Amsterdam, 22 May 2025
EMADOC-1700519818-1951858
Committee for Medicinal Products for Human Use (CHMP)

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

Zerbaxa

Ceftolozane / Tazobactam

Procedure no: EMA/PAM/0000256449

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	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2025	28 April 2025
☐	CHMP comments	12 May 2025	12 May 2025
☐	Updated CHMP Rapporteur AR	15 May 2025	15 May 2025
☒	CHMP outcome	22 May 2025	22 May 2025

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1. Introduction

On 25 February 2025, the MAH submitted data from a completed paediatric study for Zerbaxa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

About the product

Ceftolozane/tazobactam (hereafter referred to as C/T) is a fixed dose combination antibacterial product consisting of a 2:1 ratio of ceftolozane (an antipseudomonal cephalosporin β-lactam antibiotic) and tazobactam (a well-established β-lactamase inhibitor [BLI]). C/T displays potent activity against many gram-negative aerobic pathogens such as Pseudomonas aeruginosa (including MDR strains) and Enterobacterales species (including most ESBL-producing strains).

In the EU, C/T was initially approved on 18-SEP-2015 for the treatment of complicated intra-abdominal infections (cIAI) and for the treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis, in adult patients 18 years of age and older. Subsequently, on 25-JUL-2022, these adults indications were extended to include paediatric patients from birth to <18 years of age. On 23-AUG-2019, C/T was also approved for the treatment of hospital acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), in adult patients 18 years of age and older. C/T is approved in several countries globally.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the paediatric study MK-7625A-036/PN036, a Phase 1, open-label, non-comparative, multicentre clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam in paediatric participants with nosocomial pneumonia, is part of a clinical development program. A line listing of all the concerned studies is annexed.

Information on paediatric requirements

Agreed PIPs (patients from birth to less than 18 years of age) for this product are:

- EMEA-001142-PIP01 which covers treatment of urinary tract and intra-abdominal infections (cUTI+cIAI) – PIP completed, and indications approved (EMEA/H/C/1142/II/36).
- EMEA-001142-PIP02 (latest modification accepted 06.09.2024, EMEA-001142-PIP02-16-M02), which covers treatment of nosocomial pneumonia (NP), relevant for the current submission.

PIP02 is due to be completed by May 2026. There are no waivers.

2.2. Information on the pharmaceutical formulation used in study PN036

The commercial drug product approved for use in adults and paediatric patients in the EU was used in the study; a fixed dose combination product, vials contain the equivalent of 1 g ceftolozane and 0.5 g tazobactam 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 PN036 (PIP02, Study 1).

2.3.2. Clinical study

Study PN036: A Phase 1, open-label, non-comparative, multicentre clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam in paediatric participants with nosocomial pneumonia

Description

Study PN036 was a Phase 1, open label, non-comparative, multicentre study that evaluated the safety, tolerability, and PK of C/T in paediatric participants from birth to <18 years of age receiving concomitant standard of care antibiotics for NP (including HAP and VAP). The study design is shown in Figure 1 below.

The study was conducted in twelve sites in eight countries (Chile, Colombia, Estonia, Greece, Mexico, South Africa, Spain, and Ukraine). It was planned to enrol approximately 40 participants.

Each participant was in the study for approximately 30 days from documented informed consent through the final contact.

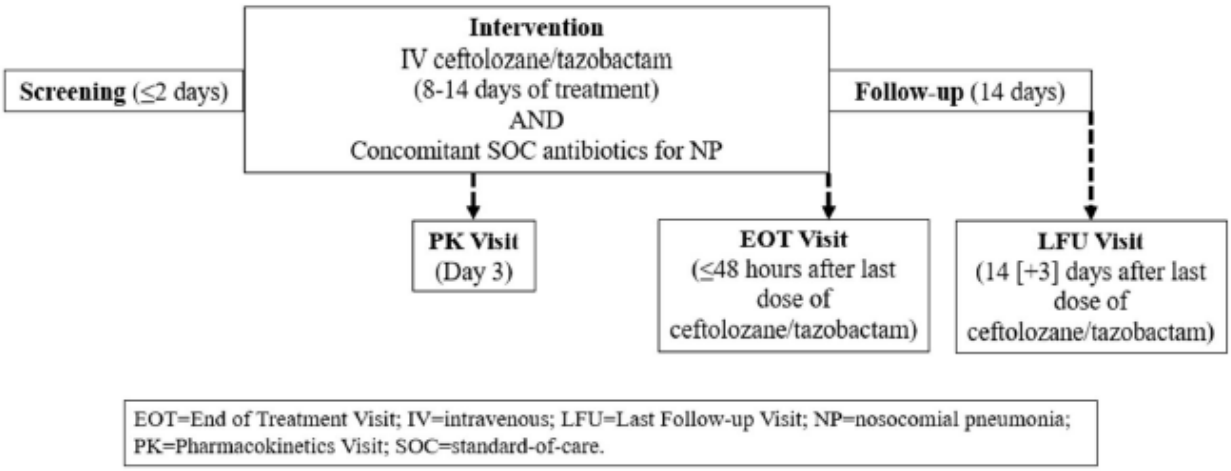

Figure 1. PN036 study design. Source: CSR PN036, Figure 9-1.

Methods

Study participants

Participants were hospitalised patients from birth (>32 weeks gestational age [GA] and ≥7 days postnatal age [PNA]) to <18 years anticipated to receive a minimum of 8 days of concomitant standard-of-care antibiotic therapy for proven or suspected NP (including HAP or VAP).

Participants were to be enrolled into five age groups (Table 1). Enrolment to all groups was opened in parallel at study start. After a minimum enrolment target of six participants for each age group was met, at least ten additional participants were to be enrolled across any of the five age groups. No more than

four additional participants (for a total of ten participants in any given age group) were to be enrolled in any given age group.

Participants with an estimated CrCL <50 mL/min/1.73 m^2 (Group 1-4) or CrCL <20 mL/min/1.73 m^2 (Group 5) based on the revised (bedside) Schwartz equation or requirement for peritoneal dialysis, haemodialysis, or hemofiltration, were excluded. Patients receiving or anticipated to receive piperacillin/tazobactam (as part of SOC) or who had received this treatment within 24 hours prior to the first dose of C/T, were excluded.

Treatments

Each participant received C/T administered as a 60-minute IV infusion (±10 minutes) every 8 hours as add-on therapy to a concomitant standard-of-care antibiotic regimen. The duration of C/T administration was a minimum of 8 days and up to a maximum of 14 days to match the treatment duration in the adult NP study (P008). Proposed initial doses of C/T for each age group were selected based on adult doses from pivotal adult Phase 3 study in participants with NP (P008), allometric scaling, and PK modelling/simulation analysis. Prespecified interim analyses of PK and safety data was performed after enrolment of three patients in any given age group to confirm or modify the proposed paediatric dose for the remaining participants in that group and/or other age groups. No dose modifications were made during the study.

Participants remained in the hospital for the duration of the intervention period; outpatient therapy was not permitted. After the end-of-study treatment, each participant was followed for 14 days.

Table 1. Study interventions. Source: CSR PN036, Table 9-1, Modified by assessor.

Group	Age	Dose	Regimen and treatment period
1	12 to <18 years	2 g ceftolozane/ 1 g tazobactam	60-minute IV infusion (±10 minutes) every 8 hours for 8-14 days
2	7 to <12 years	40 mg/kg ceftolozane/ 20 mg/kg tazobactam	
3	2 to <7 years		
4	3 months to <2 years		
5	birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months		

Objectives

The following objectives and endpoints were evaluated in hospitalised male and female paediatric participants from birth (>32 weeks GA and ≥7 days PNA) to <18 years of age with NP:

Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of ceftolozane/tazobactam for all participants	• Adverse events (AEs), including any AEs, any serious AEs, any drug-related AEs and any serious drug-related AEs • AEs leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetics (PK) of multiple doses of ceftolozane/tazobactam for each age group and/or dose level	• Plasma concentrations at each time point for ceftolozane and tazobactam • Steady state plasma area under the concentration-time curve of an 8-hour dosing interval, maximum observed concentration during a dosage interval (C_{max}), elimination half-life ($t_{1/2}$), volume of distribution (Vd), and clearance (CL) for ceftolozane and tazobactam

Outcomes/endpoints

See information under "Objectives" above.

Safety was assessed through collection of AEs, laboratory evaluations (haematology, chemistry, and coagulation), vital signs, and physical examinations.

Blood samples for PK (0.25 mL per sample) were collected over one 8-hour dosing period on Day 3 (Visit 4) of the treatment period after administration of at least six doses of ceftolozane/tazobactam at the following time points:

- at the end of infusion (1 hour after start of infusion of ceftolozane/tazobactam, collected within 10 minutes after the end of total dose administration)
- between 4 and 5 hours after start of infusion
- between 7 and 8 hours after start of infusion but prior to the start of the next dose

PK sample collection could occur on Day 4 (Visit 5) if the last dosing period of Day 3 (Visit 4) was selected for PK sample collection. Additionally, if sampling on Day 3 (Visit 4) was logistically difficult, sampling could be performed at comparable time points after Day 3 (Visit 4) in participants who were continuing to receive IV study treatment.

Plasma concentrations of ceftolozane and tazobactam were determined using a high-performance liquid chromatographic tandem mass spectrometric method. The calibrated analytical range was from 0.250 to 150 µg/mL for ceftolozane and from 0.100 to 60.0 µg/mL for tazobactam. The LLOQs were set at 0.250 µg/mL for ceftolozane and 0.100 µg/mL for tazobactam.

Sample size

The cumulative sample size of 40 participants for this study was based on obtaining sufficient data to evaluate the safety and PK of C/T in paediatric participants, in addition to feasibility considerations.

Statistical Methods

Pharmacokinetic analysis: The PK population included participants who received at least six doses of ceftolozane/tazobactam and had at least one quantifiable plasma concentration of ceftolozane or tazobactam.

A listing of the individual plasma concentration-time data for ceftolozane and tazobactam was presented (CSR 16.2.5.2).

PK data will be used to update the existing ceftolozane and tazobactam paediatric popPK models. Due to the sparse PK sampling, PK endpoints, including steady state Cmax, AUC0-8, t1/2, Vd, and CL will be characterised using a popPK modelling approach and summarised in a separate popPK modelling report (not submitted in this Art. 46 procedure).

Results

Participant flow/Recruitment/Numbers analysed

A total of 41 participants were enrolled. Of these, 40 participants received study intervention (Table below), while one patient (Group 5) was not treated with study drug.

The only reason for discontinuing the study was death (two participants in Group 4 and one participant in Group 5). The only reason for discontinuing study intervention was 'physician decision' (one participant in Group 3 and one participant in Group 5).

Safety analyses were based on the APaT (ASaT) population, which included 40 participants who received any dose (including partial doses) of C/T. Of these, 37 patients completed the study.

The PK analysis population consisted of 39 participants who received at least one dose of C/T and had at least one measurable PK sample. One participant (Group 3), who was not included in this analysis population, received at least one dose of C/T and provided PK samples; however, these samples were lost during transport to the central laboratory.

Important protocol deviations were reported for eight participants, five of these were considered clinically relevant. No subjects were excluded from analysis due to a protocol deviation.

Table 2. Disposition of Participants - All Participants as Treated (CSR Table 10-1)

	Group 1 12 to <18 y		Group 2 7 to <12 y		Group 3 2 to <7 y		Group 4 3 mo to <2 y		Group 5 Birth to <3 mo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		7		8		10		7		40	
Status for Trial												
Completed	8	(100.0)	7	(100.0)	8	(100.0)	8	(80.0)	6	(85.7)	37	(92.5)
Discontinued	0	(0.0)	0	(0.0)	0	(0.0)	2	(20.0)	1	(14.3)	3	(7.5)
Death	0	(0.0)	0	(0.0)	0	(0.0)	2	(20.0)	1	(14.3)	3	(7.5)
Status for Study Medication in Trial												
Started	8		7		8		10		7		40	
Completed	8	(100.0)	7	(100.0)	7	(87.5)	10	(100.0)	6	(85.7)	38	(95.0)
Discontinued	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(14.3)	2	(5.0)
Physician Decision	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(14.3)	2	(5.0)

mo = Months; y = Years.

Source: [P036MK7625A: adam-adsl]

Baseline data

Demographic and baseline characteristics are presented in the Table below. Overall, the majority of participants were White, from Europe (Ukraine and Spain), and not Hispanic or Latino. Approximately half of the participants were female.

As required per the study's entry criteria, all participants had received antibiotics *prior* to enrolment. The four most frequently reported prior antibiotic medications in the APaT population included meropenem (42.5%), amikacin (27.5%), vancomycin (27.5%), and metronidazole (25.0%).

All participants received ≥1 *concomitant* medication (antibiotic and nonantibiotic); except for one participant in Group 1 who did not receive any antibiotic concomitant medication (discontinued therapy after enrolment and prior to first dose of C/T) and two participants in Group 1 who did not receive any nonantibiotic concomitant medication during the study. The four most frequently reported concomitant antibiotic medications used during the study were meropenem (35.0%), meropenem trihydrate (30.0%), vancomycin (30.0%), and colistimethate sodium (17.5%).

Table 3. Participant Characteristics – All Participants as Treated (CSR Table 10-3)

	Group 1 12 to <18 y		Group 2 7 to <12 y		Group 3 2 to <7 y		Group 4 3 mo to <2 y		Group 5 Birth to <3 mo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	8		7		8		10		7		40	
Sex												
Male	2	(25.0)	5	(71.4)	2	(25.0)	8	(80.0)	4	(57.1)	21	(52.5)
Female	6	(75.0)	2	(28.6)	6	(75.0)	2	(20.0)	3	(42.9)	19	(47.5)
Age (years)												
12 to <18 y	8	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	8	(20.0)
7 to <12 y	0	(0.0)	7	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(17.5)
2 to <7 y	0	(0.0)	0	(0.0)	8	(100.0)	0	(0.0)	0	(0.0)	8	(20.0)
3 mo to <2 y	0	(0.0)	0	(0.0)	0	(0.0)	10	(100.0)	0	(0.0)	10	(25.0)
Birth to <3 mo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(100.0)	7	(17.5)
Participants with data	8		7		8		10		7		40	
Mean	14.345		9.709		3.185		0.806		0.106		5.425	
SD	1.6408		1.9100		0.7430		0.2994		0.0666		5.6884	
Median	14.110		9.687		3.138		0.789		0.129		2.956	
Range	12.345 to 16.636		7.042 to 11.858		2.010 to 4.353		0.285 to 1.383		0.027 to 0.194		0.027 to 16.636	
Race												
American Indian Or Alaska Native	0	(0.0)	1	(14.3)	0	(0.0)	2	(20.0)	0	(0.0)	3	(7.5)
Black Or African American	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	1	(14.3)	2	(5.0)
White	7	(87.5)	4	(57.1)	7	(87.5)	7	(70.0)	5	(71.4)	30	(75.0)
Multiple	1	(12.5)	2	(28.6)	1	(12.5)	0	(0.0)	1	(14.3)	5	(12.5)
Ethnicity												
Hispanic Or Latino	1	(12.5)	5	(71.4)	3	(37.5)	3	(30.0)	2	(28.6)	14	(35.0)
Not Hispanic Or Latino	7	(87.5)	2	(28.6)	5	(62.5)	7	(70.0)	5	(71.4)	26	(65.0)
Region												
North America	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	1	(2.5)
Europe	7	(87.5)	3	(42.9)	6	(75.0)	8	(80.0)	5	(71.4)	29	(72.5)
South America	1	(12.5)	4	(57.1)	2	(25.0)	2	(20.0)	0	(0.0)	9	(22.5)
South Africa	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	1	(2.5)
Height (cm)												
Participants with data	8		7		8		10		7		40	
Mean	165.8		133.3		97.8		68.3		50.9		102.0	
SD	10.78		27.69		8.86		10.27		6.69		44.25	
Median	167.5		124.0		98.0		68.0		54.0		97.0	
Range	147 to 184		97 to 170		79 to 110		53 to 82		39 to 56		39 to 184	
Weight (kg)												
Participants with data	8		7		8		10		7		40	
Mean	58.00		36.06		13.68		7.09		3.55		23.04	
SD	17.857		22.105		3.265		3.040		1.049		23.857	
Median	58.00		28.00		14.50		7.01		3.75		13.30	
Range	35.0 to 90.0		13.6 to 73.0		7.9 to 17.0		3.3 to 12.0		2.1 to 4.8		2.1 to 90.0	
Baseline Creatinine Clearance (mL/min/1.73 m2) [a]												
Participants with data	8		7		8		10		7		40	
Mean	166.73		140.96		199.69		115.07		81.59		141.00	
SD	45.409		54.940		114.139		57.284		44.727		76.721	
Median	165.52		145.22		151.96		100.13		88.89		131.20	
Range	97.4 to 234.0		75.6 to 242.1		95.4 to 397.5		50.7 to 222.1		12.1 to 135.6		12.1 to 397.5	
Prior antibiotic use												
Yes	8	(100.0)	7	(100.0)	8	(100.0)	10	(100.0)	7	(100.0)	40	(100.0)

mo = Months; SD=Standard deviation; y = Years.

[a] Creatinine clearance rates were calculated by the revised Schwartz equation at baseline.

Note: Age was derived in years with 4 decimals, from data collected in years and months when participants were enrolled. For participants less than 3 months old the number of days postnatal were collected and the age were also derived in years. (Example: The age in years of a 7 day old were derived as 7/365 = 0.0191 years.)

Source: [P036MK7625A: adam-adsl]

Pharmacokinetic results

A total of 114 quantifiable ceftolozane and 114 quantifiable tazobactam concentrations, respectively, were available for analysis. The PK data have not been summarised.

All ceftolozane plasma levels were above the lower limit of quantification. Tazobactam plasma levels were BLQ in eleven participants at 7-8h post-infusion. One of these participants had also BLQ at 4-5h and another participant had BLQ at 1h post-infusion, with low tazobactam levels (0.704 µg/mL) also at 4-5h post-infusion.

Efficacy results

No clinical efficacy data were collected in PN036. Efficacy in NP will be extrapolated from adults to the paediatric population by means of popPK modelling and simulation analyses.

Safety results

Safety and tolerability of C/T from the first dose of IV study intervention through 14 days after EOT (APaT population, which consisted of all participants who received any dose (including partial doses) of C/T. Of the 41 participants enrolled, 40 participants were evaluable for adverse events. Safety assessments included AEs (including protocol-defined ECIs), clinical laboratory evaluations, and vital signs. An adverse event summary is presented in the Table below.

Overall AEs:

- AEs were reported for the majority of participants (75.0%) in the APaT population. A higher percentage of participants in Group 4 and Group 5 had AEs compared with Group 1, Group 2, and Group 3. The percentage of participants with AEs considered by the investigator to be drug-related and SAEs were generally comparable across the age groups.
- The four most frequently reported AEs were ALT increased (12.5%), pyrexia (12.5%), anaemia (10.0%), and thrombocytosis (10.0%), all of which are known adverse reactions for C/T.
- No AEs were reported in participants (n=2) with treatment exposure from 1 to < 8 days. AEs were only reported in participants (n=38) with treatment exposure ≥8 days.
- One (2.5%) participant had two AEs of anal ulcer (mild) and diarrhoea (moderate) that were considered by the investigator to be drug related. No action was taken with the study intervention due to these AEs and both the AEs resolved.

SAEs and Other Clinically Meaningful AEs

- Deaths due to AEs were reported for three (7.5%) participants: cardiogenic shock, multiple organ dysfunction syndrome, and septic shock. None of these AEs were considered by the investigator to be drug related.
- SAEs were reported for eight (20.0%) participants. None of these SAEs were considered by the investigator to be drug-related or led to study intervention discontinuation.
- No participant discontinued study intervention due to an AE.
- One participant had laboratory values that met the protocol-defined ECI criteria for a potential DILI event. This AE was not considered by the investigator to be drug related and no action was taken with the study intervention.

Table 4. Within group analysis of adverse event summary – All participants as treated (CSR Table 12-1)

	Group 1 12 to <18 y			Group 2 7 to <12 y			Group 3 2 to <7 y		
	n	(%)	(95% CI)[b]	n	(%)	(95% CI)[b]	n	(%)	(95% CI)[b]
Participants in population	8			7			8		
with one or more adverse events	4	(50.0)	(15.7, 84.3)	5	(71.4)	(29.0, 96.3)	6	(75.0)	(34.9, 96.8)
with no adverse event	4	(50.0)	(15.7, 84.3)	2	(28.6)	(3.7, 71.0)	2	(25.0)	(3.2, 65.1)
with drug-related adverse events	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
with non-serious adverse events	4	(50.0)	(15.7, 84.3)	5	(71.4)	(29.0, 96.3)	6	(75.0)	(34.9, 96.8)
with serious adverse events	1	(12.5)	(0.3, 52.7)	2	(28.6)	(3.7, 71.0)	0	(0.0)	(0.0, 36.9)
with serious drug-related[a] adverse events	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
who died	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
who died due to a drug-related[a] adverse event	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
discontinued drug due to an adverse event	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
discontinued drug due to a serious adverse event	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 36.9)

	Group 4 3 mo to <2 y			Group 5 Birth to < 3 mo			Total		
	n	(%)	(95% CI)[b]	n	(%)	(95% CI)[b]	n	(%)	(95% CI)[b]
Participants in population	10			7			40		
with one or more adverse events	9	(90.0)	(55.5, 99.7)	6	(85.7)	(42.1, 99.6)	30	(75.0)	(58.8, 87.3)
with no adverse event	1	(10.0)	(0.3, 44.5)	1	(14.3)	(0.4, 57.9)	10	(25.0)	(12.7, 41.2)
with drug-related adverse events	0	(0.0)	(0.0, 30.8)	1	(14.3)	(0.4, 57.9)	1	(2.5)	(0.1, 13.2)
with non-serious adverse events	9	(90.0)	(55.5, 99.7)	6	(85.7)	(42.1, 99.6)	30	(75.0)	(58.8, 87.3)
with serious adverse events	3	(30.0)	(6.7, 65.2)	2	(28.6)	(3.7, 71.0)	8	(20.0)	(9.1, 35.6)
with serious drug-related[a] adverse events	0	(0.0)	(0.0, 30.8)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 8.8)
who died	2	(20.0)	(2.5, 55.6)	1	(14.3)	(0.4, 57.9)	3	(7.5)	(1.6, 20.4)
who died due to a drug-related[a] adverse event	0	(0.0)	(0.0, 30.8)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 8.8)
discontinued drug due to an adverse event	0	(0.0)	(0.0, 30.8)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 8.8)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	(0.0, 30.8)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 8.8)
discontinued drug due to a serious adverse event	0	(0.0)	(0.0, 30.8)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 8.8)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	(0.0, 30.8)	0	(0.0)	(0.0, 41.0)	0	(0.0)	(0.0, 8.8)

AE=Adverse event; CI=Confidence interval; IV=Intravenous; mo=Months; SD=Standard deviation; y=Years.
Every participant is counted a single time for each applicable row.
[a] Determined by the investigator to be related to the IV study medication.
[b] Based on the exact binomial method proposed by Clopper and Pearson.
Study treatment discontinuation refers to an AE leading to IV study medication withdrawn.

Source: [P036MK7625A: adam-adsl; adae]

2.3.3. Discussion on clinical aspects

The MAH has submitted the final clinical study report for the paediatric study MK-7625A-036 (PN036) that is part of the agreed PIP for nosocomial pneumonia (PIP02 study 1). The objectives were to evaluate safety, tolerability and PK of C/T in the paediatric target population. Efficacy was not evaluated. No changes are proposed or recommended in the SmPC or RMP in the present procedure.

The safety and efficacy of C/T have been previously demonstrated in adults (Phase 3 cUTI, cIAI, and NP studies) and in paediatric patients supported by PK-bridging (studies of cUTI and cIAI). Efficacy in NP will be extrapolated from adults to the paediatric population by means of popPK modeling and simulation (M&S) analyses (PIP02 study 2 and 3). As these analyses 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 also not been assessed. The MAH claims that C/T in paediatric patients with NP is generally well tolerated, however safety has not been assessed in detail in this report. A higher percentage of the youngest children, <2 years, experienced AEs compared to the age groups older than 2 years. However, the percentage of subjects with drug-related AEs and SAEs were generally comparable across the age groups. Most reported AEs were well known reactions related to C/T. SAEs were reported for 20.0% of the included subjects, and deaths due to AEs for 7.5 %, however none of these were considered drug

related. In conclusion, the safety findings were not unexpected, and comparable with the known safety profile of C/T.

In conclusion, the final report for Study PN036 (PIP02 study 1) which include safety and PK data has been submitted. A complete assessment of the benefit/risk balance of C/T in paediatric patients with nosocomial pneumonia will be performed based on a full relevant data package submitted within the foreseen extension of indication application.

3. Overall conclusion and recommendation

A detailed critical assessment of the data from Study PN036 has not been performed as part of this Article 46 procedure. A variation application to extend the NP indication to the paediatric population from birth to less than 18 years of age based on data from Study PN036, including popPK M&S analyses is expected, and a complete assessment of the benefit/risk balance of C/T for NP in this age group will then be performed based on the full relevant data package.

This P46 PAM 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 understanding that the MAH applies for an extension of the indication for Zerbaxa within a reasonable time frame.

☒ **PAM Fulfilled:**

No further action required, however further data are expected in the context of a variation prior any conclusion on product information amendments is made. The MAH has committed to submit this variation application.

Annex. Line listing of all the studies included in the development program

The studies included in the paediatric investigation plan for NP (EMEA-001142-PIP02) are presented below:

Non clinical studies

N/A

Clinical studies

Product Name: Zerbaxa Active substance: Ceftolozane/Tazobactam

Study title	Study number	Date of completion	Date of submission of final study report
Phase 1, open-label, non-comparative, multicentre clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam (MK-7625A) in paediatric participants with nosocomial pneumonia	MK-7625A-036 (PN036) Study 1	26.09.2024 last data available	25.02.2025
Modeling and simulation study to derive dosing of ceftolozane/tazobactam for use in children from birth to less than 18 years of age with nosocomial pneumonia.	Study 2		
Extrapolation study to evaluate ceftolozane/tazobactam for use in children from birth to less than 18 years of age with nosocomial pneumonia.	Study 3		