ/ 3 meropenem Cohort 4: 1 patient (meropenem)	AEs: 52.5% CAZ-AVI plus MTZ; 59.1% meropenem Related AEs: 1.6% CAZ-AVI plus MTZ; 9.4% meropenem SAEs: 8.2% CAZ-AVI plus MTZ; 4.5% meropenem Deaths (including deaths due to disease progression): 0 CAZ-AVI plus MTZ; 0 meropenem DAEs: 0 CAZ-AVI plus MTZ; 0 meropenem
Study C3591005 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 children 3 months to less than 18 years of age with cUTI.	Multiple doses of cefepime received at the dose, schedule and infusion duration as recommended in the local prescribing information or as prescribed by the investigator. The maximum dose of cefepime in any single infusion should not have exceeded 2000 mg	Multiple doses of CAZ-AVI (ceftazidime 50 mg/kg + avibactam 12.5 mg/kg for patients aged 6 months to <18 years up to a maximum of 2000 mg + avibactam 500 mg based on weight ≥40 kg; 2-hour IV infusion) q8h for 5 to 14 days	95 total patients 67 CAZ-AVI/28 cefepime Cohort 1 19 total patients 13 CAZ-AVI / 6 cefepime Cohort 2 22 total patients 17 CAZ-AVI/ 5 cefepime Cohort 3 18 total patients 11 CAZ-AVI/ 7 cefepime Cohort 4 36 total patients 26 CAZ-AVI/10 cefepime	AEs: 53.7% CAZ-AVI; 53.6% cefepime Related AEs: 10.4% CAZ-AVI; 3.6% cefepime SAEs: 11.9% CAZ-AVI; 7.1% cefepime Deaths (including deaths due to disease progression): 0 CAZ-AVI; 0 cefepime DAEs: 4.5% CAZ-AVI; 0% cefepime

AEs = Adverse events; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; DEAs = discontinuations due to AEs; MTZ = metronidazole; PK = pharmacokinetic; q8h = quaque octa hora (every 8 hours); SAE = serious adverse events.
* Cohort 1: Patients aged from 12 years to <18 years; Cohort 2: Patients aged from 6 years to <12 years; Cohort 3: Patients aged from 2 years to <6 years; Cohort 4: Patients aged from 3 months to <2 years, comprising Cohorts 4a and 4b as follows: Cohort 4a: Patients aged from 1 year to <2 years; Cohort 4b: Patients aged from 3 months to <1 year.

Doses of CAZ-AVI for the individual cohorts are given in the table found under the subheading Treatment below, including the dose reduction for patients with renal impairment. Due to differences in the two studies drug dosing regimens and the large fluid load that would be necessitated with double-blinded therapy, blinding of the treatment groups was not considered feasible for the study. The use of a single-blind study observer was chosen, which is a well-accepted study design feature for paediatric clinical trials. As children are a vulnerable population, this design allowed for close clinical monitoring by the Unblinded Observers while preserving the ability to assess safety and clinical response without bias through use of a Blinded Observer at each study site.

The numbers of patients included in each of the safety analysis datasets are summarised in Table 71. Of the 178 patients who were randomised to receive CAZ-AVI ± MTZ or comparator, 128 were treated in the CAZ-AVI ± MTZ group and 50 were treated in the comparator group.

In Study C3591004, most patients were recruited to Cohorts 1 and 2 with 30 (CAZ-AVI + MTZ n = 22 and meropenem n = 8) and 43 (CAZ-AVI + MTZ n = 33 and meropenem n =10) patients randomised, respectively. Cohort 3 randomised 9 patients (CAZ-AVI + MTZ (n = 6 and meropenem n = 3), and Cohort 4 randomised 1 patient (meropenem).

In Study C3591005, most patients were recruited to Cohort 4 with 38 patients (CAZ-AVI n = 27 and cefepime n = 11) randomised. Cohort 1 randomised 19 patients (CAZ-AVI n = 13 and cefepime n = 6), Cohort 2 randomised 22 patients (CAZ-AVI n = 17 and cefepime n = 5), and Cohort 3 randomised 18 patients (CAZ- AVI n = 11 and cefepime n = 7

Table 71. Safety Analysis Sets - (Randomised Patients) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=68) n (%)	Cefepime (N=29) n (%)	CAZ-AVI±MTZ (N=129) n (%)	Comparator (N=51) n (%)
Patients included in the SAS	61 (100)	22 (100)	67 (98.5)	28 (96.6)	128 (99.2)	50 (98.0)
Patients excluded from the SAS	0	0	1 (1.5)	1 (3.4)	1 (0.8)	1 (2.0)
Subject did not receive IV study therapy	0	0	1 (1.5)	1 (3.4)	1 (0.8)	1 (2.0)
Patients included in the SEAS	60 (98.4)	21 (95.5)	63 (92.6)	25 (86.2)	123 (95.3)	46 (90.2)
Patients excluded from the SEAS	1 (1.6)	1 (4.5)	5 (7.4)	4 (13.8)	6 (4.7)	5 (9.8)
Subject did not receive IV study therapy	0	0	1 (1.5)	1 (3.4)	1 (0.8)	1 (2.0)
Subject received less than 72 hours of study treatment	1 (1.6)	1 (4.5)	4 (5.9)	3 (10.3)	5 (3.9)	4 (7.8)

Percentages are based on the total number of patients in the treatment group (N). The Safety analysis set includes patients who received any amount of study treatment.
The Safety evaluable analysis set is a subset of the patients in the Safety analysis set who received at least 72 hours of treatment.
Source: CAZ-AVI Paediatric Submission Table 4.2.2.1.1

For the pooled data, the median (minimum-maximum) duration of exposure to IV study drug was 5 (1 to 13) days for the CAZ-AVI ± MTZ group and 6 (2 to 13) days for the comparator group (Table 72).

Table 72. Duration of Exposure to IV Study Drug (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
	CAZ-AVI + MTZ (N=61)	Meropenem (N=22)	CAZ-AVI (N=67)	Cefepime (N=28)	CAZ-AVI±MTZ (N=128)	Comparator (N=50)
Exposure (calendar days) n (%)						
1-4 days	11 (18.0)	2 (9.1)	43 (64.2)	17 (60.7)	54 (42.2)	19 (38.0)
5-7 days	24 (39.3)	11 (50.0)	21 (31.3)	9 (32.1)	45 (35.2)	20 (40.0)
8-10 days	23 (37.7)	5 (22.7)	2 (3.0)	1 (3.6)	25 (19.5)	6 (12.0)
11-15 days	3 (4.9)	4 (18.2)	1 (1.5)	1 (3.6)	4 (3.1)	5 (10.0)
>15 days	0	0	0	0	0	0
Exposure (calendar days)						
n	61	22	67	28	128	50
Mean	7.0	7.7	4.6	4.7	5.7	6.0
SD	2.43	2.68	1.82	1.81	2.43	2.68
Median	7.0	7.0	4.0	4.0	5.0	6.0
Minimum	2	2	1	2	1	2
Maximum	13	13	11	11	13	13

Source: CAZ-AVI Paediatric Submission Table 4.2.2.3 Percentages are based on the total number of patients in the treatment group (N).
Exposure (in calendar days) is defined as the difference between the last study therapy date and time and the first study therapy date and time rounded up to the next integer day.

Safety Analysis Datasets

This pooled paediatric safety data report presents analyses for the Safety Analysis Sets pooled for both studies, namely, all randomised patients who received any amount of IV study therapy (*i.e.* CAZ-AVI plus metronidazole or meropenem in Study C3591004, and CAZ-AVI or cefepime in Study C3591005).

Treatment

Overview of exposure of CAZ-AVI in the two pediatric studies are given in Table 73.

Table 73. Exposure to CAZ-AVI by age group

	Patients exposed to CAZ-AVI (N=128)		
Age Cohort	cIAI	cUTI	Total
Cohort 1: 12-<18 years	22	13	35
Cohort 2: 6-<12 years	33	17	50
Cohort 3: 2-<6 years	6	11	17
Cohort 4a: 1-<2 years	0	12	12
Cohort 4b: 3 months-<1 year	0	14	14
Total	61	67	128

The dosage regimens for the Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI) are given below.

Table 74. CAZ-AVI Dose Regimens by Age, Weight and Creatinine Clearance

Cohort	Age Range	Body Weight	CAZ-AVI Dose CrCl ≥50 mL/min	CAZ-AVI Dose CrCl ≥30 to <50 mL/min
			CAZ-AVI must be administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes)	
1	12 years to <18 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	12 years to <18 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
2	6 years to <12 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	6 years to <12 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
3	2 years to <6 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4a	1 year to <2 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	6 months to <1 year	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	3 months to <6 months	All	40 mg/kg CAZ/ 10 mg/kg AVI	20 mg/kg CAZ/ 5 mg/kg AVI

Source: Study D4280C00016 protocol, Table 5 (Section 16.1.1).
CAZ-AVI = ceftazidime- avibactam; CrCl = creatinine clearance.

Dosing for Metronidazole (anaerob coverage in the CAZ/AVI treatment group) in the cIAI study, C3591004

Metronidazole was included to provide anaerobic coverage, as it was in the adult trials. The suggested dose regimen of metronidazole is 10 mg/kg IV, administered over 20 to 30 minutes every 8 hours (±30 minutes), but it could also have been prescribed/adjusted by the Investigator according to local labels. The metronidazole infusion was to be started no later than 30 minutes after completion of the CAZ-AVI infusion.

Prior or concomitant medications

A great proportion (37 and 54% in the CAZ-AVI and cefepime treatment arms, respectively, in the UTI study, and approx. 86% in both treatment groups in the cIAI study) of the paediatric patients received other systemic antibiotics reported either before or concomitantly with the CAZ-AVI treatment. The most frequent systemic antibiotic administered was cefuroxime sodium in the cUTI study, whereas in the cIAI study, the most frequent concomitant systemic antibiotic administered was gentamicin. This co-medication use will possibly hamper the evaluation of CAZ-AVI treatment, both regarding efficacy and safety, in the children. [According to the MAH, the apparent high proportion of patients with concomitant systemic antibiotics could be explained by the fact that since time of dose was not collected, systemic antibiotics taken during Day 1 of IV study medication administration are reported as both prior and concomitant medications.]

More details on treatment regimens, including the comparator arms (meropenem in the cIAI study C3591004 and cefepime in the cUTI study, C3591005), and concomitant treatments, are given in section 3 on Efficacy.

Extent of exposure

For **the cUTI study,** in all cohorts combined, the median (minimum-maximum) exposure to IV study drug was 4 (1-11) days for the CAZ-AVI group and 4 (2-11) days for the CEF group.

Around 90% of patients in both treatment groups were switched to oral therapy to complete their study treatment, and most of these switched between either 3-5 or 6-9 days after initiation of study treatment. The median duration of oral drug exposure was 7 days for both treatment groups. The majority (84/95

[88.4%]) of patients received IV + oral therapy for 8-15 days, consistent with the protocol recommended treatment duration of 7 to 14 days (IV + oral therapy combined).

In **the cIAI study**, for all cohorts combined, the median (minimum-maximum) exposure to IV study drug was 7 (2-13) days for both the CAZ-AVI plus metronidazole and meropenem treatment groups. In terms of the individual components, the median (minimum-maximum) exposure was 7 (2-13) days for CAZ-AVI, metronidazole, and meropenem.

Approximately 69% of patients in both treatment groups were switched to oral therapy to complete their study treatment. The median duration of oral drug exposure was 6 and 7 days for patients in the CAZ-AVI plus metronidazole and meropenem treatment groups, respectively. The majority (67/83 [80.7%]) of patients in the study received 8 to 20 days of IV + oral therapy, consistent with the protocol recommended treatment duration of 7 to 15 days (IV + oral therapy combined).

For the pooled studies

Overall, a total of 128 subjects received CAZ-AVI±MTZ and 50 subjects received comparator. For the pooled data, the median (minimum-maximum) duration of exposure to IV study drug was 5 (1 to 13) days for the CAZ-AVI ± MTZ group and 6 (2 to 13) days for the comparator group (Table 75).

Among patients with cIAI, the median (minimum to maximum) duration of exposure to IV CAZ-AVI was 7 (1 to 21) days in adults and 7 (2 to 13) days in paediatric patients. More than 90% of adults in the studies assessed in support of the MA application received the recommended 5 to 14 days of treatment compared to 82% of paediatric patients receiving 5 to 15 days. Among patients with cUTI, the median (minimum to maximum) duration of exposure to IV CAZ-AVI was 7 (1 to 21) days in adults and 4 (1 to 11) days in paediatric patients. More than 80% of adults received the recommended 5 to 10 days of treatment compared to 34% of paediatric patients. This likely reflects the earlier switch to oral therapy seen in the paediatric studies; while the safety profile is consequently based on a shorter duration of therapy than adults, this reflects clinical practice in the paediatric population.

Table 75. Duration of Exposure to IV Study Drug – (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
	CAZ-AVI + MTZ (N=61)	Meropenem (N=22)	CAZ-AVI (N=67)	Cefepime (N=28)	CAZ-AVI ± MTZ (N=128)	Comparator (N=50)
Exposure (calendar days) n (%)						
1-4 days	11 (18.0)	2 (9.1)	43 (64.2)	17 (60.7)	54 (42.2)	19 (38.0)
5-7 days	24 (39.3)	11 (50.0)	21 (31.3)	9 (32.1)	45 (35.2)	20 (40.0)
8-10 days	23 (37.7)	5 (22.7)	2 (3.0)	1 (3.6)	25 (19.5)	6 (12.0)
11-15 days	3 (4.9)	4 (18.2)	1 (1.5)	1 (3.6)	4 (3.1)	5 (10.0)
>15 days	0	0	0	0	0	0
Exposure (calendar days)						
n	61	22	67	28	128	50
Mean	7.0	7.7	4.6	4.7	5.7	6.0
SD	2.43	2.68	1.82	1.81	2.43	2.68
Median	7.0	7.0	4.0	4.0	5.0	6.0
Minimum	2	2	1	2	1	2
Maximum	13	13	11	11	13	13

CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; MTZ = metronidazole; SD = standard deviation.
Percentages are based on the total number of patients in the treatment group (N).
Exposure (in calendar days) is defined as the difference between the last study therapy date and time and the first study therapy date and time rounded up to the next integer day.
Source: CAZ-AVI Paediatric Submission Table 4.2.2.3

Global Access program

A global access programme (GAP [compassionate use]) for individual named patient requests for CAZ-AVI has been in place for countries outside of the United States and Canada since 01 February 2015. Cumulative to 31 October 2018, CAZ-AVI has been supplied through the GAP for 946 courses for 908 individual named patients. Of the 946 courses, 26 were courses for paediatric patients (of which 20 were from EU countries).

Demographic and Other Characteristics of Study Population

Demographic Characteristics

Overall, the demographic and baseline characteristics for the 178 patients included in the pooled paediatric Safety Analysis Set (128 in the CAZ-AVI ± MTZ group and 50 in the comparator group) were generally balanced between treatment groups. The highest proportion of patients were female (about 60%), White (about 78%) and from Eastern Europe (about 40%). The mean age was approximately 8 years with a range of 3 months to 17 years. About 3/4 of patients in each treatment group were ≥6 years of age.

Patient Characteristics at Baseline

The mean (standard deviation [SD]) for all patients was balanced across treatment groups for height (126.2 ± 34.5 cm CAZ-AVI versus 123.1 ± 35.7 cm comparator), weight (32.2 ± 19.6 kg CAZ-AVI versus 31.0 ± 20.4 kg comparator), body mass index (BMI) (18.29 ± 3.83 kg/m2 CAZ-AVI versus 18.46 ± 4.41 kg/m2 comparator), and baseline CrCL (105.8 ±39.6 ml/min/1.73 m2 CAZ-AVI versus 104.0 ± 35.8 ml/min/1.73 m2 comparator). At baseline, the majority of patients (>70%) had creatinine clearance values in the normal range of ≥80 mL/min for both treatment groups. Overall 25% subjects taking CAZ-AVI ± MTZ and 18% comparator had mild renal insufficiency with creatinine clearance values ≥50 to <80 mL/min. One patient in each group had a creatinine clearance value <50 mL/min.

The CHMP acknowledged that Study D4280C00015 compared CAZ-AVI + MTZ to meropenem for treatment of cIAI. Study D4280C00016 compared CAZ-AVI to cefepime for treatment of cUTI. Since the dose regimen of CAZ-AVI is the same in each age category in the two studies, it is considered acceptable to pool the safety data from two studies even though there is different indications and different comparators used in the two studies. However, there are differences between the studies, which could impact the results of the pooling, see further below.

It should, however, be noted that the median exposure to IV study drug was quite different in the two studies; median (minimum-maximum) exposure was 7 (2-13) days for the CAZ-AVI plus metronidazole group in the cIAI study versus 4 (1-11) days for the CAZ-AVI group in the cUTI study. However, there were comparable durations in the treatment arms *within* each study. The recommended duration of treatment in the proposed SmPC is 5-14 days for both indications. It is considered that the duration of treatment actually performed in the two studies are relevant for evaluation of safety.

Study D4280C00014 was a Phase 1 single-dose PK study to determine dosing and will not be considered in the analysis of safety.

In total, 67 pediatric patients were exposed to CAZ-AVI in the cUTI study and 61 pediatric patients were exposed to CAZ-AVI + metronidazole in the cIAI study for a total of 128 patients. A total of 50 patients received the comparator drug, either meropenem or cefepime. The stratification of patients into four age cohorts is considered relevant for the safety assessment. Exposure to CAZ-AVI by age group is given in a table above, and as shown here, there are differences regarding the recruitment of patients into the different age cohorts in the cIAI and cUTI studies (study C3591004 and study C3591005, respectively). For the safety assessment of CAZ-AVI in cIAI it is noted that there were more patients in the older age groups in the cIAI study, and none included in the age group under 2 years of age. This may reflect that cIAIs are more common in the older age groups, while cUTIs are also seen in the youngest age groups. However, except abovementioned limitations, the safety database is considered by the Committee adequate in terms of size and target population. With regards to renal function, see the section on Safety in special populations.

Adverse events

The primary objective of both studies was to assess the safety and tolerability of CAZ-AVI. AEs with an onset date and time on or after the date and time of the first dose of study drug up to and including the last visit were summarised.

The primary outcome variables were:

- AEs and serious AEs (SAEs);
- Cephalosporin class effects and additional AEoSI;
- Vital signs (pulse, blood pressure, respiratory rate, temperature);
- Physical examination;
- Laboratory parameters;
- CrCl;
- Electrocardiogram (ECG).

There were no specifications provided with respect to collection of subjective AEs across various age groups in either of the 2 clinical studies. Safety data collection relied on the investigator to obtain and record on the CRF all observed or volunteered AEs and their severity (mild, moderate, or severe). All AEs were recorded in the CRF, including those spontaneously reported by the patient or care provider, reported in response to the open question from the study personnel: 'Have you/the child had any health problems since the previous visit/you were last asked?', or revealed by observations. No specific methodology beyond this assessment was required by the protocol and the MAH is not aware of any validated tools to facilitate assessment of subjective AEs in the very youngest (ie, nonverbal) paediatric patients. Therefore, as noted, some subjective AEs may not be wellcaptured in the youngest children, however less specific AEs such as irritability, inability to settle or crying might indicate if the child was experiencing such an event. Assessment of the reported cases did not identify clustering with regards to this pattern of AE reporting in the pooled paediatric safety data for CAZ-AVI.

Adverse events in all studies were collected from the time of signing the consent form until the subject completed the study, in line with GCP principles. For the purposes of the pooled paediatric dataset, comprising Studies C3591004 and C3591005, the last timepoint for collecting safety data and at which the subject ended the study was named "last visit".

The subjects received CAZ-AVI as intravenous (IV) therapy, therefore for the pooled safety dataset, the last timepoint at which they received CAZ-AVI was designated End of IV therapy (EOIV), to differentiate from any protocolled continuation of oral study therapy. For the purposes of AE analysis, this time point is 24 hours after the start of the last infusion, to ensure that any AEs that occurred before CAZ-AVI was cleared from the subject were also assessed as "on therapy" AEs.

For both studies, the end of IV therapy was designated as the EOIV visit. The total treatment period was to be between 7 and 15 days. The duration of each patient's participation in the study was to be a minimum of 27 days to a maximum of 50 days after the start of study treatment (first dose) at which time there was a late follow-up (LFU) assessment. The LFU assessment was to be performed 20 to 35 days after the last dose of any treatment.

Adverse events are presented up to EOIV and up to last visit. The EOIV is defined as the last IV dose/time + 24 hours, ie, an AE is classified as 'up to EOIV' if date of onset of AE ≤ end date/time of last IV dose + 24h. The Last visit is defined as any event which occurred from the beginning of the first dose of study drug up to the time that the subject completed the study and had their last interaction with the study site, which could be a month after last dose of study therapy.

The CHMP acknowledged that details regarding the safety data collection in the paediatric studies C3591004 and C3591005 were submitted during the course of the procedure, as requested. Safety data collection relied on the investigator to obtain and record on the CRF all observed or volunteered AEs and their severity score. All AEs were recorded in the CRF, including those spontaneously reported by the patient or care provider, reported in response to the open question from the study personnel to the parents of the child treated.

Acceptable definitions of terms and details regarding timelines for collecting AEs in the paediatric studies were also provided for clarification, as requested.

Adverse Drug Reactions (ADRs) for the Pooled Paediatric Data

Methodology

For laboratory-based medical concepts, the following algorithm was used: if either of the following criteria, or both, were fulfilled, the patient was counted as having an ADR for calculation of frequency (each patient was counted only once):

1. Subject had at least 1 AE defined by a MedDRA PT which aligned with that laboratory based medical concept, and/or

2. Subject had at least 1 potentially clinically significant (PCS) laboratory value for an ADR, as defined for each laboratory investigation, based on a value with multiples of > upper limit of normal (ULN) or < lower limit of normal (LLN) and percentage change from baseline (eg, with respect to thrombocytopenia and thrombocytosis, the number of PCS events for platelets was the number of patients with both baseline and post-baseline values <0.65 x LLN and >50% decrease from baseline, or number of patients with both baseline and post-baseline values >1.5 x ULN and >100% increase from baseline, respectively).

Only AEs with an onset date and time (and lab samples with a sample date and time) on or after the date and time of first dose and up to last visit were included.

Methodology for Coombs Test seroconversion

The estimated Coombs seroconversion rate was based on data from 81 (63.3%) CAZ-AVI ± MTZ patients in the Paediatric pool who had an initial negative Coombs test and at least 1 follow-up test. Overall, Coombs seroconversion rate at any time up to the last visit for patients with a baseline negative result and at least 1 post-baseline result was 3.7% (3 of 81 patients; 1 with cIAI and 2 with cUTI). Further analysis was conducted to also include patients who had at least 2 post-baseline Coombs results, of which the first was negative. This was to include patients with a missing baseline value but with evidence of seroconversion. No additional patients were identified.

The ADR rates of positive Coombs test were higher in the comparators group than the CAZ-AVI. No patients in the paediatric clinical development program had an AE of haemolytic anaemia during their respective study.

Analysis of ADR Frequencies

The frequency in the paediatric pool is compared with the frequency in the adult pool in Table 76. Also shown is the frequency category as presented in the IB and SmPC approved in adults. The frequencies were generally in line with those of the adult pool and the known paediatric safety profile of ceftazidime. In addition, the FORTUM SmPC for ceftazidime monotherapy was also used to define the frequencies presented in the IB and the European SmPC; if the Fortum frequency was higher than that observed in the adult pooled CAZ-AVI studies, the higher frequency category was used. Any differences between the paediatric and adult

CAZ-AVI frequencies should be interpreted with caution given the limited numbers of paediatric patients. However, some differences, such as headache and nausea, can be explained by the fact that very young children are naturally less likely than adults to report AEs associated with these symptoms, and other symptoms such as vomiting can be explained by the fact that decreasing age increases the risk of post-operative nausea and vomiting.[1]

In addition, as expected for the low numbers of patients, no ADRs were seen which are expected to be observed in less than 1 in 100 patients (i.e. frequency categories of uncommon, rare, very rare, and frequency unknown).

The Coombs seroconversion rate was lower than that seen in the adult program (14.0% in adults vs 3.7% in children) and is similar to that known for ceftazidime monotherapy, as presented in the FORTUM UK SmPC which is 5%, and the FORTAZ USPI which is 1 in 23. No evidence of haemolysis was seen in either paediatric study.

Table 76. Comparison of ADR Frequencies

ADR	Frequency Category in Adult SmPC and IB	Frequency in Adult Pool	Frequency in Paediatric Pool (N=128)[a]
Coombs direct test positive	Very common	138/987 (13.981)	3/81 (3.7)
Thrombocytosis	Common	60/2024 (2.964)	3 (2.3)
Thrombocytopenia	Common	21/2024 (1.038)	0
Neutropenia	Uncommon	16/2024 (0.791)	0
Lymphocytosis	Uncommon	6/2024 (0.296)	0
Eosinophilia	Common*	5/2024 (0.247)	1 (0.8) (uncommon)
Leucopenia	Uncommon	3/2024 (0.148)	0
Agranulocytosis	Frequency not known	0	0
Haemolytic anaemia	Frequency not known	0	0
Diarrhoea	Common	150/2024 (7.411)	6 (4.7)
Nausea	Common	102/2024 (5.040)	3 (2.3)
Vomiting	Common	78/2024 (3.854)	11 (8.6)
Abdominal pain	Common	65/2024 (3.211)	2 (1.6)
Dysgeusia	Uncommon	5/2024 (0.247)	0
Pyrexia	Common	65/2024 (3.211)	4 (3.1)
Infusion site phlebitis	Common*	13/2024 (0.642)	4 (3.1)
Infusion site thrombosis	Common*	1/2024 (0.049)	0
Aspartate aminotransferase increased	Common	98/2024 (4.842)	1 (0.8) (uncommon)
Alanine aminotransferase increased	Common	97/2024 (4.792)	1 (0.8) (uncommon)
Gamma-glutamyltransferase increased	Common	83/2024 (4.101)	4 (3.1)
Blood alkaline phosphatase increased	Common	58/2024 (2.866)	0
Blood lactate dehydrogenase increased	Common*	3/2024 (0.148)	0
Jaundice	Frequency not known	0	0
Anaphylactic reaction	Frequency not known	0	0
Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)	Common	25/2024 (1.235)	0
Clostridium difficile colitis	Uncommon	7/2024 (0.346)	0
Pseudomembranous colitis	Uncommon	1/2024 (0.049)	0
Headache	Common	83/2024 (4.101)	1 (0.8) (uncommon)
Dizziness	Common	21/2024 (1.038)	2 (1.6)
Paraesthesia	Uncommon	3/2024 (0.148)	0
Blood creatinine increased	Uncommon	16/2024 (0.791)	0
Acute kidney injury	Uncommon	12/2024 (0.593)	0
Blood urea increased	Uncommon	4/2024 (0.198)	0
Tubulointerstitial nephritis	Very Rare*	0	0
Rash maculo-papular	Common	26/2024 (1.285)	5 (3.9)
Pruritis	Common	21/2024 (1.038)	1 (0.8) (uncommon)
Urticaria	Common*	5/2024 (0.247)	0
Toxic epidermal necrolysis	Frequency not known	0	0
Stevens-Johnson syndrome	Frequency not known	0	0
Erythema multiforme	Frequency not known	0	0
Angioedema	Frequency not known	0	0
DRESS	Frequency not known	0	0

ADR = adverse drug reaction; CAZ-AVI = ceftazidime-avibactam; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; IB = Investigator's Brochure; SmPC = Summary of Product Characteristics.
Very Common ≥1/10, Common ≥1/100 to <1/10, Uncommon ≥1/1,000 to <1/100, Rare ≥1/10,000 to <1/1,000
Very Rare <1/10,000, Frequency not known - cannot be estimated from the available data
* Frequencies based on Fortum UK SmPC 2016 which is higher than the observed frequency in the CAZ-AVI program.
[a] CAZ-AVI Paediatric Submission Table 4.2.3.1 and Table 4.2.3.3

Acceptable clarifications regarding the table above, which compares ADR frequencies between the "adult pool" and "paediatric pool" were provided by the MAH, as requested by CHMP.

The patients and numbers for the "adult pool" come from the adult studies in the MAA and Study D4281C00001 (REPROVE) which was submitted as a post authorization variation in January 2017. The

current SmPC ADR frequencies are based on the denominator N=2024 and refers only to adult subjects in Phase 2 and Phase 3 studies who received CAZ-AVI ± MTZ. One paediatric safety pool ("paediatric pool") has been submitted to EMA, comprising the studies C3591004 and C3591005 (N=126).

As the MAH pointed out, any differences between the paediatric and adult CAZ-AVI frequencies should be interpreted with caution given the limited numbers of paediatric patients. The presented rates are acceptable and are deemed to change after larger paediatric exposure to CAZ-AVI. As expected due to the low numbers of patients, none the ADRs listed as uncommon/rare for adults in the current SmPC were seen in the paediatric population in the two studies.

Analysis of Adverse Events

An overview of AEs observed in the cUTI study is given in Table 77 below.

Table 77. Adverse events in any category (Safety Analysis Set) in study C3591005

Adverse Event category	CAZ-AVI (N = 67)	CEF (N = 28)
	n (%)	n (%)
Any AE	36 (53.7)	15 (53.6)
Any AE with outcome = death	0	0
Any SAE	8 (11.9)	2 (7.1)
Any AE leading to discontinuation of study treatment[a]	3 (4.5)	0
Any AE with severe intensity	6 (9.0)	2 (7.1)
Any AE of special interest	10 (14.9)	4 (14.3)
Any AE related to study IV treatment[b]	7 (10.4)	1 (3.6)

Source: Table 14.3.1.1

An overview of AEs observed in the cIAI study is given in Table 78 below.

Table 78. Adverse events in any category (Safety Analysis Set) in study C3591004

Adverse event category	CAZ-AVI + MTZ (N = 61)	MER (N = 22)
	n (%)	n (%)
Any AE	32 (52.5)	13 (59.1)
Any AE with outcome = death	0	0
Any SAE	5 (8.2)	1 (4.5)
Any AE leading to discontinuation of study treatment[a]	0	0
Any AE with severe intensity	4 (6.6)	1 (4.5)
Any AE of special interest	4 (6.6)	4 (18.2)
Any AE related to study IV treatment[b]	1 (1.6)	2 (9.1)

Source: Table 14.3.1.1

Pooled studies

The incidence of AEs up to the last visit in the overall patient population was balanced between treatment groups: 53.1% and 56.0% in the CAZ-AVI ± MTZ and comparator treatment groups, respectively (Table 79). The incidence of AEs occurring up to the End of IV therapy was generally similar to those occurring up to the last visit.

In contrast to the observed adult data, the incidence of AEs in paediatric patients was similar in patients with cIAI and cUTI. On analysis, the paediatric population which has cUTI tended to be more sick at baseline and have more significant comorbidities such as congenital abnormalities or renal or cardiac disease, compared with the adults, and this was assessed to be the reason for the observed difference.

Table 79. Adverse Events up to Last Visit in any Category - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
AE Category	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=67) n (%)	Cefepime (N=28) n (%)	CAZ-AVI ± MTZ (N=128) n (%)	Comparator (N=50) n (%)
Any AE	32 (52.5)	13 (59.1)	36 (53.7)	15 (53.6)	68 (53.1)	28 (56.0)
Any AE with an outcome of death	0	0	0	0	0	0
Any SAE	5 (8.2)	1 (4.5)	8 (11.9)	2 (7.1)	13 (10.2)	3 (6.0)
Any AE leading to discontinuation of IP[a]	0	0	3 (4.5)	0	3 (2.3)	0
Any AE of severe intensity	4 (6.6)	1 (4.5)	6 (9.0)	2 (7.1)	10 (7.8)	3 (6.0)

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; IP = investigational product; MTZ = metronidazole; SAE = serious adverse event.
Patients with multiple adverse events (AEs) in the same category are counted only once in that category. Patients with AEs in more than 1 category are counted once in each of those categories.
a Action taken, study drug permanently discontinued.
Includes adverse events with an onset date/time on or after the date/time of first infusion and up to and including the last visit. Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.10

The CHMP noted that the frequency of AEs up to the last visit in the overall patient population was similar between pooled treatment arms (53.1% in the CAZ-AVI ± MTZ vs. 56.0% in comparator treatment groups, respectively). There are some differences observed, the most obvious of which was a higher frequency of SAEs in disfavour of the pooled CAZ-AVI group.

Three (3) patients had AEs that led to discontinuation in the CAZ-AVI arm in the cUTI study (See below under the section concerning discontinuation due to AEs), none in the comparator arm. No patient discontinued due to AEs in the cIAI study. There were no deaths in either study.

Common Adverse Events

The most frequently reported system organ class (SOC) for the CAZ-AVI treatment group, for the overall paediatric population, was Infections and infestations (23.4% [30 patients]. A summary of the incidence of AEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) reported up to the last visit in ≥3 patients in the CAZ-AVI ± MTZ treatment group is presented in Table 80.

The most frequently reported (≥4%) AEs by PT for the CAZ-AVI treatment group, for the overall paediatric population, were Vomiting (8.6% [11 patients]) and Diarrhoea (4.7% [6 patients]), both of which are known common ADRs included in Section 4.8 of the EU-SmPC approved in adults.

Table 80. Adverse Events up to Last Visit in Decreasing Order (of the total) of Incidence for CAZ-AVI ± Metronidazole in ≥3 Patients - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
Preferred Term	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=67) n (%)	Cefepime (N=28) n (%)	CAZ-AVI ± MTZ (N=128) n (%)	Comparator (N=50) n (%)
Patients with any AE	32 (52.5)	13 (59.1)	36 (53.7)	15 (53.6)	68 (53.1)	28 (56.0)
Vomiting	9 (14.8)	2 (9.1)	2 (3.0)	2 (7.1)	11 (8.6)	4 (8.0)
Diarrhoea	1 (1.6)	0	5 (7.5)	3 (10.7)	6 (4.7)	3 (6.0)
Urinary tract infection	0	0	5 (7.5)	0	5 (3.9)	0
Infusion site phlebitis	4 (6.6)	0	0	0	4 (3.1)	0
Pyrexia	2 (3.3)	0	2 (3.0)	1 (3.6)	4 (3.1)	1 (2.0)
Rash	1 (1.6)	1 (4.5)	3 (4.5)	2 (7.1)	4 (3.1)	3 (6.0)
Rhinitis	0	0	4 (6.0)	2 (7.1)	4 (3.1)	2 (4.0)
Upper respiratory tract infection	1 (1.6)	1 (4.5)	3 (4.5)	0	4 (3.1)	1 (2.0)
Cough	1 (1.6)	2 (9.1)	2 (3.0)	1 (3.6)	3 (2.3)	3 (6.0)
Nausea	1 (1.6)	1 (4.5)	2 (3.0)	1 (3.6)	3 (2.3)	2 (4.0)
Seroma	3 (4.9)	0	0	0	3 (2.3)	0

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; MedDRA = Medical Dictionary for Regulatory Activities; MTZ = metronidazole.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
AEs are sorted by system organ class in international order and by preferred term in MedDRA V20.0.
Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.24

The CHMP noted that the most frequently reported SOC for the CAZ-AVI treatment group, for the overall paediatric population, was Infections and infestations (23.4%). The most frequently reported (≥4%) AEs by PT for the CAZ-AVI treatment group for the overall paediatric population, were Vomiting (8.6%) and Diarrhoea (4.7%), both of which are known common ADRs from Zavicefta /ceftazidime-avibactam/CAZ-AVI in adults. When including PTs reported up to the last visit in ≥3 patients, infusion site phlebitis (4 pts), seroma (3 pts), UTI (5 pts), rash (3 pts), rhinitis (4 pts), upper respiratory tract infection (3 pts) are AEs reported in addition to vomiting (11 pts) and diarrhoea (6 pts) in the CAZ-AVI group. These are reactions, except for seroma, that are previously observed in adults and hence, are not unexpected. No new signal is observed in the paediatric population in these studies. The AE of seroma is reported in 3 paediatric patients with cIAIs and might be related to surgical procedures. Seroma is apparently not related to study drug.

A great proportion (54% in the CAZ-AVI and cefepime treatment arms, respectively, in the UTI study, and approx. 86% in both treatment groups in the cIAI study) received other systemic antibiotics reported either before or concomitantly with the CAZ-AVI treatment. To what degree concomitant treatment contributed to the AEs reported is uncertain and was not discussed by the MAH, but does not seem to have impacted in a detrimental way when looking at the treatment-related AE reported, which is reassuring.

Frequency of AEs according to severity

The majority of AEs reported in both studies were mild in intensity (Table 81). The incidence of AEs by maximum reported intensity, for PTs of severe intensity is summarised in Table 82. On review of the data, the AEs with severe intensity tended to be those expected to occur in patients with severe infections and therefore reflect the underlying infection or associated surgery.

Table 81. Adverse Events up to Last Visit by Maximum Reported Intensity - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
Maximum Reported Intensity	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=67) n (%)	Cefepime (N=28) n (%)	CAZ-AVI ± MTZ (N=128) n (%)	Comparator (N=50) n (%)
Total	32 (52.5)	13 (59.1)	36 (53.7)	15 (53.6)	68 (53.1)	28 (56.0)
Mild	23 (37.7)	8 (36.4)	26 (38.8)	10 (35.7)	49 (38.3)	18 (36.0)
Moderate	5 (8.2)	4 (18.2)	4 (6.0)	3 (10.7)	9 (7.0)	7 (14.0)
Severe	4 (6.6)	1 (4.5)	6 (9.0)	2 (7.1)	10 (7.8)	3 (6.0)

CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; MTZ = metronidazole.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.36

Table 82. Severe Intensity Adverse Events up to Last Visit - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

Preferred Term	Number (%) of patients					
	cIAI		cUTI		Total	
	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=67) n (%)	Cefepime (N=28) n (%)	CAZ-AVI ± MTZ (N=128) n (%)	Comparator (N=50) n (%)
Patients with any Severe AE	4 (6.6)	1 (4.5)	6 (9.0)	2 (7.1)	10 (7.8)	3 (6.0)
Cystitis	0	0	0	1 (3.6)	0	1 (2.0)
Pyelonephritis acute	0	0	2 (3.0)	1 (3.6)	2 (1.6)	1 (2.0)
Viral infection	0	0	1 (1.5)	0	1 (0.8)	0
Nervous system disorder	0	0	1 (1.5)	0	1 (0.8)	0
Tachycardia	0	0	1 (1.5)	0	1 (0.8)	0
Constipation	0	0	1 (1.5)	0	1 (0.8)	0
Ileus	1 (1.6)	1 (4.5)	0	0	1 (0.8)	1 (2.0)
Intestinal obstruction	1 (1.6)	0	0	0	1 (0.8)	0
Abdominal pain	0	0	1 (1.5)	0	1 (0.8)	0
Vomiting	1 (1.6)	0	0	0	1 (0.8)	0
Large intestine perforation	1 (1.6)	0	0	0	1 (0.8)	0
Renal colic	1 (1.6)	0	0	0	1 (0.8)	0
Nephrolithiasis	0	0	1 (1.5)	0	1 (0.8)	0
Postoperative ileus	1 (1.6)	0	0	0	1 (0.8)	0

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; MedDRA =
Medical Dictionary for Regulatory Activities; MTZ = metronidazole.
Patients with multiple adverse events for the same preferred term are counted only once for that preferred term.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
AEs are sorted in international order and by preferred term in MedDRA V20.0.
Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.36

The CHMP noted that in the CAZ-AVI±MTZ group there were 9 and 10 patients experiencing moderate and severe AEs, respectively, in total 14.8% (19/128). Based on the numbers in the table above, there is mostly one case per preferred term, and it is not possible to observe any trend in severity of AEs. Overall, the incidence of any severity AEs was similar in the study and comparator drugs, however, there were cases of study drug discontinuation due to AEs, and that was not the case for the comparators. Otherwise, the AEs incidence seems to be balanced between the compared groups.

The patient who experienced AE in the SOC Nervous system disorder is described in the subheading "Serious adverse events (SAEs)" further below.

Frequency of study drug related AEs

Overall, most AEs were assessed as not related to the study drug. The AEs assessed as related to study drug are presented by PT in Table 83. The majority of related AEs are known adverse drug reactions (ADRs) included in the Investigator's Brochure (IB) and SmPC approved in adults or are expected due to the underlying disease. The AE of Nervous system disorder was considered by the Blinded Observer to be related due to the temporal relationship to the infusion, however the patient had a history of similar episodes before the study drug was started and the event had a plausible alternative explanation.

Table 83. Adverse Events up to Last Visit and Reported as Related to Study Drug - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
Preferred Term	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=67) n (%)	Cefepime (N=28) n (%)	CAZ-AVI ± MTZ (N=128) n (%)	Comparator (N=50) n (%)
Patients with any AE	1 (1.6)	2 (9.1)	7 (10.4)	1 (3.6)	8 (6.3)	3 (6.0)
Dizziness*	0	0	1 (1.5)	0	1 (0.8)	0
Nervous system disorder	0	0	1 (1.5)	0	1 (0.8)	0
Diarrhoea*	0	0	2 (3.0)	1 (3.6)	2 (1.6)	1 (2.0)
Nausea*	0	1 (4.5)	1 (1.5)	0	1 (0.8)	1 (2.0)
Vomiting*	1 (1.6)	1 (4.5)	1 (1.5)	0	2 (1.6)	1 (2.0)
Dermatitis diaper	0	0	1 (1.5)	0	1 (0.8)	0
Intertrigo	0	0	0	1 (3.6)	0	1 (2.0)
Rash*	0	1 (4.5)	2 (3.0)	0	2 (1.6)	1 (2.0)

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; IB = Investigator's Brochure; MedDRA = Medical Dictionary for Regulatory Activities; MTZ = metronidazole.
* Known ADRs/ expected terms according to IB
Patients with multiple adverse events for the same preferred term are counted only once for that preferred term. Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit. AEs are sorted in international order and by preferred term in MedDRA V20.0.
Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.40

The CHMP noted that there were few (8 pts) of the observed AEs which are deemed related to study drug (6.3%) by blinded observer. It is agreed that all of the related AEs, except for term Nervous system disorder, are known adverse drug reactions (ADRs) included in the SmPC approved in adults. The numbers of AEs related to study drug are acknowledged to be similar in the study and the comparator group. No new safety concerns are detected in the paediatric population.

The patient who experienced the AE Nervous system disorder is described in the subheading "Serious adverse events (SAEs)" further below.

Adverse events of special interest (AEoSI)

The incidence of AEoSI representing 5 topics of special interest

- liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders were programmatically assessed based on pre-defined AE PTs (MedDRA Version 20.0).

The incidence of AEoSI PTs for each of the 5 categories up to Last Visit for the Safety Analysis Set, is presented in Table 84. One patient had ALT and AST rises which were not accompanied by a bilirubin rise. No new safety findings were identified on review of these events and the majority of AEs in the AEoSI topics were known ADRs. Hepatotoxicity, and risk of neurological sequelae when the dose is not appropriately reduced in patients with renal impairment are important potential risks.

Table 84. Adverse Events of Special Interest Up to Last Visit - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

Safety topic Preferred Term	Number (%) of patients					
	cIAI		cUTI		Total	
	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22)	CAZ-AVI (N=67)	Cefepime (N=28)	CAZ-AVI ± MTZ (N=128)	Comparator (N=50)
Liver Disorders	**0**	**0**	**1 (1.5)**	**0**	**1 (0.8)**	**0**
Gamma-glutamyltransferase increased*	0	0	1 (1.5)	0	1 (0.8)	0
Diarrhoea	**1 (1.6)**	**0**	**5 (7.5)**	**3 (10.7)**	**6 (4.7)**	**3 (6.0)**
Diarrhoea *	1 (1.6)	0	5 (7.5)	3 (10.7)	6 (4.7)	3 (6.0)
Hypersensitivity/Anaphylaxis	**3 (4.9)**	**3 (13.6)**	**5 (7.5)**	**2 (7.1)**	**8 (6.3)**	**5 (10.0)**
Cough	1 (1.6)	2 (9.1)	2 (3.0)	1 (3.6)	3 (2.3)	3 (6.0)
Pruritus *	1 (1.6)	0	0	1 (3.6)	1 (0.8)	1 (2.0)
Rash *	1 (1.6)	1 (4.5)	3 (4.5)	2 (7.1)	4 (3.1)	3 (6.0)
Haematological Disorders	**0**	**1 (4.5)**	**0**	**0**	**0**	**1 (2.0)**
Anaemia	0	1 (4.5)	0	0	0	1 (2.0)
Renal Disorders	**0**	**0**	**0**	**0**	**0**	**0**

Patients with multiple adverse events for the same preferred term are counted only once for that preferred term. Patients with AEs for more than 1 preferred term are counted once for that SOC.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
AEs are sorted by system organ class in international order and by preferred term in MedDRA V20.0 High Level Group Term and High Level Term from the hierarchy. Percentages are based on the total number of patients in the treatment group (N).
* Known ADRs/ expected terms according to IB
Source: CAZ-AVI Paediatric Submission Table 4.2.2.8.2, Table 4.2.2.8.4, Table 4.2.2.8.6, Table 4.2.2.8.8 and Table 4.2.2.8.10

The CHMP noted that AEoSI for CAZ-AVI are predefined to be liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders. The AEoSI that are observed in the studies, are shown in the table above. In this table, the actual number of patients with events are lacking from the columns for each treatment arm. These numbers are, however, given in the individual overview tables from each of the two studies in cUTI and cIAI, see Table 77 and Table 78 (from the CSR).

The AEoSI for CAZ-AVI were defined based upon warnings and precautions wording for ceftazidime monotherapy in the Fortum UK SmPC, and later the same text was included in the CAZ-AVI SmPC. No clinically relevant differences were identified when the pooled paediatric safety data was assessed, or in the individual studies, and therefore no change to the current SmPC text is considered necessary, the Applicant claims.

The AEoSI called "renal disorders" was not defined using the MedDRA SOC "Renal and urinary disorder" that is represented in the text stated in the SmPC. The AEoSI "renal disorders" is rather defined in the paediatric pooled safety dataset using the MedDRA v20.0 Acute renal failure broad Standard Medical Query (SMQ). No MedDRA PTs that are included in this SMQ were reported as AEs in the pooled paediatric safety dataset. This is the explanation for the discrepancies observed and asked about in this application. Reported events with terms nephrolithiasis, renal colic and urethral meatus stenosis are not included in the SMQ used by the MAH and therefore not reflected as renal disorders in Table 83 even though they are terms belonging to SOC Renal and urinary disorder. However, there were only single cases observed, and none of them were deemed related to CAZ-AVI treatment, which makes the concern less worrisome. The CHMP did not consider inclusion of these reactions in the SmPC relevant.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths or AEs with a fatal outcome reported in either study; Studies C3591004 (cIAI) and C3591005 (cUTI).

Serious adverse events (SAEs)

SAEs were reported by 13 patients in the CAZ-AVI ± MTZ treatment group (10.2%) and 3 patients in the comparator treatment group (6.0%). SAEs by SOC and PT up to Last Visit, for the Safety Analysis Set are presented in Table 85. The reported SAEs were in line with what would be expected for the underlying indications, surgical treatment and paediatric population. There were no new safety findings, according to the MAH.

One SAE, reported in Study C3591005 in the CAZ-AVI group, was judged to be related to study treatment by the Blinded Observer:

One patient (Cohort 1; CAZ-AVI), a 16 year old female, experienced severe Nervous system disorder (verbatim term: neurologic disorder on the lower leg extremity), which was considered a medically important event and occurred 2 days after the start of the IV study drug. The patient's ongoing medical history included anxiety, depression and hypertension secondary to polycystic kidney disease and it was reported that she had experienced the same symptoms prior to enrolment in the study, which provides a plausible alternative explanation. The Blinded Observer stated that causality of this case is considered to be possibly related to study drug based on implied temporal relationship. Concomitant medications and treatments received during the SAE were sertraline, ramipril, vitamins with minerals, and amlodipine. The event was considered resolved on Day 3. The SAE led to permanent discontinuation of study treatment.

Table 85. Serious Adverse Events up to Last Visit by System Organ Class and Preferred Term - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Number (%) of patients					
	cIAI		cUTI		Total	
System Organ Class Preferred Term	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22) n (%)	CAZ-AVI (N=67) n (%)	Cefepime (N=28) n (%)	CAZ-AVI ± MTZ (N=128) n (%)	Comparator (N=50) n (%)
Patients with any SAE	5 (8.2)	1 (4.5)	8 (11.9)	2 (7.1)	13 (10.2)	3 (6.0)
Infections and infestations	**0**	**0**	**6 (9.0)**	**2 (7.1)**	**6 (4.7)**	**2 (4.0)**
Cystitis	0	0	0	1 (3.6)	0	1 (2.0)
Pyelonephritis acute	0	0	2 (3.0)	1 (3.6)	2 (1.6)	1 (2.0)
Urinary tract infection	0	0	3 (4.5)	0	3 (2.3)	0
Viral infection	0	0	1 (1.5)	0	1 (0.8)	0
Nervous system disorders	**0**	**0**	**1 (1.5)**	**0**	**1 (0.8)**	**0**
Nervous system disorder	0	0	1 (1.5)	0	1 (0.8)	0
Gastrointestinal disorders	**2 (3.3)**	**1 (4.5)**	**1 (1.5)**	**0**	**3 (2.3)**	**1 (2.0)**
Constipation	0	0	1 (1.5)	0	1 (0.8)	0
Ileus	1 (1.6)	1 (4.5)	0	0	1 (0.8)	1 (2.0)
Intestinal obstruction	1 (1.6)	0	0	0	1 (0.8)	0
Abdominal pain	0	0	1 (1.5)	0	1 (0.8)	0
Large intestine perforation	1 (1.6)	0	0	0	1 (0.8)	0
Renal and urinary disorders	**2 (3.3)**	**0**	**1 (1.5)**	**0**	**3 (2.3)**	**0**
Urethral meatus stenosis	1 (1.6)	0	0	0	1 (0.8)	0
Renal colic	1 (1.6)	0	0	0	1 (0.8)	0
Nephrolithiasis	0	0	1 (1.5)	0	1 (0.8)	0
Injury, poisoning and procedural complications	**1 (1.6)**	**0**	**0**	**0**	**1 (0.8)**	**0**
Postoperative ileus	1 (1.6)	0	0	0	1 (0.8)	0

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; MedDRA = Medical Dictionary for Regulatory Activities; MTZ = metronidazole; SAE = serious adverse event.
Patients with multiple adverse events for the same preferred term are counted only once for that preferred term. Patients with AEs for more than 1 preferred term are counted once for that System Organ Class.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
AEs are sorted by system organ class in international order and by preferred term in MedDRA V20.0 High Level Group Term and High Level Term from the hierarchy. Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.6.2

The CHMP noted that there were no deaths in either study.

SAEs were reported by 13 patients in the CAZ-AVI ± MTZ treatment group (10.2%) and 3 patients in the comparator treatment group (6.0%). One SAE (Nerveous system disorder), reported in Study C3591005 (cUTI) in the CAZ-AVI group, was judged to be possibly related to study treatment by the Blinded Observer, and also led to permanent discontinuation of study treatment and is described above. The two other cases were deemed not related to treatment (see below).

More specifically, when looking into the study documentation, the reported numbers of SAEs for the separate studies are:

cIAI study: There were 6 SAEs in total with 5 in the CAZ-AVI + metronidazole group and 1 in the meropenem group, of which none led to discontinuation of study drug. The SAE experienced in the meropenem arm was ileus. The patients in the CAZ-AVI + metronidazole group experienced events classified into several SOCs [Gastrointestinal disorder (2 pts), Renal and urinary disorders (2 patients), and Injury, poisoning and procedural complications (1 patient)]. None of these cases was deemed related to treatment, which was agreed by the Committee.

cUTI study: There were 10 SAEs in total in this study, with 8 in the CAZ-AVI group and 2 in the cefepime group. The 2 patients in the cefepime group had SAEs of cystitis and pyelonephritis. Among the patients in the CAZ-AVI group, 1 patient experienced SAE within the SOC Gastrointestinal disorder and 1 patient within Nervous system disorder, which both led to discontinuation. The majority (6 pts), however, experienced SAEs within the SOC Infections and infestations, and which were cases of UTI and pyelonephritis following the study, which may represent either treatment failures or new infections, rather than AEs. As described above, the SAE in the Nervous system disorder, was the only one case deemed (to be) possibly related to treatment with CAZ-AVI by the blinded observer. However, as the symptoms also seem to be consistent with pre-existing complaints that the patient had before prior to enrolment in the study, it seems less likely to be caused by the study drug, even though CAZ-AVI cannot be ruled out.

The CHMP agreed that the reported SAEs were in line with what would be expected based on known safety profile for CAZ-AVI in adults, and that there were no new safety findings specifically identified for the paediatric population.

Laboratory findings

- Clinical Laboratory Evaluations

Potentially clinically significant (PCS) post-baseline hematology values, anytime up to Last Visit, for the Safety Analysis Set, are presented in Table 86, and for clinical chemistry values, in Table 87.

Table 86. Potentially Clinically Significant Post-baseline Hematology Values, anytime Up to Last Visit - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

Clinical Laboratory variable (SI Unit)	PCS Criteria	Number (%) of patients					
		cIAI		cUTI		Total	
		CAZ-AVI + MTZ (N=61) n/N[a] (%)	Meropenem (N=22) n/N[a] (%)	CAZ-AVI (N=67) n/N[a] (%)	Cefepime (N=28) n/N[a] (%)	CAZ-AVI ± MTZ (N=128) n/N[a] (%)	Comparator (N=50) n/N[a] (%)
Platelets, Particle Concentration (10**9/L)	>2xULN and >100% increase from baseline	2/60 (3.3)	0/22	1/64 (1.6)	0/26	3/124 (2.4)	0/48
Coombs Test, Direct	Negative baseline and positive post baseline	1/30 (3.3)	1/16 (6.3)	2/51 (3.9)	2/21 (9.5)	3/81 (3.7)	3/37 (8.1)

CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; MTZ = metronidazole; PCS= potentially clinically significant; SI = international system of units; ULN = upper limit of normal value.
Na Number of patients with both baseline and post-baseline values.
(a) For the period 'up to last visit' all lab data will be used for reporting of PCS data. Percents are based on patients with a baseline and post-baseline value.
Baseline is defined as the last assessment made prior to the first dose of study drug.
Source: CAZ-AVI Paediatric Submission Table 4.2.2.10.2

Table 87. Potentially Clinically Significant Post-baseline Clinical Chemistry Values, anytime Up to Last Visit - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

Clinical Laboratory variable (SI Unit)	PCS Criteria	Number (%) of patients					
		cIAI		cUTI		Total	
		CAZ-AVI + MTZ (N=61) n/N[a] (%)	Meropenem (N=22) n/N[a] (%)	CAZ-AVI (N=67) n/N[a] (%)	Cefepime (N=28) n/N[a] (%)	CAZ-AVI ± MTZ (N=128) n/N[a] (%)	Comparator (N=50) n/N[a] (%)
Bicarbonate, Standard (mmol/L)	>1.3xULN and >30% increase from baseline	1/36 (2.8)	0/16	1/52 (1.9)	0/23	2/88 (2.3)	0/39
Calcium (mmol/L)	<0.7xLLN and >30% decrease from baseline	1/53 (1.9)	0/21	0/62	0/25	1/115 (0.9)	0/46
Gamma-Glutamyltransferase (ukat/L)	>3xULN and >200% increase from baseline	3/54 (5.6)	0/19	0/59	1/25 (4.0)	3/113 (2.7)	1/44 (2.3)
Alanine Aminotransferase (ukat/L)	>3xULN and >300% increase from baseline	1/59 (1.7)	0/22	0/64	1/26 (3.8)	1/123 (0.8)	1/48 (2.1)
Aspartate Aminotransferase (ukat/L)	>3xULN and >300% increase from baseline	1/55 (1.8)	0/21	0/64	0/26	1/119 (0.8)	0/47

CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; LLN = lower limit of normal value; MTZ = metronidazole; PCS= potentially clinically significant; SI = international system of units; ULN = upper limit of normal value.
Na Number of patients with both baseline and post-baseline values.
(a) For the period 'up to last visit' all lab data will be used for reporting of PCS data. Percents are based on patients with a baseline and post-baseline value.
Baseline is defined as the last assessment made prior to the first dose of study drug.
Source: CAZ-AVI Paediatric Submission Table 4.2.2.10.4

The MAH concluded:

- No clinically significant shifts in serum electrolytes were seen.
- The C-reactive protein and white cells fell from a raised mean at baseline, reflecting the patients' bacterial infection, and this fall is interpreted as reflecting recovery from the infection.
- A general rise in platelet count was seen and this was interpreted as thrombocytosis caused by bacterial infection, which is well recognised in children.
    - 3 patients met PCS criteria for platelets, 2 were on CAZ-AVI + MTZ, and one was on CAZ-AVI. Both patients with cIAI had intra-abdominal abscesses and one had a cannula

infection. The patient with cUTI did not have any AEs. No AEs related to thromboembolic events were reported by any patient.

The CHMP considered that there were no unexpected observations reported in the clinical laboratory data.

- Vital Signs, Physical Findings, and Other Observations Related to Safety

For the purposes of this Summary of Clinical Safety, ECG, vital sign and physical examination data for the 2 studies have not been pooled.

Changes in vital signs from baseline to those recorded at end of IV treatment, end of treatment, test of cure and late follow-up, were generally small and clinically insignificant. There was a trend for temperature to decrease, which is consistent with patients recovering from infection.

Infrequently, clinically significant vital sign abnormalities were observed. These findings were assessed and considered consistent with variations expected for this study population and not suggestive of an effect by CAZ-AVI.

The majority of patients had QTcB and QTcF values ≤500 ms. There were no ECG abnormalities that were deemed clinically significant.

There were 15 cases of sinus tachycardia in Study C3591004, 4 of which were judged by the investigator to be clinically significant. All 4 of these patients were from the same site (Site 5120) and had tachycardia at baseline that was also judged to be clinically significant. One patient in Study C3591005 had tachycardia on Days 1 and 2 and deemed clinically significant by the investigator and resulted in permanent discontinuation of CAZ-AVI.

The CHMP noted that the majority of patients had normal physical examination results at each study visit. Only infrequently were clinically significant vital sign abnormalities observed. These were, however, explainable and did not indicate an effect by CAZ-AVI.

The MAH stated that the majority of patients had QTcB and QTcF values ≤500 ms, which is not unexpected.

The MAH claimed that there were no ECG abnormalities deemed clinically significant. No patients taking CAZ-AVI in the paediatric studies C3591004 and C3591005 had post baseline QT values >450msec, which is reassuring. Among the 15 cases of tachycardia in cIAI study, four cases were found to be clinically significant, but all of them had significant tachycardia at baseline. One patient who experienced tachycardia in the cUTI study, discontinued study.

The CHMP agreed that no safety issues were identified in the category of vital signs, physical findings, and other observations related to safety in this section.

Safety in special populations

The purpose of this variation is to extend the use of Zavicefta in paediatric patients aged 3 months to < 18 years for the treatment of cIAI and cUTI based on data from two phase 2 paediatric studies and the population PK modelling/simulation analyses, and hence, this section is only applicable for age categories/cohort, gender and by renal function.

- Safety by Age Cohort

The Age Cohorts in the studies were defined according to the definitions agreed with PIP.

Overall, fewer patients were recruited into the lower age ranges. Each AE category was generally balanced between treatment groups. The incidence of AEs reported by adolescents is consistent with the adult

frequency and they were more likely to report symptoms such as tinnitus or back pain than younger patients. There is a higher rate of SAEs in the paediatric cUTI population than the adult cUTI population; however, this reflects the difference in the complicated recurrent urinary tract infection (UTI) study population compared with the adults who tended to be least sick at baseline of the three adult indication populations (cIAI, cUTI and hospital-acquired pneumonia).

The frequency of AEs up to the last visit was generally similar across age cohorts and treatment groups. Any differences should be interpreted with caution given the limited numbers (Table 88).

Data for the following age ranges were also reviewed: Infants and toddlers- 3 months to <2 years, Children- 2 to <12 years, and Adolescents- 12 to <18 years. No clinical differences were observed.

Table 88. Adverse Events up to Last Visit in any Category by Age Cohort - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

	Total (N=178)									
	Number (%) of patients									
	CAZ-AVI ± MTZ					Comparator				
	Cohort 1 (N=35) n (%)	Cohort 2 (N=50) n (%)	Cohort 3 (N=17) n (%	Cohort 4a (N=12) n (%)	Cohort 4b (N=14) n (%)	Cohort 1 (N=14) n (%)	Cohort 2 (N=15) n (%)	Cohort 3 (N=10) n (%)	Cohort 4a (N=6) n (%)	Cohort 4b (N=5) n (%)
Any AE	19 (54.3)	27 (54.0)	8 (47.1)	6 (50.0)	8 (57.1)	9 (64.3)	8 (53.3)	4 (40.0)	4 (66.7)	3 (60.0)
Any AE with an outcome of death	0	0	0	0	0	0	0	0	0	0
Any SAE	4 (11.4)	3 (6.0)	3 (17.6)	0	3 (21.4)	1 (7.1)	0	0	1 (16.7)	1 (20.0)
Any AE leading to discontinuation of IP[a]	2 (5.7)	1 (2.0)	0	0	0	0	0	0	0	0
Any AE of severe intensity	4 (11.4)	2 (4.0)	2 (11.8)	0	2 (14.3)	1 (7.1)	0	0	1 (16.7)	1 (20.0)

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; IP = investigational product; MTZ = metronidazole; SAE = serious adverse event.
Cohort 1: 12 - <18 years; Cohort 2: 6 - <12 years; Cohort 3: 2 - <6 years; Cohort 4a: 1 - <2 years; Cohort 4b: 3 months - <1 year.
Patients with multiple adverse events (AEs) in the same category are counted only once in that category. Patients with AEs in more than 1 category are counted once in each of those categories.
a Action taken, study drug permanently discontinued.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.12

- Safety by Gender

The incidence of AEs in any category up to the last visit was generally similar between gender and treatment groups (Table 89). Any differences should be interpreted with caution given the limited numbers of patients.

Table 89. Adverse Events up to Last Visit in any Category by Gender - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

AE Category	Total (N=178)			
	Number (%) of patients			
	CAZ-AVI ± MTZ		Comparator	
	Male (N=55) n (%)	Female (N=73) n (%)	Male (N=16) n (%)	Female (N=34) n (%)
Any AE	27 (49.1)	41 (56.2)	8 (50.0)	20 (58.8)
Any AE with an outcome of death	0	0	0	0
Any SAE	4 (7.3)	9 (12.3)	0	3 (8.8)
Any AE leading to discontinuation of IP[a]	0	3 (4.1)	0	0
Any AE of severe intensity	2 (3.6)	8 (11.0)	0	3 (8.8)

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; IP = investigational product; MTZ = metronidazole; SAE = serious adverse event.
Patients with multiple adverse events (AEs) in the same category are counted only once in that category.
Patients with AEs in more than 1 category are counted once in each of those categories.
a Action taken, study drug permanently discontinued.
Includes adverse events with an onset date/time on or after the date/time of first infusion up to and including the last visit.
Percentages are based on the total number of patients in the treatment group (N).
Source: CAZ-AVI Paediatric Submission Table 4.2.2.4.11

- Effect of Renal Function

Analysis of the effect of renal function on the safety profile of CAZ-AVI in paediatric patients is not possible in this pooled population. Overall 25% subjects taking CAZ-AVI ± MTZ and 18 % comparator had mild renal insufficiency with creatinine clearance values ≥50 to <80 mL/min at baseline. One patient in each group had a creatinine clearance value <50 mL/min. One patient in each group had a baseline CrCl ≤50 ml/min and experienced an AE (Urinary tract infection with CAZ-AVI; Diarrhoea, Coombs test positive with comparator.

The EU-RMP v2.0 currently includes pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy as a missing information topic. The MAH proposes to add pre-existing moderate renal impairment in paediatric population as an additional missing information topic. The proposed labelling includes information on the administration and posology of CAZ-AVI in paediatric patients with renal impairment.

With regards to age, the MAH claimed that there was no clinically meaningful differences identified in the individual indications. The frequency of AEs up to the last visit was generally similar across age cohorts and treatment groups. Of notice, no patients from cohort 4 (3 months – <2 years) with cIAIs were included in the study.

The CHMP considered that there was in general a slightly higher frequency in AEs in female children vs. males (56.2% vs 49.1%), also for SAEs (12.3% vs. 5.3%) and AEs of severe intensity (11.0% vs. 3.6%), In addition all the 3 patients who discontinued study due to AEs were females. However, the number of events was limited, and in both categories (age cohorts and gender), any differences should be interpreted with caution.

There was a high degree (25%) of patients treated with CAZ-AVI ± MTZ having mild renal impairment, but only a few, single patients with more declined renal functions were included. The Committee therefore acknowledged that analysis of the effect of moderate to severe renal dysfunction on the safety profile of CAZ-AVI in paediatric patients is not possible in this pooled population.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Three (3) (2.3%) patients in the CAZ-AVI ±MTZ group had AEs leading to permanent discontinuation of study treatment. AEs by SOC and PT up to End of IV, for the Safety Analysis Set are presented in Table 90.

One patient, who experienced a SAE of nervous system disorder, is briefly discussed under Serious adverse events.

On assessment of the measurements of heart rate by the sponsor, the patient who experienced tachycardia did not have clinically significant tachycardia and this was assessed to not be a new safety finding.

The patient who discontinued due to nausea and vomiting was a 17 year old female with an existing benign adrenal mass, chronic constipation and nausea requiring Ondansetron, who was also taking intravenous morphine for pain control of her cUTI (acute pyelonephritis), which may offer a plausible explanation for her symptoms requiring discontinuation.

Table 90. Adverse Events Leading to Discontinuation of Investigational Product up to End of IV by System Organ Class and Preferred Term - (Safety Analysis Set) Pooled Phase 2 Paediatric Studies C3591004 (cIAI) and C3591005 (cUTI)

System Organ Class Preferred Term	Number (%) of patients					
	cIAI		cUTI		Total	
	CAZ-AVI + MTZ (N=61) n (%)	Meropenem (N=22)	CAZ-AVI (N=67)	Cefepime (N=28)	CAZ-AVI ± MTZ (N=128)	Comparator (N=50)
Patients with any AE leading to discontinuation of IP	0	0	3 (4.5)	0	3 (2.3)	0
Nervous system disorders	**0**	**0**	**2 (3.0)**	**0**	**2 (1.6)**	**0**
Dizziness	0	0	1 (1.5)	0	1 (0.8)	0
Nervous system disorder	0	0	1 (1.5)	0	1 (0.8)	0
Cardiac disorders	**0**	**0**	**1 (1.5)**	**0**	**1 (0.8)**	**0**
Tachycardia	0	0	1 (1.5)	0	1 (0.8)	0
Gastrointestinal disorders	**0**	**0**	**1 (1.5)**	**0**	**1 (0.8)**	**0**
Nausea	0	0	1 (1.5)	0	1 (0.8)	0
Vomiting	0	0	1 (1.5)	0	1 (0.8)	0

AE = adverse event; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; IV= intravenous; MedDRA = Medical Dictionary for Regulatory Activities; MTZ = metronidazole. Patients with multiple adverse events for the same preferred term are counted only once for that preferred term. Patients with AEs for more than 1 preferred term are counted once for that System Organ Class.
Includes adverse events with an onset date/time on or after the date/time of first infusion and up to and including the date/time of last infusion + 24 hours.

AEs are sorted by system organ class in international order and by preferred term in MedDRA V20.0 High Level Group Term and High Level Term from the hierarchy. Percentages are based on the total number of patients in the treatment group (N). Source: CAZ-AVI Paediatric Submission Table 4.2.2.7.1

The CHMP noted that, in the pooled population, three (2.3%) patients in the CAZ-AVI ±MTZ group had AEs leading to permanent discontinuation of study treatment, all of which were experienced in CAZ-AVI arm in the cUTI study. There were no discontinuations due to AEs in the comparator (cefepime) arm. One discontinuation were due to a SAE - (Nervous system disorder), previously described and deemed possibly related to treatment and discussed under the subheading *Serious adverse events*. One patient had a SAE in the Gastrointestinal disorder SOC, - moderate dizziness, nausea and vomiting - and one patient experienced tachycardia, which were deemed no to be clinically significant, and therefore no new safety finding. Both permanently discontinued study drug.

There were no discontinuations of study drug due to AEs reported in the cIAI study.

No specific pattern of reasons for discontinuation can be seen, but the number of patients is too low to conclude much about AEs causing discontinuation.

Post marketing experience

As of 24 February 2019, 83 events in 57 post marketing cases (15.8% of all 360 cases received) involved paediatric patients, including 5 patients treated in the compassionate use Global Access Program (GAP).

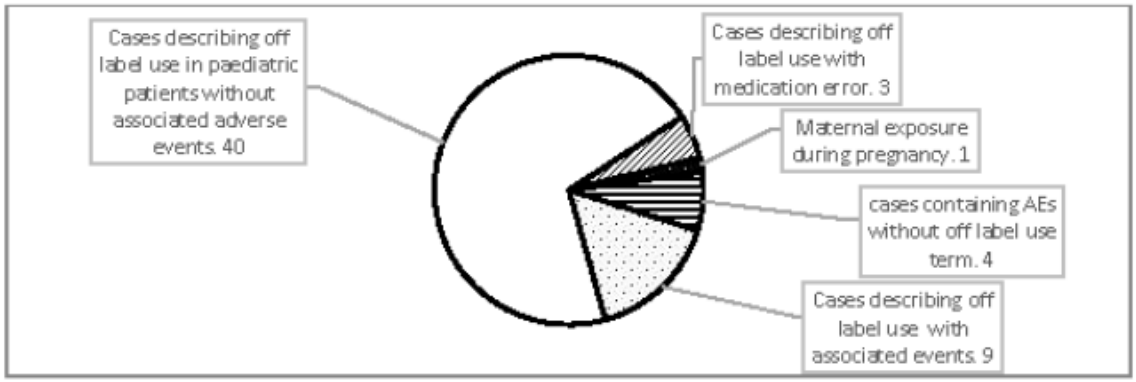


Figure 17. Pie Chart Summary of Post-Marketing Cases involving Paediatric Patients

Fifty-two cases describe off label use in paediatric patients. Of these, 47 events in 41 cases describe off label use without associated adverse events: Off label use [10 events], Product administered to patient of inappropriate age [3], Product use issue [33] and Product use in unapproved indication (use in patients with cystic fibrosis) [2].

The remaining 11 off label use cases, included 14 associated events: in 2 cases, off label use was reported with a medication error (Incorrect product administration duration [1], Product label issue [1];

In 9 cases, off label use was reported with the following 12 associated AEs: Alanine aminotransferase increased [1], Anaemia [1], *Enterobacter* infection [1], Hepatitis [1], Pathogen resistance [1], Septic shock [1], Platelet count decreased [2] and Hypernatraemia [4].

The remaining 7 cases did not report off-label use terms and the events described were Dug resistance [2], Intracranial pressure increased [1], Pneumonia [1], Drug ineffective [1] and Multiple-drug resistance [1]. There was one case of premature birth following maternal exposure during pregnancy.

With the exception of one event of anaemia, the AEs associated with laboratory abnormalities were reported from one unit, and were assessed to be associated with the patients' underlying medical conditions.

One paediatric case included an AE of hepatitis. A 4-year-old patient received CAZ-AVI for *Klebsiella pneumoniae* infection. The patient's medical history included neuroblastoma, bone marrow transplantation and graft versus host disease. Concomitant medications included meropenem trihydrate and tigecycline. According to the reporting physician, there was no causal relationship between hepatitis and CAZ-AVI and the event was more likely caused by the patient's general condition. The patient's underlying pneumonia, carcinoma and graft versus host disease offer a plausible alternative explanation for the reported event and this case does not provide any evidence of a possible causal association between CAZ-AVI administration and hepatitis.

The CHMP considered that no new safety issues have been identified in the paediatric population from post marketing surveillance.

2.6.1. Discussion on clinical safety

This application was submitted to extend the indication of Ceftazidime-avibactam (CAZ-AVI) to include paediatric patients (3 months to <18 years old) with cIAIs and cUTIs. This safety assessment is based on two phase 2 single-blind, randomized, multicenter active-controlled studies of pediatric patients aged ≥3

months to 18 years with either cIAI or cUTI, the studies are denoted C3591004 and C3591005. In addition, the MAH presented the data for global usage and paediatric patients who received the drug off-label.

According to Draft guideline EMA/187859/2017 "Addendum to guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements", no appropriately powered efficacy studies are requested in the paediatric population as efficacy can be extrapolated from adults provided that similar exposure is achieved in the paediatric population. Furthermore, sufficient safety data have to be generated with the intended dose regimen in the paediatric population. In both the paediatric studies submitted to support the indication extensions, safety and tolerability are primary endpoint, while pharmacokinetic and efficacy variables are secondary.

Of the 178 patients who were randomised to receive CAZ-AVI ± MTZ or comparator across the 2 paediatric studies, 128 were treated in the CAZ-AVI ± MTZ group and 50 were treated in the comparator group. They were stratified into four age cohorts: 12-18 years, 6-<12 years, 2-<6 years, and 3 months-<2 years (further divided into 1-<2 years and 3 months-<1 year).The differences in recruitment in each age group between the two studies is not considered of great importance for the safety assessment, but the total number of patients <2 years treated with CAZ-AVI is only 26, which brings uncertainty to the safety assessment of this cohort. Even though there were no patients age 2 years or less in the cIAI study, the total numbers of patients in different cohorts were balanced. In the total overview, the numbers of infants and toddlers in the CAZ-AVI±MTZ group, compared to total comparators, were well balanced.

Since the dose regimen of CAZ-AVI is the same in each age category in the two studies, it is considered acceptable to pool the safety data from two studies even though there is different indications and different comparators used in the two studies. It should, however, be noted that the median exposure to IV study drug was quite different in the two studies; median exposure was 7 (2-13) days for the CAZ-AVI plus metronidazole group in the cIAI study versus 4 (1-11) days for the CAZ-AVI group in the cUTI study.

For the pooled data, however, the median duration of exposure to IV study drug was 5 (1 to 13) days for the CAZ-AVI ± MTZ group and 6 (2 to 13) days for the comparator group. With reference to studies in adults assessed in the MA Application, a greater proportion of adults received the recommended duration of IV CAZ-AVI treatment compared to children; this likely reflects the earlier switch to oral therapy seen in the paediatric studies. While the safety profile is consequently based on a shorter duration of therapy than adults, this may as well reflect clinical practice in the paediatric population, but however, also represent an uncertainty to and hampers the safety evaluation. The median duration of treatment is however within the range of recommended duration of treatment that is proposed in the product information (5-14 days) and is considered relevant for the safety assessment.

In the cUTI and cIAI study, a great proportion (37 and 86%, respectively) of the paediatric patients in the CAZ-AVI arm received other systemic antibiotics reported either before or concomitantly with the CAZ-AVI. This co-medication use will possibly impact the evaluation of CAZ-AVI treatment, both regarding efficacy and safety, in the children.

- Adverse events

The frequency of AEs up to the last visit in the overall patient population was similar between the treatment groups: 68 patients (53.1%) and 28 patients (56.0%) in the CAZ-AVI ± MTZ and comparator treatment groups, respectively. Numerically, the overall rate of any AEs was higher in the comparator group. But there were more AEs leading to treatment discontinuation the CAZ-AVI±MTZ patients, however, the number is low (3 patients, 2.3%). The majority of AEs were up to moderate severity. More severe AEs were registered in the CAZ-AVI±MTZ group. The driver here was the "Infections and infestations", commonly reported in the cUTI study.

The most frequently reported SOC for the CAZ-AVI treatment group, for the overall paediatric population, was Infections and infestations (23.4%). The most frequently reported (⩾4%) AEs by PT for the CAZ-AVI

treatment group for the overall paediatric population were vomiting (8.6%) and diarrhoea (4.7%), both of which are known common ADRs from ceftazidime-avibactam in adults. When including PTs reported up to the last visit in ≥3 patients, infusion site phlebitis (4 pts), seroma (3 pts), UTI (5 pts), rash (3 pts), rhinitis (4 pts), upper respiratory tract infection (3 pts) are AEs reported in addition to vomiting (11 pts) and diarrhoea (6 pts) in the CAZ-AVI group.

There are few (8 pts) of the observed AEs which are deemed *related to study drug* (8 pts, 6.3%) by blinded observer. It is agreed that the all of the related AEs, except for term Nervous system disorder, are known adverse drug reactions (ADRs) included in the SmPC approved in adults.

- Adverse events of special interest

The AEoSI for CAZ-AVI are predefined to be liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders. Up to 6.3% of patients in the CAZ-AVI±MTZ group experienced the hypersensitivity/anaphylaxis related AESI, however, this rate was higher in the comparator group. Some AEoSI (PTs within liver disorders, diarrhoea, hypersensitivity/anaphylaxis) are observed in the studies.

- Deaths and serious adverse events

Deaths

There were no deaths in either study.

Serious adverse events:

SAEs were reported by 13 patients in the CAZAVI ± MTZ treatment group (10.2%) and 3 patients in the comparator treatment group (6.0%). One SAE (Nervous system disorder) reported in Study C3591005 in the CAZ-AVI group, was judged possibly related to study treatment and led to permanent discontinuation.

- Discontinuation

Three (2.3%) patients in the CAZ-AVI ±MTZ group had AEs leading to permanent discontinuation of study treatment, all in CAZ-AVI arm of cUTI study (nervous system disorder, tachycardia, and dizziness, nausea and vomiting).

- Laboratory findings, vital signs, physical findings

As of laboratory finding, there was increase in the numbers of platelets, but no thrombotic events were reported, the said increase is common in children with infections, however, such increase was not observed in the comparator group. The positive Coombs test was more prevalent in the comparator group, and no haemolytic anaemias were registered. There are no unexpected observations reported in the clinical laboratory evaluations, vital signs or physical findings.

- Special patient groups

The rate of ADRs was compared to the rate in adult population. Using this comparison, no new safety issues were recognised. The presented rates are acceptable, but are deemed to change after larger paediatric exposure to CAZ-AVI.

Age and gender did not appear to be associated with a safety profile different from that already known, but there is a trend towards higher frequencies of (S)AEs in the females versus females, and all the three patients who discontinued were females.

Lack of inclusion in age group in the cIAI study

No children in the ages 3 months < 2 years was included in the cIAI study C3591004. Evaluation of the present data did not identify any differences in the safety profile of clinical significance between Zavicefta in

children 3 months to <18 years (evaluation of pooled safety data from paediatric studies in cUTI and cIAI) and what is known for the safety profile of Zavicefta from adult studies. However, there is an uncertainty regarding safety data for cIAI, including serious infections, as data in the population age 3 months to <2 years is lacking.

Lack of inclusion of children with moderate/severe renal impairment

No safety concerns regarding decreasing renal function were reported in these studies, however studies included patients with relatively good kidney function. There was a high degree (25%) of patients treated with CAZ-AVI ± MTZ having mild renal impairment, but single patients with more declined renal functions.

- Post-marketing experience:

As of 24th February 2019, 83 events in 57 post marketing cases (15.8% of all 360 cases received) involved paediatric patients, including 5 patients treated in the compassionate use Global Access Program (GAP). Taking into account the post-marketing off-label use data, no clear trends are observed and no new safety issues have been identified in the paediatric population.

Additional expert consultations

Not applicable.

Assessment of paediatric data on clinical safety

See above.

2.6.2. Conclusions on clinical safety

Safety analysis of the pooled phase 2 paediatric studies comprising 128 paediatric patients (aged 3 months to <18 years) exposed to intravenous ceftazidime-avibactam has been conducted. All randomised patients who received any amount of IV study therapy (CAZ-AVI±MTZ) were included. About half (68 patients, 53.1%) of the patients treated with CAZ-AVI±MTZ experienced AEs, however, only 8 AEs were considered treatment-related.

The overall safety profile in paediatric patients seems to be in line with the expected safety profile for CAZ-AVI in adults, and no new safety issues have been identified in the two studies performed. However, the data on safety is limited based on the small number of patients included. In particular is safety in patients <2 years of age including serious cases of cIAI is limited. Safety in children with moderate/severe renal impairment is missing, and currently, no dose recommendations in the severe group are proposed.

It is concluded that the data provide overall clinical evidence that CAZ-AVI has an acceptable safety profile for use in paediatric patients aged 3 months to <18 years of age with cUTI and cIAI.

2.6.3. 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.

2.7. Risk management plan

The MAH submitted an updated RMP version 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 3.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

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

Pharmacovigilance plan

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.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important potential risks		
Hepatotoxicity	Statements within SmPC Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU questionnaire for post-marketing reports related to hepatoxicity. Additional PV activities: None
Bacterial resistance development	Statement within SmPC Section 5.1 (Pharmacodynamic properties) Product labels provide information concerning resistant organisms and instructions for proper use in an attempt to limit bacterial resistance development. No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: targeted FU questionnaire for resistance and lack of effect-associated events for post-marketing reports. Additional PV activities: Monitor and follow-up on any clinical and/or microbiological failures in the clinical studies where there is potential for development of resistance whilst on therapy. Post-approval commitment for monitoring resistance and increasing levels through the Resistance Surveillance Programme
Missing information		
Pregnancy exposure	Statements within SmPC Sections 4.6 (Fertility, pregnancy, and lactation) and 5.3 (Nonclinical safety data). No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Lactation exposure	Statements within SmPC Sections 4.6 (Fertility, pregnancy, and lactation) and 5.3 (Nonclinical safety data). No additional RMMs.	Routine PV activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Immunocompromised population exposure	None proposed	Routine PV activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	No additional RMMs.	Additional pharmacovigilance activities: None.

2.8. Update of the Product information

As a consequence of this extension of indications, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are being updated to reflect the additional population, the paediatric posology, paediatric safety information, the description of the clinical trials and handling instructions for paediatric dosing.

Due to the complex handling instructions, and particularly inconvenient concentrations/reconstitution volumes for calculation of individual paediatric doses, as a result of the assessment, a warning was included in the section 4.4 of the SmPC (under the subheading "Paediatric population") to highlight that for the youngest children (from 3 months to less than 12 months of age) there is a potential risk of overdosing which is related to the difficulties to calculate the volume of administration of the dose, with a cross-reference to the section 4.9.

In Section 6.6 of the SmPC a paediatric-specific wording for the youngest population (from 3 months to less than 12 months of age) was also included, together with tabulated dosing volumes calculated based on different weights. The tabulated instructions are presented separately for paediatric patients with normal renal function as well as for those with mild or moderate renal impairment. Although these instructions are not inclusive of all possible calculated doses, they include a broad range of the doses to be expected, and provide clear and detailed information to the user on how to calculate doses and prepare the infusions.

The Package Leaflet was updated in accordance.

In addition, the MAH took the opportunity to correct the sodium content to SmPC sections 2 and 4.4 and PL section 2 and the volumes of distribution of ceftazidime and avibactam in SmPC section 5.2.

For full details of the PI changes, please refer to Attachment 1.

2.8.1. User consultation

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

2.9. Significance of paediatric studies

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH initially applied for an extension of the indications of Zavicefta to include treatment of paediatric patients from the age of 3 months to <18 years with the following infectious diseases:

- Complicated intra-abdominal infection (cIAI)

- Complicated urinary tract infection (cUTI)

The CHMP, during this variation suggested that the scope of the application would be extended to include treatment of paediatric patients from the age of 3 months to <18 years with the following other approved indications for Zavicefta:

- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Treatment of infections due to aerobic Gram-negative organisms in adults, infants (aged 3 months and older), children and adolescents patients with limited treatment options

3.1.2. Available therapies and unmet medical need

cIAI - available therapies

According to IDSA guideline 2017, selection of specific antimicrobial therapy for paediatric patients with cIAI should be based on considerations of the origin of infection (community vs health care), severity of illness, and safety of the antimicrobial agents in specific paediatric age groups.

Acceptable broad-spectrum antimicrobial regimens for paediatric patients with cIAI include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole.

cUTI - available therapies

The EAU/ESPU guidelines 2015 for UTI in children recommend therapy with an antimicrobial regimen for paediatric cUTI patients, such as an aminoglycoside with or without amoxicillin, or a second or third generation cephalosporin, or an extended-spectrum penicillin with or without an aminoglycoside. The most frequently used agents for treatment of paediatric UTI are parenteral cephalosporins (e.g. cefotaxime, ceftazidime and ceftriaxone) or oral cephalosporins (such as cefexime and cefuroxime axetil), trimethoprim and trimethoprim-sulphamethoxazole, ampicillin, amoxicillin, amoxicillin/clavulanic acid, piperacillin, aminoglycosides (i.e. tobramycin and gentamycin), ciprofloxacin, and nitrofurantoin. The dosing regimen selected should be based on local resistance data and urine culture results.

HAP/VAP

Hospital acquired pneumonia, including VAP is a severe disease, and can be a life-threatening condition. The mortality risk increases when these infections are caused by MDR bacteria and in patients with concurrent bacteraemia. The mortality rate attributable to HAP/VAP ranges from 33% to 50%.

Due to the increasing prevalence of resistant bacteria, few antibiotic agents are broadly active against the gram-negative organisms frequently isolated from NP infections. The WHO (2017) identified carbapenem-resistant *P. aeruginosa* as a critical threat with an urgent need of new antibiotics. Recent data show an increase in the prevalence of NP caused by MDR pathogens, most commonly *P. aeruginosa*, with documented resistance to β-lactams, carbapenems, aminoglycosides, and fluoroquinolones. Although increasing drug resistance has diminished the utility of established antipseudomonal β-lactam antibiotics, there are still some antibacterial agents that are effective in treatment of HAP/VAP patients. However, considering the high prevalence and severity of these infections, as well as increasing prevalence of antibiotic-resistant bacteria, effective treatment options are still needed. Particularly, there is an unmet medical need for treatment of patients infected with certain pathogens such as MDR-resistant *P. aeruginosa*.

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 studies

D4280C00015 (C3591004) - cIAI

Clinical phase 2 study to evaluate Safety, tolerability, pharmacokinetics and efficacy of ceftazidime-avibactam when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs). Of the 86 enrolled patients, 83 were randomised in a 3:1 ratio to receive CAZ-AVI + MTZ or meropenem and all of these patients received treatment (61 were treated in the CAZ-AVI + MTZ group and 22 were treated in the meropenem group). The paediatric age groups who received CAZ-AVI plus metronidazole were as follows: 12 to <18 years, (n=22), 6 to < 12 years, (n=33), 3 to < 6 years (n=6). No patients less than 2 years of age received CAZ-AVI plus metronidazole.

D4280C00016 (C3591005) - cUTI

Clinical phase 2 study to evaluate safety, tolerability, pharmacokinetics and efficacy of CAZ-AVI compared to CEF in children from 3 months to less than 18 years of age with cUTIs. Of the 101 enrolled patients, 97 were randomised in a 3:1 ratio to receive CAZ-AVI or CEF and 95 received treatment (67 were treated in the CAZ-AVI group and 28 were treated in the CEF group). The paediatric age groups who received CAZ-AVI were as follows: 12 to <18 years (n=13), 6 to < 12 years (n=17), 3 to < 6 years (n=11), and from the age of 3 months to <2 years (n=27).

3.2. Favourable effects

An updated popPK analysis (CAZ-MS-PED-02) was conducted to assess the PK of CAZ-AVI in paediatric patients and to support the proposed paediatric dose recommendations as well as to support the PK bridging for extrapolation of efficacy and safety. In the updated popPK model, the paediatric PK data from phase II studies (C3591004 and C3591005) and Study D4280C00014 were pooled with PK data from adults (phase I to phase III). At the proposed dose regimens, individual model-predicted Cmax and $AUC_{ss,0-24}$ values for both CAZ and AVI in cIAI and cUTI paediatric patients were generally similar to the corresponding adult population, with geometric mean values from most study cohorts deviating from adults by $\pm$15%.

Simulated paediatric exposures for all age groups (1000 subjects per age group, for indications cIAI, cUTI and HAP/VAP, and renal impairment group) for CAZ and AVI were overall comparable to the corresponding adult exposures.

The PTA simulations, using the joint PKPD target, demonstrated PTA achievement of >90% at the proposed dose regimens for almost all paediatric subgroups (including renal impairment groups) 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.

<u>cIAI indication</u>

Clinical cure rates were 91.8% (56/61) in the CAZ-AVI plus metronidazole treatment arm and 95.5% (21/22) in the meropenem arm in the ITT population at TOC. In the CE population, the cure rates were 92.9% (52/56) in the CAZ-AVI plus metronidazole treatment arm and 95.0% (19/20) in the meropenem at TOC.

cUTI indication

The microbiological response rates were 79.6% (43/54) in the CAZ-AVI group and 60.9% (14/23) in the CEF group in the micro-ITT population at TOC. The combined response in the micro-ITT population were 72.2% (39/54) in the CAZ-AVI group and 60.9% (14/23) in the CEF group at TOC.

The clinical success rates were 88.9% (48/54) in the CAZ-AVI treatment group and 82.6% (19/23) in the CEF group in the micro-ITT population at TOC. In the ME population, the cure rates were 92.7% (38/41) in the CAZ-AVI group and 87.5% (14/16) in the CEF group at TOC.

The eradication rates of infections due to *E.coli* in the micro-ITT analysis set at the TOC visit were 79.6% (39/49) in the CAZ-AVI group and 59.1% (13/22) in the CEF group, and 86.5% (32/37) and 66.7% (10/15), respectively, in the ME analysis set.

3.3. Uncertainties and limitations about favourable effects

No exposure data from paediatric patients with HAP/VAP are available at present. A PK study on NP, HAP/VAP (for children >3 months old to 18 years of age) requested by PDCO as part of the PIP is ongoing. The assessment of this indication is thus based on extrapolation without a supportive PK bridge.

Limited PK data from cIAI patients <6 years and from paediatric patients <2 years were included in the popPK dataset on which the exposure and PTA predictions were based.

Although total exposure (AUC) appeared to be comparable, the predicted exposures for both CAZ and AVI showed higher peak (C_{max}) and lower trough (C_{min}) values in the paediatric population compared to the adult population, which could translate into a shorter time above MIC. Nevertheless, a PTA of >90% was achieved in almost all paediatric subgroups (including renal impairment subgroups), except from cIAI patients aged 1 to <6 years of age who achieved a lower PTA of 82%.

3.4. Unfavourable effects

Adverse events

The frequency of AEs up to the last visit in the overall pooled patient population (N=128) was similar between the treatment groups: 68 patients (53.1%) and 28 patients (56.0%) in the CAZ-AVI ± MTZ and comparator treatment groups, respectively. There are few of the observed AEs which are deemed *related to study drug* (8 pts, 6.3%) to CAZ-AVI±MTZ by blinded observer. Study drug related AEs were dizziness, nervous system disorder, diarrhoea, nausea, vomiting, dermatitis diaper, intertrigo and rash, all observed in one patient each with except for diarrhoea and vomiting with 2 patients each. All the related AEs, except for term Nervous system disorder, are known adverse drug reactions (ADRs) included in the SmPC approved in adults.

The AEoSI for CAZ-AVI are predefined to be liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders. Clarification on the data presented is requested.

Deaths

There were no deaths in either study.

Serious adverse events:

SAEs were reported by 13 patients in the CAZAVI ± MTZ treatment group (10.2%) and 3 patients in the comparator treatment group (6.0%). One SAE (Nervous system disorder) reported in Study C3591005 in the CAZ-AVI group, was judged possibly related to study treatment and led to permanent discontinuation.

Discontinuation:

Three (2.3%) patients in the CAZ-AVI ±MTZ group had AEs leading to permanent discontinuation of study treatment, all in CAZ-AVI arm of cUTI study (i.e. due to nervous system disorder, tachycardia, and dizziness, nausea and vomiting).

3.5. Uncertainties and limitations about unfavourable effects

With reference to studies in adults assessed in the MA Application, a greater proportion of adults received the recommended duration of IV CAZ-AVI treatment compared to children, and this likely reflects the earlier switch to oral therapy seen in the paediatric studies. While the safety profile is consequently based on a shorter duration of therapy than adults, this may as well reflect clinical practice in the paediatric population. However, it also represents an uncertainty to (and hampers the) safety evaluation, especially as it is to be compared to the adult population.

A great proportion (from 37 to 86%) of the paediatric patients is reported to have received other antibiotics either before or concomitantly with the CAZ-AVI treatment. The majority of these have received cefuroxime (for cUTI) or gentamicin (for cIAI). This co-medication use will hamper the evaluation of CAZ-AVI treatment in children and was not discussed by the MAH.

As no children below the age of 2 years (i.e. >3 months and up to 2 years of age) is recruited into the paediatric cIAI study (C3591005) submitted in the present application, there is an uncertainty with respect to the risk of exposing the youngest children to CAZ-AVI.

The handling instructions in the PI were complex, and particularly concentrations/reconstitution volumes were inconvenient (SmPC section 6.6). To highlight this risk and prevent the resulting potential significant risk of severe dosing errors for paediatric patients from 3 months to less than 12 months of age, a warning was recommended for inclusion in section 4.4 of the SmPC.

Safety in children with moderate and severe renal impairment is lacking and the dosing recommendation is only based on simulations.

Overall, the number of children included is low and can only contribute to detect common AEs.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Assuming that similar PK exposure to adults should lead to similar response to ceftazidime and avibactam, a population PK modelling approach was employed to identify appropriate doses of CAZ and AVI to be used in children >3 months to 18 years of age. Therefore, the extension of the proposed indications to the paediatric patients depends on the adequacy of the proposed dose regimens in different age subgroups and renal impairment categories based on the comparability of PK to adults and whether the paediatric safety profile is acceptable.

The comparability of PK in paediatric patients to adults was demonstrated, using popPK modelling and PTA simulations. It is reassuring that acceptable PTAs of >90% were achieved at the proposed dose regimens using the same joint PKPD target as that employed in the original MAA for adults. This was shown for almost all paediatric subgroups (including renal impairment groups) with cIAI, cUTI and HAP/VAP, except for cIAI patients aged 1 to <6 years. However, the slightly lower PTA is not considered to be of major concern due to the following: (i) the individual model-predicted PTA was supportive, (ii) the PDT against which PTA was estimated was 1-log kill (stasis might have sufficed for cIAI) and (iii) clinical outcomes of cIAI are strongly driven by adequate surgery. In addition, the proposed dose regimen for this age group is consistent with doses for other indications for CAZ-AVI. Of note, the proposed ceftazidime dose in the CAZ-AVI combination is consistent with CAZ alone, for which there is an extensive experience with the paediatric use.

The extrapolation for HAP/VAP was based on popPK/PTA simulations, using adult datasets across all 3 site-specific indications (cIAI, cUTI, and HAP/VAP) and PK data from paediatric patients with cUTI and cIAI, including children with severe cUTI infections requiring IV treatment. This strategy is considered acceptable. In adult patients, the same CAZ-AVI dose regimen of 2/0.5 g q8h was found efficacious for treatment of all site-specific infections (cUTI, cIAI and HAP/VAP). There were no significant differences in the plasma exposures for ceftazidime and avibactam between these patient populations. Considering also similarity of PK data for both components in paediatric patients with cIAI and cUTI, it is expected that ceftazidime and avibactam plasma exposures will also be similar in paediatric patients with HAP/VAP. Nonetheless, it is reassuring that the adequacy of the dose regimen and PK bridge will be reassessed when the HAP/VAP exposure data from the ongoing PIP trial in children >3 months to <18 years of age become available.

As stated in the Zavicefta SmPC section 4.4, the use of ceftazidime/avibactam for treatment of aerobic Gram-negative infections in adult patients with limited treatment options is based on experience with ceftazidime alone and on analyses of the PK-PD relationship for ceftazidime/avibactam. This holds true for paediatric patients. 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 is supported.

The overall safety profile in paediatric patients seems to be in line with the expected safety profile for CAZ-AVI in adults, and no new safety issues have been identified in the two studies performed. The safety in children 3 months to <2 years of age with cIAI and in children with moderate and severe renal impairment could not be evaluated because there were none or only few patients included in the two paediatric studies.

3.7.2. Balance of benefits and risks

The totality of the data and the consideration that ceftazidime is already approved for use in children, with dosing recommendations down to birth, allows for concluding that the proposed dosing recommendations are adequate for both ceftazidime and avibactam and that the exposures are sufficiently similar to allow extrapolation of safety and efficacy for cIAI, cUTI and HAP/VAP as well as in aerobic Gram-negative infections in paediatric patients with limited treatment options from adults.

3.7.3. Additional considerations on the benefit-risk balance

There was a potential risk of overdosing for the youngest children from 3 months to less than 12 months of age, related to the difficulties to calculate the volume of administration of the dose. Therefore, a warning was included in section 4.4 of the SmPC to highlight this risk, with a cross-reference to section 4.9. In addition, a table with dosing volumes calculated based on different weights was added to section 6.6. Although these instructions are not inclusive of all possible calculated doses, they include a broad range of the doses to be expected, and provide clear and detailed information to the user on how to calculate doses and prepare the infusions.

3.8. Conclusions

The overall B/R of CAZ-AVI (Zavicefta) is positive for the extension of indication to broaden the current indications to include treatment of paediatric patients with cIAI, cUTI, HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options from the age of 3 months to less than 18 years.

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 paediatric patients aged 3 months to less than 18 years for Zavicefta (for the treatment of cIAI and cUTI, HAP/VAP and aerobic Gram-negative infections in patients with limited treatment options), based on data from paediatric studies D4280C00014, C3591004 and C3591005 and the population PK modelling/simulation analyses (CAZ-MS-PED-01 and CAZ-MS-PED-02). 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 in order to reflect this additional population, the paediatric posology, paediatric safety information, the description of the clinical trials and handling instructions for paediatric dosing. The Package Leaflet is updated in accordance.

A warning was included in section 4.4 of the SmPC, with a cross-reference to section 4.9, to highlight a potential risk of overdosing for the youngest children from 3 months to less than 12 months of age, related to the difficulties to calculate the volume of administration of the dose. In addition, a table with dosing volumes calculated based on different weights was added to section 6.6.

The Marketing authorisation holder (MAH) took the opportunity to correct the sodium content to SmPC sections 2 and 4.4 and PL section 2 and the volumes of distribution of ceftazidime and avibactam in SmPC section 5.2.
The RMP version 3.2 has been approved with this variation.

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 Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0340/2018 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-4027-II-0015'