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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zavicefta

ceftazidime / avibactam

Procedure no: EMEA/H/C/004027/P46/005

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	17 July 2023	17 July 2023	☐
☐	CHMP Rapporteur Assessment Report	21 Aug 2023	25 Aug 2023	☐
☐	CHMP members comments	04 Sep 2023	04 Sep 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Sep 2023	07 Sep 2023	☐
☒	CHMP adoption of conclusions:	14 Sep 2023	14 Sep 2023	☐

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1. Introduction

On 21 June 2023, the MAH submitted the final clinical study report for a paediatric study for Zavicefta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview was provided.

About the product

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

Ceftazidime is an injectable third generation cephalosporin antibiotic which has been in clinical use worldwide for more than 25 years for the treatment of infections caused by aerobic Gram-negative pathogens. Ceftazidime has been shown to be safe and effective in adult and paediatric patients (neonates to adolescents <18 years of age) for a range of indications. However, over the past 15 years, resistance to ceftazidime has been increasing worldwide. The most common mechanism of resistance is bacterial production of β-lactamases, in particular, extended spectrum β-lactamases (ESBLs).

Avibactam is a 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 KPC). Avibactam has no inhibitory effect on class B metallo-beta-lactamases.

The fixed dose combination of CAZ-AVI was approved in the United States in 2015 for use in adults with cIAI (in combination with metronidazole), cUTI, or HAP/VAP, and in 2019 for use in children 3 months of age and older with cIAI (in combination with metronidazole), or cUTI, under the brand name AVYCAZ. Approval for use in adults in the EU was granted in 2016 under the brand name Zavicefta. Extension of indication was approved in October 2020 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).

2. Scientific discussion

2.1. Information on the development programme

The MAH stated that the paediatric study C3591024*, a Phase 2a, 2-Part, Open-Label, Non-Randomized, Multicenter, Single and Multiple Dose Trial to Evaluate Pharmacokinetics, Safety and Tolerability of Ceftazidime and Avibactam in Neonates and Infants From Birth to Less Than 3 Months of Age With Suspected or Confirmed Infections due to Gram-Negative Pathogens Requiring Intravenous Antibiotic Treatment*, is part of a clinical development programme. A Type II variation application consisting of the full relevant data package is expected to be submitted in Q4 2023.

2.2. Information on the pharmaceutical formulation used in the study

The commercial drug product was used in the study. The formulation approved in the EU is a fixed dose combination product; vials contain the equivalent of 2 g ceftazidime and 0.5 g avibactam powder for concentrate for solution for infusion.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the paediatric study C3591024 (PIP, Measure 6).

2.3.2. Clinical study

Study C3591024: *A Phase 2a, 2 Part, Open Label, Non-Randomized, Multicenter, Single and Multiple Dose Trial to Evaluate Pharmacokinetics, Safety and Tolerability of Ceftazidime and Avibactam in Neonates and Infants From Birth to Less Than 3 Months of Age With Suspected or Confirmed Infections due to Gram Negative Pathogens Requiring Intravenous Antibiotic Treatment*

Description

Study C3591024 was a multicentre, open-label, single and multiple dose pharmacokinetic (PK) study. The primary objective of the study was to characterise PK of CAZ-AVI and assess its safety and tolerability in neonates and young infants aged from birth to <3 months. The efficacy was assessed as a secondary objective in the multiple dose part of the trial. The study outline is provided in Figure 1. The sequence of cohort startup is provided in Figure 2.

This study was conducted in about 39 sites in 9 countries (Estonia, Greece, Hungary, India, Italy, Philippines, Slovakia, Taiwan, and USA). It was planned to enrol approximately 48 participants. However, the study was terminated early by the sponsor on 30 December 2022 due to slow recruitment and the collected PK data were by the MAH considered sufficient to support dose recommendations and safety/efficacy extrapolation for the neonatal age range. According to the MAH this decision was not due to safety concerns.

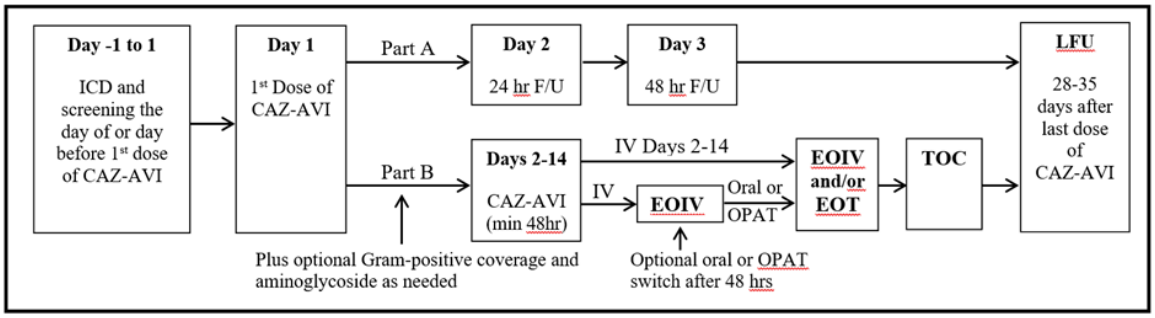
Methods

Study participants

Participants were hospitalised neonates and infants who were receiving IV therapy for treatment of bacterial infection (**Part A**), and who were requiring IV antibacterial therapy due to suspected or confirmed aerobic Gram-negative bacterial infection (**Part B**). Patients with suspected or confirmed central nervous system infection were excluded. Patients with moderate or severe renal impairment defined as serum creatinine ≥2 times the upper limit of normal (ULN) for age OR urine output <0.5 mL/kg/h (measured over at least 8 hours) OR requirement for dialysis were excluded.

Parts A and B were divided in 3 age cohorts:

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



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

Figure 1. Study Outline. Source: Appendix 16.1.1, Protocol Section 3

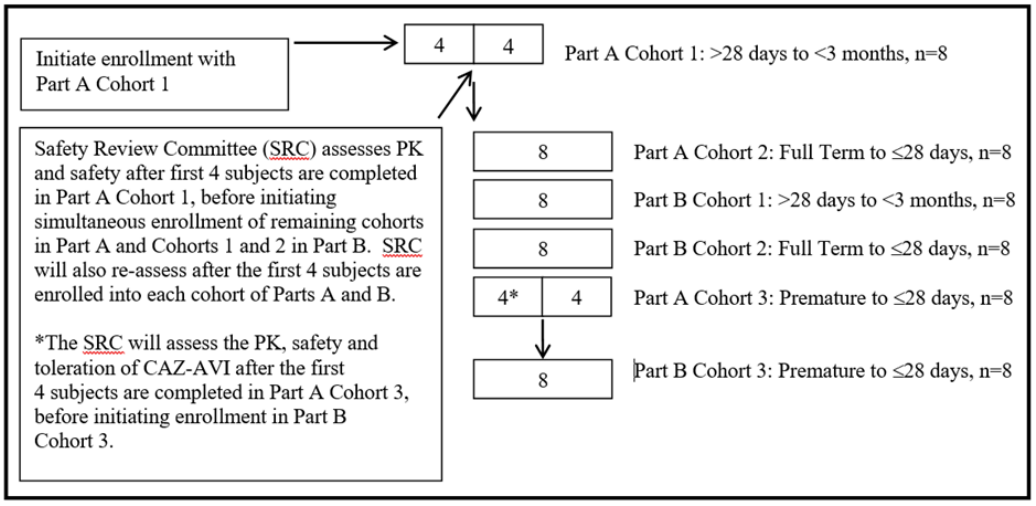


Figure 2. Cohort Startup. Source: C3591024 CSR Protocol Figure 2

Treatments

In **Part A**, participants received a single IV infusion of CAZ-AVI over 2-hours (±10 min) on Day 1, according to their cohort as indicated in Table 1.

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

Table 1. CAZ-AVI weight-based doses for each Cohort

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

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

(chronological age) was used for determining eligibility of pre-term neonates in Cohort 3. Source: Appendix 16.1.1, Protocol Table 2

Dose rationale

Dosing for this study was based on modelling and simulation study CAZ-MS-PED-02 which included data from the adult Phase 1, 2, and 3 studies, and three prior paediatric studies (patients aged 3 months to <18 years): D4280C00014, D4280C00015/C3591004 and D4280C00016/C3591005. The exposure target was defined as achieving at least 50 percent of time during the dosing interval that CAZ and AVI are simultaneously above the minimum inhibitory concentration (MIC) of 8 mg/mL for CAZ and Critical threshold concentration (CT) of 1.0 mg/L for AVI, respectively. These are the same joint PK/PD targets used to support approval in adults.

Of note, dosing recommendation for CAZ as monotherapy are 100-150 mg/kg/day (divided in three doses) and 25-60 mg/kg/day (divided in two doses) for infants >2 months and neonates/infants ≤2 months, respectively.

Objective(s)

The following objectives and main endpoints were evaluated in paediatric patients from birth to less than 3 months who are hospitalised and receiving IV antibiotic therapy.

Table 2. Study Objectives and Endpoints – Part A. Source: C3591024 CSR Protocol Section 2

Type	Objective	Endpoint
Primary		
PK (C3591024 Report Body Section 5.3)	To characterise the PK of a single intravenous dose of CAZ-AVI in hospitalised neonates and infants from birth to <3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
Secondary		
Safety (C3591024 Report Body Section 5.2)	To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in hospitalised neonates and infants from birth to <3 months.	Safety and tolerability endpoints included AEs, SAEs, deaths, discontinuations due to AEs, and laboratory abnormalities.

Source: C3591024 CSR Protocol Section 2

Table 3. Study Objectives and Endpoints – Part B

Type	Objective	Endpoint
Primary		
Safety (C3591024 CSR Body Section 5.2)	To evaluate the safety and tolerability of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.	Safety and tolerability endpoints included AEs, SAEs, deaths, discontinuations due to AEs and laboratory abnormalities.
Secondary		
PK (C3591024 CSR Body Section 5.3)	To evaluate the pharmacokinetic profile of multiple intravenous doses of CAZ-AVI in hospitalised neonates and infants from birth to <3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
Efficacy (C3591024 CSR Body Section 5.1)	To evaluate the efficacy of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.	Efficacy outcome measures included: • All-cause mortality. • Clinical outcome at EOIV, EOT, TOC, and LFU. • Cure defined as clinical improvement and no need for further antibacterial treatment, 7 to 14 days after EOT. • Microbiological eradication 7 to 14 days after EOT (Micro-ITT Analysis Set). • Emergent infections.

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

For microbiology evaluations, blood, urine or other specimen and tissue samples from the infection site were obtained at TOC. All isolates were sent to the central laboratory for organism identification and susceptibility testing.

Outcomes/endpoints

See information under "Objectives" above.

Blood samples for PK (0.3 mL per sample) were collected on Day 1 (Part A) or after at least 3 doses had been administered (Part B) at the following time points:

1) anytime within 15 minutes prior to or 15 minutes after stopping CAZ-AVI infusion,

2) anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and

3) anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion.

Preference was to be given to the first and third collection time if only two PK samples were obtained for any reason.

PK samples were analysed using a validated analytical method (not specified) in compliance with Pfizer's applicable SOPs by Labcorp Bioanalytical Laboratory. No bioanalytical reports has been included in the current submission.

Sample size

The planned sample size (48 subjects; 3 cohorts of 16 subjects) was considered adequate to evaluate the pharmacokinetics of CAZ-AVI in neonates and infants and to provide critical insight into safety and toleration in this population. Similarly, the planned sample size in Part B (24 subjects, 3 cohorts of 8 subjects) was considered adequate to provide insight into efficacy in this suspected or confirmed aerobic Gram-negative bacterial infection population.

Statistical Methods

Pharmacokinetic analysis: The PK analysis set was defined as subjects who received a single IV dose of CAZ-AVI in Part A or at least 3 consecutive doses of CAZ-AVI in Part B with at least 1 ceftazidime and/or avibactam plasma PK measurement available.

For each Part, A and B and each Cohort 1, 2, and 3, the plasma concentrations were summarised by nominal sampling time using descriptive statistics (e.g., number, mean, standard deviation [SD], minimum, median, maximum, geometric mean, and coefficient of variation [CV]).

For 1 participant (Part A, Cohort 1), there was a deviation in the procedure for dilution of the stock volume of the study intervention. It is presumed an unknown and undocumented error occurred in the dose administered as a result of the documented procedural deviation based on the participant's plasma CAZ and AVI concentrations being markedly higher than expected; therefore, additional pharmacokinetic analyses were provided excluding this 1 participant.

The MAH states that the avibactam and ceftazidime concentration, paediatric subject demographics, and disease status data from Cohorts 1 to 3 will be combined with the data from appropriate previous clinical studies in paediatric subjects and/or adults for a population PK (popPK) analysis. The actual dosing and plasma sampling times will be used for the analysis. A stand-alone population PK modelling and simulation analysis plan will be prepared, and the results will be reported in a stand-alone report, for each Part A and Part B, outside of the clinical study report (not submitted in this Art. 46 procedure).

Results

Recruitment/Number analysed

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

Table 4. Participant Evaluation Groups by Part. Source: CSR C3591024 Table 6

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

Eleven participants in Part B were excluded from the Micro-ITT Analysis Set at Screening because no baseline Gram-negative pathogen was isolated: 1 participant in Cohort 1, all 5 participants in Cohort 2, and 5 participants in Cohort 3.

Baseline data

In Part A (N=25), over half of the participants were female (60%) and were White (72%). The median (min, max) age was 25 (2, 89) days and the median (min, max) corrected age was 45 (34, 56) days.

In Part B (N=21), over half of the participants were male (52.4%) and were White (85.7%). The median (min, max) age was 23 (6, 86) days.

Gestational age across cohorts is given in Table 5. All participants in Cohorts 1 and 2 were ≥37 weeks gestational age, except 2 participants in Part A, Cohort 1 (34-36 weeks). Most participants in Cohort 3 were 30 to 33 weeks gestational age (7 and 5 participants in Part A and Part B, respectively). The youngest participants were 31 weeks gestation (7 and 1 participants in Part A and Part B, respectively). Four participants in Cohort 3 were 34-36 gestational age (1 and 3 participants in Part A and Part B, respectively).

Table 5. Baseline Gestational Age– Safety Analysis Set (CSR, part of Table 8)

	Part A				Part B				Part A + Part B
Number (%) of Participants	Cohort 1 (N=9) n (%)	Cohort 2 (N=8) n (%)	Cohort 3 (N=8) n (%)	Total (N=25) n (%)	Cohort 1 (N=8) n (%)	Cohort 2 (N=5) n (%)	Cohort 3 (N=8) n (%)	Total (N=21) n (%)	Total (N=46) n (%)
Gestational Age (weeks)									
< 26 weeks	0	0	0	0	0	0	0	0	0
26 - 29 weeks	0	0	0	0	0	0	0	0	0
30 - 33 weeks	0	0	7 (87.5)	7 (28.0)	0	0	5 (62.5)	5 (23.8)	12 (26.1)
34 - 36 weeks	2 (22.2)	0	1 (12.5)	3 (12.0)	0	0	3 (37.5)	3 (14.3)	6 (13.0)
>= 37 weeks	7 (77.8)	8 (100.0)	0	15 (60.0)	8 (100.0)	5 (100.0)	0	13 (61.9)	28 (60.9)

Part A: Single-Dose & Part B: Multi-Dose.
Cohort 1: > 28 days to < 3 months; Cohort 2: Full Term to <= 28 days; Cohort 3: Premature to <= 28 days.
N = Number of participants in each cohort group. n = Number of participants with the specified characteristic.
Percentages are based on the total number of participants in each cohort group and total (N).
PFIZER CONFIDENTIAL SDTM Creation: 23JAN2023 (03:37) Source Data: adsl Table Generation: 06APR2023 (10:43)
(Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR Figaro/C3591024 CSR/adsl infa
Table 14.1.2.4 Ceftazidime-Avibactam is for Pfizer internal use.

Median (min, max) weight was 4.9 (3.3, 6.4) kg, 3.5 (3.1, 4.0) kg, and 1.7 (1.3, 2.6) kg for Part A, Cohorts 1, 2, and 3, respectively, and 4.3 (2.9, 6.0) kg, 2.9 (2.2, 3.6) kg, and 1.8 (1.5, 2.5) kg for Part B, Cohorts 1, 2, and 3, respectively.

The most common primary infectious diagnoses were sepsis (18 participants [39.1%]) and urinary tract infection (7 participants [15.2%]). For Part B, median time from the diagnosis to the study intervention administration was 2 days.

In Part B, the most frequently reported baseline pathogen (Micro-ITT Set) was *Escherichia coli*. In the Micro-ITT Analysis Set, 2 participants in Part B (Cohorts 1 and 3) had isolates that were resistant to ceftazidime (*E. coli* and *Klebsiella pneumoniae*). No isolates tested were reported as resistant to CAZ-AVI.

In Part A, 24 participants (96.0%) reported prior antibiotic medications. The most frequently reported prior antibiotic medications were vancomycin, amikacin and ampicillin.

In Part B, 13 (61.9%) and 17 participants (81.0%) received permissible concomitant antibiotic medications during the Treatment Phase and the Follow-Up Phase, respectively. Two participants received nonpermitted antibiotics during the Treatment Phase, including cefazolin, meropenem, and commercial CAZ-AVI. Concomitant antibiotic medications were not restricted during the Follow-Up Phase and the majority of Part B participants received other antibiotics during this phase.

Pharmacokinetic results

Overall, 45 participants had at least 1 CAZ and/or AVI plasma measurement available and were included in the PK Analysis Set. Summaries of CAZ and AVI plasma concentrations according to nominal sampling time points are given in Table 6 and Table 7. Box and whisker plots of plasma concentrations versus nominal time are presented by cohort for Parts A and B in Figure 3.

The MAH states that median plasma concentrations of CAZ and AVI were generally similar across Cohorts 1 to 3 in Parts A and B although concentrations were slightly lower in Cohort 2 compared to those observed in Cohorts 1 and 3 in Part A. Plasma concentrations were higher for early samples taken near the EOI at 2 hours and lower for samples taken near the end of the dosing interval at 7 hours. Inter-participant variability (CV%) was higher for Cohort 1 in Part A due to one medication error in 1 participant and for samples taken at 7 hours in both Part A and Part B due to wide window of PK sampling collection times.

Box and whisker plots of plasma concentrations versus nominal time excluding the participant with medication error are presented in Figure 4.

Table 6. Summary of Plasma Concentrations (ng/mL) of Ceftazidime by Nominal Time Post Dose – Pharmacokinetic Analysis Set. Source: CSR C3591024 Table 28

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

Table 7. Summary of Plasma Concentrations (ng/mL) of Avibactam by Nominal Time Post Dose – Pharmacokinetic Analysis Set. Source: CSR C3591024 Table 29

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

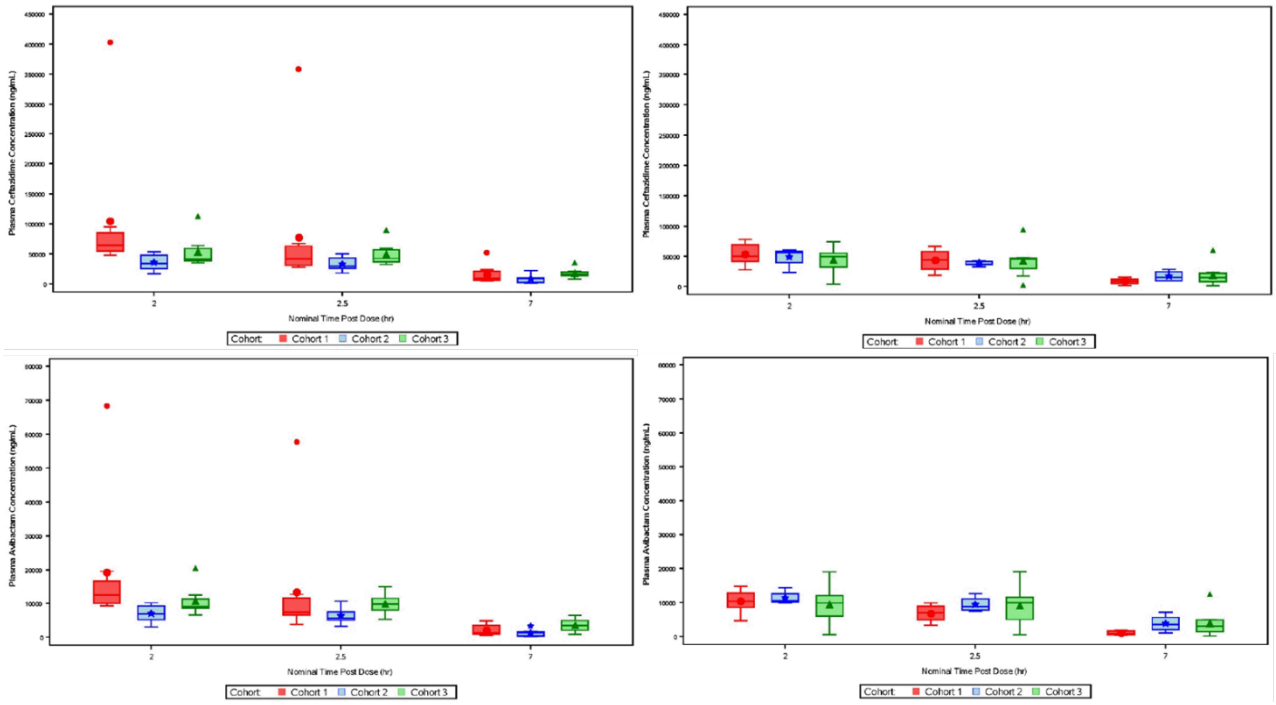


Figure 3. Box and Whisker Plots of Plasma Ceftazidime (upper plots) and Avibactam (lower plots) Concentration Versus Nominal Time Post Dose by Cohort for Part A (left) and Part B (right). Source: CSR C3591024 Figure 8, 9, 14 and 15.

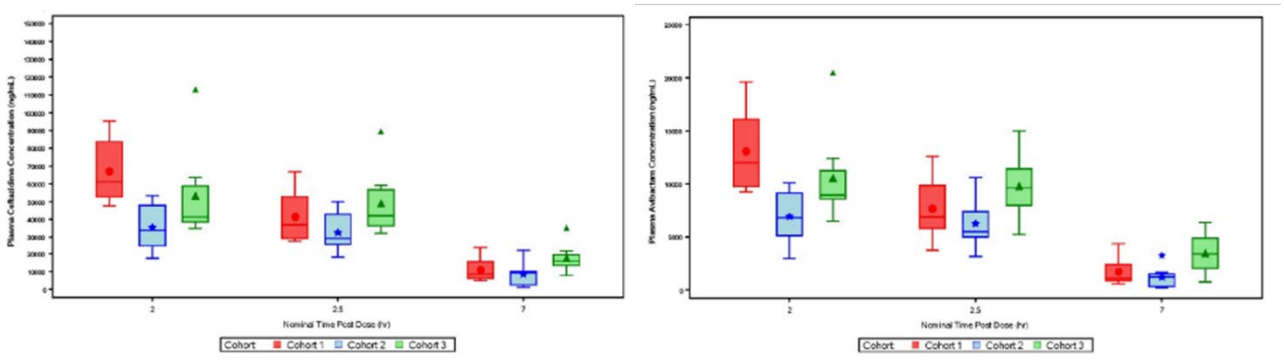


Figure 4. Box and Whisker Plots of Plasma Ceftazidime (left) and Avibactam (right) Concentration Excluding Participant with Medication Error Versus Nominal Time Post Dose by Cohort (Part A). Source: CSR C3591024 Figure 16 and 17.

Efficacy results

In Study C3591024, efficacy was assessed as secondary endpoint and the results presented below are descriptive.

All-Cause Mortality (Part B)

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

In addition, 1 participant (Part B, Cohort 1) died on Study Day 67, after completing the LFU Visit. As this event occurred outside the active data collection period, it was not included in the analysis of all-cause mortality.

Clinical Outcome at TOC (Part B)

The proportion of participants with a favourable clinical outcome at TOC was 81% (17 of 21 participants) in the ITT Analysis Set, and the proportion of participants with a favourable microbiological response at TOC was 80% (8 of 10 participants) in the Micro-ITT Analysis Set.

At TOC, 12 of 16 participants (75.0%) in the Modified-ITT Analysis Set had a favourable clinical outcome (clinical cure or clinical improvement).

Table 8. Clinical Outcome at EOIV, EOT, TOC and LFU (Part B) - ITT Analysis Set

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

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

Microbiological Response (Part B)

At TOC, a favourable per-participant microbiological response rate (eradication or presumed eradication) of 80.0% was observed in the Micro-ITT Analysis Set (N=21).

Nine baseline Enterobacterales were isolated in 10 participants. An unfavourable microbiological response was reported for one pathogen because the participant was assessed as a clinical failure at EOIV.

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

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

Safety results

Extent of Exposure

In Part A, the median duration of CAZ-AVI treatment was 2.00 hours (min-max:1.8-2.4 h). In Part B, the median duration of CAZ-AVI treatment was 7.00 days (min-max:1.0-12.0 d).

Adverse events

Table 9. Overview of Treatment-Emergent Adverse Events up to LFU (All Causalities) by Part - Safety Analysis Set

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

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

Incidence of Adverse Events

Overall, up to LFU, the most frequently reported all-causality TEAEs by PT in 3 or more participants (≥ 5%) were sepsis, anaemia, and vomiting (Table 10). The majority of all-causality TEAEs were mild or moderate in severity. Five participants (10.9%) reported severe all-causality TEAEs up to LFU, all of which were considered not related to study intervention by the investigator.

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

Table 10. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term up to LFU (All Causalities) by Part - Safety Analysis Set

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

Number (%) of Participants Evaluable for AEs by SYSTEM ORGAN CLASS and Preferred Term	Part A (N=25) n (%)	Part B (N=21) n (%)	Part A + Part B (N=46) n (%)
International normalised ratio increased	1 (4.0)	0	1 (2.2)
Oxygen saturation decreased	1 (4.0)	1 (4.8)	2 (4.3)
Transaminases increased	0	2 (9.5)	2 (4.3)
METABOLISM AND NUTRITION DISORDERS	3 (12.0)	1 (4.8)	4 (8.7)
Fluid retention	1 (4.0)	0	1 (2.2)
Hypercholesterolaemia	0	1 (4.8)	1 (2.2)
Hypermagnesaemia	1 (4.0)	0	1 (2.2)
Hypertriglyceridaemia	0	1 (4.8)	1 (2.2)
Hypoalbuminaemia	1 (4.0)	0	1 (2.2)
Hyponatraemia	1 (4.0)	0	1 (2.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (4.0)	0	1 (2.2)
Growth retardation	1 (4.0)	0	1 (2.2)
NERVOUS SYSTEM DISORDERS	0	1 (4.8)	1 (2.2)
Clonus	0	1 (4.8)	1 (2.2)
PSYCHIATRIC DISORDERS	1 (4.0)	0	1 (2.2)
Delirium	1 (4.0)	0	1 (2.2)
RENAL AND URINARY DISORDERS	2 (8.0)	2 (9.5)	4 (8.7)
Hydronephrosis	1 (4.0)	0	1 (2.2)
Oliguria	1 (4.0)	1 (4.8)	2 (4.3)
Renal failure	0	1 (4.8)	1 (2.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (4.0)	2 (9.5)	3 (6.5)
Acute respiratory failure	0	1 (4.8)	1 (2.2)
Bronchomalacia	1 (4.0)	0	1 (2.2)
Bronchopulmonary dysplasia	0	1 (4.8)	1 (2.2)
Pneumothorax	0	1 (4.8)	1 (2.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (4.0)	3 (14.3)	4 (8.7)
Decubitus ulcer	0	2 (9.5)	2 (4.3)
Dermatitis diaper	0	1 (4.8)	1 (2.2)
Erythema	1 (4.0)	0	1 (2.2)
VASCULAR DISORDERS	0	1 (4.8)	1 (2.2)
Hypertension	0	1 (4.8)	1 (2.2)

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

Other Serious Adverse Events

Eight participants experienced SAEs: 3 participants in Part A and 5 participants in Part B. No participant experienced a treatment-related SAE.

Table 11. Summary of Serious Adverse Events by System Organ Class and Preferred Term up to LFU (All Causalities) by Part - Safety Analysis Set Reporting period: Cumulative Through - Cut off date 18JAN2023

Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	Part A (N=25) n (%)	Part B (N=21) n (%)	Part A + Part B (N=46) n (%)
Blood and lymphatic system disorders	0	1 (4.8)	1 (2.2)
Neutropenia neonatal	0	1 (4.8)	1 (2.2)
Cardiac disorders	0	1 (4.8)	1 (2.2)
Cardiac failure acute	0	1 (4.8)	1 (2.2)
Congenital, familial and genetic disorders	0	1 (4.8)	1 (2.2)
Gene mutation	0	1 (4.8)	1 (2.2)
Gastrointestinal disorders	1 (4.0)	1 (4.8)	2 (4.3)
Necrotising colitis	1 (4.0)	1 (4.8)	2 (4.3)
General disorders and administration site conditions	0	1 (4.8)	1 (2.2)
Condition aggravated	0	1 (4.8)	1 (2.2)
Infections and infestations	1 (4.0)	4 (19.0)	5 (10.9)
COVID-19	1 (4.0)	0	1 (2.2)
Candida sepsis	0	1 (4.8)	1 (2.2)
Enterobacter sepsis	0	1 (4.8)	1 (2.2)
Enterococcal sepsis	0	1 (4.8)	1 (2.2)
Sepsis	0	1 (4.8)	1 (2.2)
Sepsis neonatal	0	1 (4.8)	1 (2.2)
Septic shock	0	1 (4.8)	1 (2.2)
Investigations	1 (4.0)	1 (4.8)	2 (4.3)
Electrocardiogram QT prolonged	0	1 (4.8)	1 (2.2)
Hepatic enzyme increased	1 (4.0)	0	1 (2.2)
Renal and urinary disorders	0	2 (9.5)	2 (4.3)
Oliguria	0	1 (4.8)	1 (2.2)
Renal failure	0	1 (4.8)	1 (2.2)
Respiratory, thoracic and mediastinal disorders	0	1 (4.8)	1 (2.2)
Neonatal respiratory failure	0	1 (4.8)	1 (2.2)
Total preferred term events[b]	3	15	18
Total Number of Cases[c]	3	10	13
Total Number of Participants with Serious Adverse Events[d]	3	5	8
Total Number of Participants with Serious Adverse Events[e] 8			

Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	Part A (N=25) n (%)	Part B (N=21) n (%)	Part A + Part B (N=46) n (%)

Part A: Single Dose & Part B: Multi-Dose.
A case is a single event or a series of related events not separated in time occurring in a single participant. Source for SAE is ARGUS database.
a. SAEs are counted at MedDRA preferred term/group with each individual SAE counted only once per participant per group.
b. Total number of events per participant per group.
c. Number of cases that started in the group.
d. Total number of participants having an event that started in the group.
e. Overall count of participants that had a Serious adverse Event in any group.
MedDRA v.25.1J coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 06APR2023 (09:08) Source Data: adsaec Table Generation: 06APR2023 (10:43) (Data cutoff date: 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_CSR/adsae_s001_a Table 14.3.2.2.5 Ceftazidime-Avibactam is for Pfizer internal use.

Clinical Laboratory Evaluation

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

In Part B, elevated C-reactive protein levels were observed, consistent with signs of infection, which normalised during the course of treatment in most participants (where data were available). In addition, increases in lymphocyte counts, lymphocyte/leukocyte ratio, eosinophil counts, and eosinophil/leukocyte ratio were observed in several participants, consistent with their underlying condition.

No clinically meaningful changes from baseline were observed in urinalysis parameters in Part B.

Some laboratory abnormalities were reported as TEAEs, all of which were considered unrelated to study intervention by the investigator.

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

Vital Signs and Physical Findings

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

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

In Part B, the majority of participants had normal physical examination findings at each study visit with the exception of general appearance and skin (e.g., poor general clinical condition, appearance of ill

neonate, and jaundiced skin; which is consistent with and not unexpected for hospitalised neonates and infants (up to 3 months of age) with suspected or confirmed aerobic Gram-negative bacterial infection requiring IV antibacterial therapy.

2.3.3. Discussion on clinical aspects

The MAH has submitted the final clinical study report for the paediatric study C3591024/D4280C00017, which is part of the agreed PIP (study 6). The primary objectives of the study were to characterise PK and evaluate safety of CAZ-AVI in hospitalised neonates and infants from birth to <3 months, including preterm neonates. The weight- and age-based doses used in the study were selected based on simulations by a popPK model previously developed using data from adult and paediatric patients in the age range of 3 months-18 years (CAZ-MS-PED-02, submitted in procedure EMEA/H/C/004027/II/0015).

Single or multiple dose PK data was obtained from in total 17 infants aged >28 days to <3 months, 12 full-term neonates ≤28 days and 16 pre-term neonates ≤28 days. Two of the infants >28 days were pre-term (gestational age 34-36 weeks). Of the pre-term neonates ≤28 days, 12 had a gestational age of 31-33 weeks and 4 had a gestational age of 34-36 weeks.

There are no expected differences in the mechanism of action of CAZ-AVI based on age as both CAZ and AVI exert their effects by acting on the causative pathogen, and the Gram-negative causative pathogens are similar in adults and children. The same joint PK/PD targets are therefore relevant for dose selection in paediatric patients, and extrapolation of efficacy is possible provided that exposure levels are comparable to adults (EMA/CHMP/187859/2017). The acceptability of extending the indication to paediatric subpopulations relies therefore largely on the demonstration of comparable exposures to those achieved in the Phase III studies in adult patients, and on demonstration of an acceptable safety profile.

Sparse sampling was performed in the current study with three blood samples collected from each patient. Consequently, PK parameters could not be calculated by non-compartmental analysis, and the MAH has presented tabular and graphical summaries of CAZ and AVI plasma concentrations according to nominal time points [2h (end of infusion), 2.5h and 7h post-dose]. The exposures achieved in these paediatric cohorts in comparison to adults receiving the approved CAZ-AVI doses and attainment of the PK/PD targets have not been discussed by the MAH. Therefore, the appropriateness of the dose regimens used in this study cannot be assessed at this stage. An updated popPK analysis including all available paediatric PK data and PTA simulations in the relevant age cohorts is awaited.

CAZ and AVI are eliminated by the kidneys, and Zavicefta is dosed to paediatric patients according to age, type of infection and estimated BSA-normalised creatinine clearance (Schwartz bedside formula). In the paediatric PK data set supporting the extension of indication down to 3 months of age, data in patients with moderate or severe renal impairment was very limited and only 1 patient had a CrCL <50 mL/min/1.73 m^2 with a reported baseline value of 43 mL/min/kg^2. Still, dosing recommendations have been approved for all renal function categories for children >2 years, and for children aged 3 months-2 years with creatinine clearance down to 16 mL/min/1.73 m^2 (EMEA/H/C4027/II/005). Dose recommendations in renally impaired children <2 years were based on simulations in which the effect of moderate and severe renal impairment on CL was accounted for by adjustment factors derived from adult renal function categories. This approach was at that time considered acceptable considering that (i) dosing recommendations are given for ceftazidime as monotherapy in children <40 kg with a CrCL down to 5 mL/min, (ii) the exposure of avibactam has been shown to be roughly parallel to that of ceftazidime also in this age cohort, and (iii) the conducted simulations supported adequate PTAs for the investigated dosing regimens.

Data is now available from pre-term and term neonates and infants <3 months. Children born at term are expected to have a GFR of approximately 10-20 mL/min/1.73m^2 the first day of life. Thereafter, rising up to approximately 30-40 mL/min/1.73m^2 after two weeks, adult levels are reached first at two years of age. In preterm neonates, the expected GFR is even lower than in children born at term and rises more slowly than in children born at term. Estimated CrCL/GFR values for patients included in study C3591024 were not provided. Even though patients with moderate and severe renal impairment (defined as serum creatinine ≥2 times the ULN for age, urine output <0.5 mL/kg/h or requirement for dialysis) were excluded, it is therefore expected that the range of renal function in the current study will span lower compared to the previous paediatric studies. In the updated popPK analyses, exposure/PK characteristics of CAZ-AVI according to age, weight, renal function (and other covariates if relevant) for children <2 years should therefore be re-explored. The updated popPK models should be used to establish dosing regimens according to age (and weight/renal function if appropriate) in patients <3 months. The updated model could also be used to confirm previous model predictions at low weight and low renal function, and thereby support already approved dosing regimens for children ≥3 months to <2 years.

In Study C3591024, efficacy was assessed as secondary endpoint, and hence the presented data were only descriptive. At TOC 81% (17/21) of participants in the ITT Analysis Set had a favourable clinical outcome, and 80% (8/10) of participants in the Micro-ITT Analysis Set had a favourable microbiological response. The interpretation of the efficacy outcomes in newborns to <3 months of age is hampered by the low number of participants with confirmed infection due to Gram negative bacteria (n=10).

Safety was a secondary endpoint in part A, and a primary endpoint in part B of this study. The study enrolled 27 participants (only 25 were evaluable for adverse events) in part A and 21 participants in part B. As expected, the incidence of adverse events was lower in the single-dose part A of the study, 32 %, compared to the multiple-dose in part B (71.4%). Although low number of events, serious adverse events were observed twice as frequent in part B, 23.8%, compared to part A, 12%. However, none of the SAEs were considered treatment-related by the investigator.

Severe adverse events were reported almost 5-times as frequent in part B (19%) compared to Part A (4.0%), however, none were considered treatment-related.

Discontinuation of study drug due to AEs were only reported in part B; 2/21 subjects.

Two deaths were reported, one during the study and one 55 days after end of study treatment. Both were considered due to underlying conditions and not related to treatment.

Of note, some of the TEAEs classified as unrelated to study treatment are known ADR listed for Zavicefta, such as candidiasis, diarrhoea, vomiting and pyrexia. The classification of these events as unrelated must be further discussed and justified by the MAH in the upcoming type II variation application. No other new or unexpected safety findings were identified.

In conclusion, the final report for Study C3591024 including PK, safety and efficacy data has been submitted. The MAH stated that sufficient PK data was collected to support dose recommendations and safety/efficacy extrapolation for the neonatal age range. As the updated popPK analysis and PTA simulations have not been submitted in the current Article 46 procedure, the PK bridge and appropriateness of the dose regimens used in the above-mentioned study have not been assessed. Therefore, no conclusions can be drawn regarding the benefit/risk balance of CAZ-AVI in neonates and young infants aged birth to <3 months at this stage. An application for extension of indication to this age group based on the data submitted is expected.

3. Overall conclusion and recommendation

A detailed critical assessment of the data from Study C3591024 has not been performed as part of this Article 46 procedure P46 005. The MAH has notified to EMA (21 June 2023) that they intend to submit a Type II variation in Q4 2023. A variation application to extend the indication to the paediatric population from birth to less than 3 months of age based on data from Study C3591024 and modelling and simulation analyses is thus expected, and a complete assessment of the benefit/risk balance of CAZ-AVI in this age group will then be performed based on the full relevant data package.

This PAM (P46 005) is considered fulfilled, solely based on the fact that the study data have been provided. No changes to the SmPC are recommended as part of this procedure's assessment. However, this conclusion is based on the prerequisite that the MAH applies for an extension of the indication for Zavicefta within a reasonable time frame. I is expected that the relevant application will be submitted by the MAH by the end of 2023.

☒ Fulfilled:

No further action is required in the current procedure. However, additional modelling and simulation data are expected in the context of a variation application for extension of indication prior to any conclusion on product information amendments. The MAH should submit this extension application within 2023.