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Human Medicines Evaluation Division

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

Zerbaxa

ceftolozane / tazobactam

Procedure no: EMEA/H/C/003772/P46/002

Note

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

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1. Introduction

On 15th December 2017, the MAH submitted a completed paediatric study for ceftolozane/ tazobactam, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CXA-PEDS-13-08 [Open-label, single dose study to evaluate the pharmacokinetics and safety of ceftolozane/ tazobactam in children (0-18 years) with proven or suspected Gram-negative infection receiving standard antibiotic therapy] is part of a clinical development program. The variation application consisting of the full relevant data package (containing several studies) is expected to be submitted by 12/21. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

There is no specific paediatric formulation for ceftolozane/tazobactam; the formulation approved for use in adults was administered in this study. A fixed ratio of 2:1 ceftolozane/tazobactam was used in this trial.

Route of Administration and Dosage Form: Intravenous (IV) infusion over 60 (±10) minutes.

Physical Description: A 1.5 g dose of ceftolozane/tazobactam lyophilized powder contains 1000 mg of active ceftolozane and tazobactam sodium at a quantity equivalent of 500 mg of tazobactam free acid when it is reconstituted and diluted for use. Inactive ingredients include sodium chloride as a stabilizer and L-arginine and citric acid for pH adjustment.

To minimize the infusion volume in younger cohorts, varying age-appropriate volumes from the fixed concentration, not to exceed 15 mg/mL, of ceftolozane/ tazobactam will be administered to achieve the intended dose in each paediatric patient. Infusion rates will differ based on the volume of each dose in each patient.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CXA-PEDS-13-08 Open-label, single dose study to evaluate the pharmacokinetics and safety of ceftolozane/ tazobactam in children (0-18 years) with proven or suspected Gram-negative infection receiving standard antibiotic therapy.

Assessor's comments:

Ceftolozane/tazobactam (Zerbaxa) is licensed in the European Union (18th September 2015) for the treatment of complicated intra-abdominal infections (cIAI), in combination with metronidazole, as well as for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, in patients

aged 18 years and older.

This is the first completed paediatric clinical trial of ceftolozane/ tazobactam and one of 3 deferred clinical studies in the agreed paediatric investigation plan (PIP). This PIP was first agreed in October 2012, with 2 subsequent modifications, the last (EMEA-001142-PIP01-11-M02), agreed in January 2017 (P/0088/2017). This PIP is due to be completed by June 2021. There are no waivers. A positive opinion on the interim compliance check of completed non-clinical studies was adopted in June 2014, prior to filing for adult MA. (EMEA-C2-001142-PIP01-11-M01). All concerned studies are listed in the Annex of this report.

2.3.2. Clinical study

CXA-PEDS-13-08

Open-label, single dose study to evaluate the pharmacokinetics and safety of ceftolozane/tazobactam in children (0-18 years) with proven or suspected Gram-negative infection receiving standard antibiotic therapy

Description

This was a Phase 1, single-dose, non-comparative, open-label trial to evaluate the pharmacokinetics (PK) and safety of ceftolozane/tazobactam in paediatric subjects from birth (7 days postnatal) to <18 years receiving concurrent standard-of-care antibiotic therapy for treatment of proven or suspected gram negative infection or peri-operative prophylaxis.

Subjects received a single age-based intravenous (IV) dose of ceftolozane/tazobactam as a 60 (±10)-minute (min) infusion. The doses were subject to change (up to a maximum of 30 mg/kg ceftolozane and 15 mg/kg tazobactam, not to exceed a fixed dose of 1.5 g ceftolozane/tazobactam) based upon interim analysis of PK and safety data.

A data monitoring or endpoint adjudication committee was not utilized.

Methods

Objectives

The primary objective of this study was to evaluate the PK of a single dose of IV ceftolozane/ tazobactam in paediatric subjects from birth to <18 years receiving standard-of-care antibiotic therapy for proven or suspected gram-negative infection, including subjects receiving peri-operative prophylactic antibiotics.

The secondary objective of this study was to assess the safety and tolerability of a single dose of IV ceftolozane/tazobactam in paediatric subjects from birth to <18 years receiving standard-of-care antibiotic therapy for proven or suspected gram-negative infection, including subjects receiving peri-operative prophylactic antibiotics.

Study design

A Phase 1, Non-Comparative, Open-Label Study to Characterize the Pharmacokinetics of a Single Intravenous Dose of Ceftolozane/tazobactam in Paediatric Patients Receiving Standard of Care Antibiotic Therapy for Proven or Suspected Gram-Negative Infection or for Peri-Operative Prophylaxis.

Study population /Sample size

A total of 36 subjects (6 subjects per 6 age groups) were planned to be enrolled in this trial. This sample size was chosen based primarily on empirical considerations and feasibility, and was considered sufficient to meet the trial objectives. With 6 subjects in each age group, the probability of detecting at least 1 AE with a true event rate of 5% was 26%. With a total of 36 subjects across all age groups, the probability of detecting at least 1 AE with a true event rate of 5% was 84%.

Treatments

The initial paediatric doses of ceftolozane/tazobactam were chosen based on adult PK data with the objective of achieving the therapeutic exposure levels seen in healthy adults. Subjects enrolled received a single age-based IV dose of ceftolozane/tazobactam as a 60 (±10)-minute (min) infusion. The age-based doses were subject to change (up to a maximum of 30 mg/kg ceftolozane and 15 mg/kg tazobactam, not to exceed a fixed dose of 1.5 g ceftolozane/ tazobactam) based upon interim analyses of PK and safety data. The groups with their initial dosing regimens and proposed recruitment numbers are outlined below:

- Group 1 (N=6) ≥12 to <18 years
    - Single IV dose, 1.5 g fixed dose of ceftolozane/tazobactam (1000 mg ceftolozane and 500 mg tazobactam).
- Group 2 (N=6) ≥7 to <12 years
    - Single IV dose, 18 mg/kg ceftolozane and 9 mg/kg tazobactam.
- Group 3 (N=6) ≥2 to <7 years
    - Single IV dose, 18 mg/kg ceftolozane and 9 mg/kg tazobactam.
- Group 4 (N=6) ≥3 months to <2 years
    - Single IV dose, 18 mg/kg ceftolozane and 9 mg/kg tazobactam.
- Group 5 (N=6) Birth (>32 weeks gestation, 7 days postnatal) to <3 months
    - Single IV dose, 12 mg/kg ceftolozane and 6 mg/kg tazobactam.
- Group 6 (N=6) Birth (≤32 weeks gestation, 7 days postnatal) to <3 months
    - Single IV dose, 12 mg/kg ceftolozane and 6 mg/kg tazobactam.

Subjects participated in the trial for 6 to 12 days. Screening and/or baseline assessments to determine eligibility took place within 48 hours of trial treatment administration (Day 1).

Outcomes/endpoints

Primary endpoint: AUC and Cmax

The primary endpoints were area under the plasma concentration-time curve (AUC) and maximum concentration (Cmax) for ceftolozane, tazobactam, and the tazobactam metabolite (M1) as data allowed.

Secondary endpoint

The secondary endpoint was the safety and tolerability of single doses of IV ceftolozane/tazobactam in paediatric subjects and it was evaluated through assessments of adverse events (AEs), physical examinations, vital signs, and clinical laboratory tests in the Safety population.

Statistical Methods

Descriptive statistics were used to guide decisions as to the clinical relevance of findings. No formal hypothesis testing was planned or performed. All statistical analyses were performed using SAS statistical software version 9.4, unless otherwise noted. For all analyses, baseline was defined as the most recent measurement prior to the first administration of study drug, unless otherwise specified.

Plasma PK parameters for ceftolozane, tazobactam, and tazobactam M1 were determined using noncompartmental methods (WinNonlin Phoenix version 6.30). The following PK parameters were determined for all analytes (ceftolozane, tazobactam, and M1, except as noted below) as allowed by the data.

- Cmax
- Time of maximum concentration (Tmax)
- Last quantifiable concentration (Clast)
- Time of last quantifiable concentration (Tlast)
- Area under the plasma concentration-time curve from time 0 to last quantifiable concentration (AUClast)
- Area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC0-∞)
- Terminal half-life (T1/2)
- Volume of distribution at steady state (Vss) (ceftolozane and tazobactam only)
- Plasma clearance (CL) (ceftolozane and tazobactam only)

The AUC was calculated by the trapezoidal method using the linear-up/ log-down rule. All predose below-limit-of quantification (BLQ) values in period 1 were set to zero; missing or BLQ values obtained after the first quantifiable concentration were treated as missing. Actual blood draw times were used to calculate PK parameters.

The PK population included all subjects who received a full dose of trial treatment and provided blood samples with quantifiable plasma levels at the Cmax (1-hour post infusion start time point) and at least 2 time points after Cmax (2, 4, or 6 hours post infusion time points) to allow an estimation of AUC.

Safety was assessed through collection of AEs, laboratory evaluations (haematology, chemistry, and coagulation), vital signs, and physical examinations. The safety evaluation was based on clinical review of the following safety parameters:

- Incidence of AEs and serious adverse events (SAEs);
- AEs and SAEs by relationship to trial treatment;

- AEs and SAEs by severity;
- Deaths;
- Premature discontinuation from the trial and trial treatment due to an AE, regardless of relationship to trial treatment;
- Clinical laboratory data;
- Vital signs; and
- Concomitant medications
- The Safety population included all subjects who received any amount of trial treatment.

Results

Recruitment/ Number analysed

A total of 43 subjects were enrolled; 6 (14.0%) were enrolled but not dosed, and 37 (86.0%) received trial treatment and were included in the Safety population. All 37 (100.0%) subjects in the Safety population completed the trial; 34 of 37 were included in the PK population. No subjects were excluded from the analysis populations (PK or Safety) due to a protocol deviation.

Baseline data

Nineteen subjects (51.4%) were male and 18 (48.6%) were female, and the majority of subjects were white (67.6%). Other than 1 subject in Group 4 who was receiving antibiotics for perioperative prophylaxis, all subjects were receiving antibiotics for a proven or suspected gram-negative infection. (Table 1.)

All subjects in the Safety population were taking at least 1 concomitant medication. The types of medications subjects were taking were typical of hospitalized paediatric subjects with gram-negative infections. Treatment compliance was not measured. All subjects received a single IV dose of ceftolozane/ tazobactam on Day 1, which was administered in a hospital or clinic. Study personnel at the site recorded the dosage and timing of treatment administration.

Table 1: Baseline Patient data.

Summary of Demographic and Baseline Characteristics
(Safety Population)

	Group 1 (Dose 1.5 g) (N=6)	Group 2 (Dose 18/9 mg/kg) (N=6)	Group 3 (Dose 18/9 mg/kg) (N=3)	Group 3 (Dose 30/15 mg/kg) (N=3)	Group 4 (Dose 18/9 mg/kg) (N=1)
Age (yr)[1]					
Mean	16.06945	8.37500	5.44443	4.38890	PPD
SD	1.399797	1.325761	0.917912	1.937052	-
Median	PPD				
Min					
Max					
Sex[n (%)]					
Male	1 (16.7)	4 (66.7)	2 (66.7)	1 (33.3)	1 (100.0)
Female	5 (83.3)	2 (33.3)	1 (33.3)	2 (66.7)	0 (0.0)
Race[n (%)]					
White	PPD				
Black or African American					
Other					
Ethnicity[n (%)]					
Hispanic or Latino	PPD				
Not Hispanic or Latino					
Height (cm)					
Mean	157.98	130.25	113.17	103.40	PPD
SD	5.312	6.432	9.438	9.681	-
Median	PPD				
Min					
Max					

	Group 1 (Dose 1.5 g) (N=6)	Group 2 (Dose 18/9 mg/kg) (N=6)	Group 3 (Dose 18/9 mg/kg) (N=3)	Group 3 (Dose 30/15 mg/kg) (N=3)	Group 4 (Dose 18/9 mg/kg) (N=1)
Weight (kg)					
Mean	51.98	29.93	20.67	17.30	PPD
SD	7.716	8.615	5.658	5.110	-
Median	PPD				
Min					
Max					
Creatinine Clearance (mL/min/1.73m²)[2]					
Mean	144.00597	135.19592	130.76960	117.95250	181.26110
SD	41.931025	27.913947	9.224500	29.062538	-
Median	139.86835	135.17600	130.98000	133.12370	181.26110
Min	86.9881	104.0760	121.4417	84.4438	181.2611
Max	216.1367	180.3433	139.8871	136.2900	181.2611
Reason for SOC Antibiotics[n (%)]					
Proven/Suspected Gram Negative Infection	6 (100.0)	6 (100.0)	3 (100.0)	3 (100.0)	1 (100.0)
Peri-Operative Prophylaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Group 4 (Dose 30/15 mg/kg) (N=5)	Group 5 (Dose 20/10 mg/kg) (N=7)	Group 6 (Dose 12/6 mg/kg) (N=2)	Group 6 (Dose 20/10 mg/kg) (N=4)	Overall (N=37)
Age (yr)[1]					
Mean	0.78334	0.10841	0.08770	0.19453	4.93818
SD	0.366097	0.045666	0.011597	0.057379	5.885822
Median	PPD				
Min					
Max					
Sex[n (%)]					
Male	3 (60.0)	4 (57.1)	2 (100.0)	1 (25.0)	19 (51.4)
Female	2 (40.0)	3 (42.9)	0 (0.0)	3 (75.0)	18 (48.6)
Race[n (%)]					
White	PPD				
Black or African American					
Other					
Ethnicity[n (%)]					
Hispanic or Latino	PPD				
Not Hispanic or Latino					
Height (cm)					
Mean	69.40	52.90	37.10	46.00	92.80
SD	9.127	4.588	1.273	4.397	42.740
Median	PPD				
Min					
Max					

	Group 4 (Dose 30/15 mg/kg) (N=5)	Group 5 (Dose 20/10 mg/kg) (N=7)	Group 6 (Dose 12/6 mg/kg) (N=2)	Group 6 (Dose 20/10 mg/kg) (N=4)	Overall (N=37)
Weight (kg)					
Mean	8.86	4.06	1.30	2.73	18.98
SD	2.490	0.725	0.283	0.655	18.187
Median	PPD				
Min					
Max					
Creatinine Clearance (mL/min/1.73m²)[2]					
Mean	121.25484	79.80840	30.90185	86.61010	112.85990
SD	42.470666	15.521112	4.547474	14.766244	41.701312
Median	108.75670	74.34000	30.90185	86.10580	108.88180
Min	75.7167	62.5574	27.6863	69.8923	27.6863
Max	180.6875	108.8818	34.1174	104.3368	216.1367
Reason for SOC Antibiotics[n (%)]					
Proven/Suspected Gram Negative Infection	4 (80.0)	7 (100.0)	2 (100.0)	4 (100.0)	36 (97.3)
Peri-Operative Prophylaxis	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)

[1] Age was derived in years with 4 decimals, from data collected in years and months at the start of study medication. For subjects less than 3 months old, the number of days postnatal was collected and the age was also derived in years. (Example: The age in years of a 7 day old was derived as 7/365 = 0.0192 years.)
[2] Creatinine clearance rates were calculated by the revised Schwartz equation at baseline.
Source: [P010V05: adam-adsl]

Assessor's comments:

Thirty-seven (37) paediatric patients representing all the study-defined paediatric age groups were enrolled. One (1) subject in Group 4 received antibiotics for perioperative prophylaxis and all other patients had either proven or suspected Gram negative infection. These conditions were defined within the study parameters.

Efficacy results

There are no efficacy results.

Assessor's comments:

This completed Phase I study was designed to assess the PK and safety of ceftolozane/ tazobactam, thus no assessment or conclusion regarding the efficacy of ceftolozane/ tazobactam in the paediatric population can be made.

Safety results

Overall, 11 subjects (29.7%) experienced at least 1 treatment emergent adverse event (TEAE). No severe TEAEs or TEAEs leading to discontinuation of trial treatment were reported, and there were no deaths during the trial. Two subjects had non-serious treatment-related TEAEs which were mild in severity and resolved by the end of the study (1 subject in Group 1 with dizziness and 1 subject in Group 3 [30/15 mg/kg dose] with bradycardia and tachycardia). Three subjects had serious adverse events (SAEs) (1 subject from Group 1 with pneumonia, 1 subject from Group 2 with infective pulmonary exacerbation of cystic fibrosis, and 1 subject from Group 4 [30/15 mg/kg dose] with device-related sepsis), which were all deemed unrelated to trial treatment. In Groups 5 or 6, no subject experienced a treatment-related TEAE. However, three subjects had at least 1 adverse events (AE) (1 subject in Group 5 and 2 subjects in Group 6 [12/6 mg/kg dose]). Only 1 of the reported AE was experienced by more than 1 subject; anaemia was experienced by 1 Subject in Group 5 and 1 subject in Group 6 (Table 2). Anaemia, diarrhoea, and hypokalaemia were the only AEs reported twice.

No subjects had abnormal liver function tests that met the criteria for closely monitored events. There were no events indicative of hypersensitivity reactions or haemolytic disorders, nor any events involving *Clostridium difficile*. No clinically significant laboratory abnormalities or changes in electrocardiograms (ECGs) were observed after administration of ceftolozane/tazobactam.

The safety profile observed in the trial was similar to the safety profile observed in the adult population, and no new safety signals were identified. Treatment with ceftolozane/tazobactam was well tolerated. In general, adverse events occurred with low frequency, were widely distributed across multiple body systems, and were typical of hospitalized paediatric subjects with gram-negative infections.

Table 2

Overall Summary of Subjects With Treatment-Emergent Adverse Events [1]
(Safety Population)

	Group 1 (Dose 1.5 g) (N=6) n (%)	Group 2 (Dose 18/9 mg/kg) (N=6) n (%)	Group 3 (Dose 18/9 mg/kg) (N=3) n (%)	Group 3 (Dose 30/15 mg/kg) (N=3) n (%)	Group 4 (Dose 18/9 mg/kg) (N=1) n (%)
At Least One Adverse Event	2 (33.3)	1 (16.7)	1 (33.3)	1 (33.3)	1 (100.0)
No Adverse Event	4 (66.7)	5 (83.3)	2 (66.7)	2 (66.7)	0 (0.0)
At Least One Serious Adverse Event(SAE)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
At Least One Study Drug-Related SAE[2]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Events By Relationship To Study Drug[2, 3]					
Related	1 (16.7)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Not Related	1 (16.7)	1 (16.7)	1 (33.3)	0 (0.0)	1 (100.0)
Adverse Events By Severity[3]					
Mild	2 (33.3)	1 (16.7)	1 (33.3)	1 (33.3)	1 (100.0)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study Drug Related AE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to a Study Drug Related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Overall Summary of Subjects With Treatment-Emergent Adverse Events [1]
(Safety Population)

	Group 4 (Dose 30/15 mg/kg) (N=5) n (%)	Group 5 (Dose 20/10 mg/kg) (N=7) n (%)	Group 6 (Dose 12/6 mg/kg) (N=2) n (%)	Group 6 (Dose 20/10 mg/kg) (N=4) n (%)	Overall (N=37) n (%)
At Least One Adverse Event	2 (40.0)	1 (14.3)	2 (100.0)	0 (0.0)	11 (29.7)
No Adverse Event	3 (60.0)	6 (85.7)	0 (0.0)	4 (100.0)	26 (70.3)
At Least One Serious Adverse Event(SAE)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.1)
At Least One Study Drug-Related SAE[2]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Events By Relationship To Study Drug[2, 3]					
Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)
Not Related	2 (40.0)	1 (14.3)	2 (100.0)	0 (0.0)	9 (24.3)
Adverse Events By Severity[3]					
Mild	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	7 (18.9)
Moderate	2 (40.0)	1 (14.3)	1 (50.0)	0 (0.0)	4 (10.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study Drug Related AE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to a Study Drug Related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[1] Adverse events that occurred from the first dose of study drug through the last study evaluation or pre-existing adverse events that were aggravated in severity and frequency during the dosing period.
[2] Deemed by the Investigator as related to study drug.
[3] Every subject was counted a single time for each applicable row and column; subjects were only counted once with the highest relationship to study drug; subjects were only counted once with the most severe event.
Source: [P010V05: adam-adae]

Assessor's comments:

All paediatric patients recruited into the study and who received ceftolozane/ tazobactam were included in the safety analysis. There were no deaths in the study and no SAEs or TEAEs leading to the discontinuation of the trial product. Two subjects had non-serious TEAEs and 3 subjects had SAEs unrelated to trial treatment.

Changes in laboratory parameters were recorded in all patients over the duration of the study, however, these were not clinically significant. Regarding closely monitored events, no paediatric subjects had abnormal liver function tests that met the critical study threshold for this adverse event. No clinically significant changes in electrocardiograms (ECGs) were noted.

The study was not planned to detect uncommon or rare ceftolozane/ tazobactam AEs; however, it is acknowledged that such paediatric-specific adverse events are unlikely to be detected in a trial for early paediatric development that is limited in size and duration. Furthermore, the safety profile of ceftolozane/ tazobactam is also confounded by use of other concomitant antibiotics.

Despite these limitations, this study provides preliminary paediatric safety data for a single dose of ceftolozane/ tazobactam which were similar to those observed in adults. In addition, the AEs were low in frequency and no safety signals of concern were reported in the paediatric study population. Thus, the available safety data support further paediatric development. As such, the MAH's conclusions on the safety of ceftolozane/ tazobactam in the paediatric population are acceptable.

Pharmacokinetic results

The PK population included all subjects who received a full dose of trial treatment and provided blood samples with quantifiable plasma levels at the Cmax (1-hour post infusion start time) and at least 2 time points after Cmax (2-, 4-, or 6-hour post infusion time points). Of the 37 subjects who received a complete dose of trial treatment, 34 were included in the PK population. The following 3 subjects were excluded from the PK population:

- 1 subject from Group 1 with drug concentration BLQ at the end of infusion. This subject had measurable pre-dose concentrations, suggesting a possible sample switch.
- 1 subject from Group 5 with a site-reported infusion issue wherein drug was not completely flushed through the infusion line after administration.
- 1 subject from Group 6 (20/10 mg/kg dose) with insufficient plasma available in the PK samples for drug quantification.

Three dose modifications occurred during the conduct of the study:

- The dose for Groups 3 and 4 was increased from 18/9 mg/kg ceftolozane/tazobactam to 30/15 mg/kg, following the Group 3 interim analysis.
- The dose for Groups 5 and 6 was increased from 12/6 mg/kg ceftolozane/tazobactam to 20/10 mg/kg, following the Group 4 interim analysis.
- A dose of 12/6 mg/kg ceftolozane/tazobactam was implemented for Group 6 subjects with a baseline calculated CrCL of 20 to 49 mL/min/1.73m^2.

The plasma PK of ceftolozane, tazobactam, and tazobactam M1 were characterized following administration of single IV doses of ceftolozane/tazobactam to Groups 1-6. The mean ceftolozane concentration-time profiles were generally comparable across Groups 1-4, while the terminal half-life was slightly increased in Group 5 and 6 subjects. After accounting for weight, ceftolozane clearance (CL) was generally comparable across Groups 1-4, while CL values trended lower in Groups 5 and 6 for those with creatinine clearance (CrCL) ≥50 mL/min/1.73m^2. For Group 6 subjects who received the dose of 12/6 mg/kg ceftolozane/tazobactam, the geometric mean (GM) CL was approximately 2-fold lower, consistent with the lower CrCL function in these subjects. (Table 3.)

Following the interim analysis in Group 3, the dose was increased from 18/9 mg/kg to 30/15 mg/kg, an increase of 1.7-fold, which resulted in an increase in the GM AUC (0-∞) of approximately 1.9-fold in Group 3, suggesting that the PK of ceftolozane is approximately dose-proportional. After accounting for weight, the ceftolozane GM volume of distribution at steady state (Vss) ranged from 0.274 to 0.394 L/kg across all age groups, suggesting that the Vss was comparable across all age groups, with a slight trend in increased Vss in subjects aged birth (7 days postnatal) to <3 months (Groups 5 and 6 subjects).

Differences in the mean tazobactam concentration-time profiles were observed, and were more pronounced for Groups 5 and 6; the comparison of the profiles was limited due to the limited concentration-time data at the 6-hour time point. A comparison of the CL across Groups 1-6 generally suggests a slight trend of decreasing tazobactam CL in neonates and infants. The CL for Group 6 subjects who received the 12/6 mg/kg dose of ceftolozane/tazobactam was available for only 1 subject and was 0.076 L/h/kg. As this subject had a CrCL of 27.69 mL/min/1.73m2, it is likely that the low CL is due to the immature renal function of this subject.

With an increase in dose of 1.7-fold following the Group 3 interim analysis, an increase of approximately 1.6-fold in the GM tazobactam AUC (0-∞) was observed in Group 3, suggesting that the PK of tazobactam is approximately dose-proportional. Tazobactam Vss increased with increasing age. After accounting for weight, the tazobactam GM Vss ranged from 0.421 to 0.740 L/kg in Groups 1-6 (Group 6 subjects who received the 20/10 mg/kg dose). The Vss was available for only 1 subject in Group 6 (12/6 mg/kg dose) and was 0.338 L/kg. These results point to variability in the tazobactam data (Table 3).

Not enough data points were available for an accurate assessment of tazobactam metabolite (M1) PK parameters. The arithmetic mean tazobactam plasma concentration-time profiles showed an increase in tazobactam M1 concentrations with time, which peaked at approximately 4 hours post start of infusion of ceftolozane/tazobactam. Thus, the terminal elimination phase was not captured within the 6-hour PK sampling time and AUC (0-∞) could not be determined for most subjects. Two subjects had predose tazobactam M1 concentrations.

Table 3

Summary Statistics of Ceftolozane Plasma Pharmacokinetic Parameters, Following the Administration of Single IV Doses of Ceftolozane/Tazobactam to Group 1-6 Subjects, Presented as GM and 95% CI
(PK Population)

	Group 1 (Dose 1.5 g) (N=5)	Group 2 (Dose 18/9 mg/kg) (N=6)	Group 3 (Dose 18/9 mg/kg) (N=3)	Group 3 (Dose 30/15 mg/kg) (N=3)	Group 4 (Dose 18/9 mg/kg) (N=1)
AUC0-inf (h*ug/mL)	133 (104,171)	107 (85.7,135)	99.4 (72.2,137)	186 (135,255)	103 (59.4,180)
AUClast (h*ug/mL)	124 (103,150)	102 (86.2,121)	94.2 (74.1,120)	172 (135,219)	98.8 (65.1,150)
Cmax (ug/mL)	63.5 (50.2,80.4)	56.2 (45.3,69.7)	51.4 (37.9,69.7)	96.6 (71.2,131)	50.5 (29.8,85.6)
Tmax (h)	1.02 (1.00,1.10)	1.07 (0.58,1.13)	1.02 (1.02,1.03)	1.03 (1.03,1.12)	1.00 (1.00,1.00)
Clast (ug/mL)	4.01 (40.4)	2.85 (37.3)	2.47 (29.1)	5.69 (59.5)	2.53 (-)
Tlast (h)	6.00 (5.85,6.03)	6.01 (5.82,6.15)	6.08 (5.85,6.25)	5.77 (5.72,5.93)	6.00 (6.00,6.00)
t1/2 (h)	1.45 (16.7)	1.29 (9.6)	1.34 (14.0)	1.48 (35.5)	1.30 (-)
CL (L/h)	7.51 (23.3)	4.87 (21.4)	3.66 (26.5)	2.72 (20.8)	1.89 (-)
CL ((L/h)/kg)	0.146 (27.0)	0.168 (21.3)	0.181 (3.8)	0.162 (31.1)	0.176 (-)
Vss (L)	14.1 (28.9)	8.59 (31.5)	6.68 (23.6)	5.25 (31.9)	3.02 (-)
Vss (L/kg)	0.274 (25.7)	0.296 (22.0)	0.331 (15.6)	0.312 (19.5)	0.282 (-)

Summary Statistics of Ceftolozane Plasma Pharmacokinetic Parameters Following the Administration of Single IV Doses of Ceftolozane/Tazobactam to Group 1-6 Subjects, Presented as GM and 95% CI
(PK Population)

	Group 4 (Dose 30/15 mg/kg) (N=5)	Group 5 (Dose 20/10 mg/kg) (N=6)	Group 6 (Dose 12/6 mg/kg) (N=2)	Group 6 (Dose 20/10 mg/kg) (N=3)
AUC0-inf (h*ug/mL)	202 (158,259)	164 (131,205)	165 (112,244)	137 (99.6,189)
AUClast (h*ug/mL)	178 (148,214)	131 (111,155)	118 (88.2,159)	119 (93.7,151)
Cmax (ug/mL)	91.3 (72.1,116)	45.0 (36.3,55.9)	34.9 (24.1,50.7)	45.2 (33.3,61.2)
Tmax (h)	1.05 (0.58,1.95)	1.08 (0.95,1.90)	1.80 (1.03,2.57)	1.07 (1.07,1.18)
Clast (ug/mL)	5.72 (96.1)	8.70 (49.1)	10.2 (49.2)	6.26 (39.2)
Tlast (h)	6.00 (5.72,6.75)	6.01 (5.88,6.18)	6.40 (6.05,6.75)	5.85 (5.72,6.02)
t1/2 (h)	1.63 (69.0)	2.21 (37.6)	3.14 (0.9)	1.73 (29.7)
CL (L/h)	1.27 (49.5)	0.467 (57.5)	0.0929 (9.5)	0.408 (27.7)
CL ((L/h)/kg)	0.149 (43.2)	0.118 (36.0)	0.0723 (32.2)	0.147 (6.8)
Vss (L)	2.90 (45.2)	1.56 (20.4)	0.442 (13.6)	1.07 (2.5)
Vss (L/kg)	0.340 (21.1)	0.394 (12.6)	0.344 (36.6)	0.388 (26.9)

AUC0-inf = area under the plasma concentration-time curve from time zero extrapolated to infinity, AUClast = area under the plasma concentration-time curve from time zero to last quantifiable concentration, Cmax = maximum concentration, CL = clearance, Clast = last quantifiable concentration, T1/2 = terminal half-life, Tlast = time to last quantifiable concentration, Tmax = time to maximum concentration, Vss = volume of distribution at steady state. "-" = Not applicable. PK parameter values that could not be appropriately determined due to inadequate concentration data were not included in summary.
CL values were presented as weight-normalized ((L/h)/kg) and non-weight normalized (L/h).Vss values were presented as weight-normalized (L/kg) and non-weight normalized (L).
One Group 1 subject, one Group 5 subject, and one Group 6 subject were excluded from the PK population because of a likely sample switch, improper drug administration, and insufficient plasma volume, respectively.
One Group 4 (Dose 30/15 mg/kg) subject had a prolonged infusion time of ~2 hours due to loss of intravenous access. One Group 5 subject received a lower dose of C/T due to use of a different screening weight of the subject.
Statistics for AUC0-inf, AUClast, and Cmax: Geometric least-squares mean and confidence interval based on back-transformed least-squares mean and confidence interval from linear mixed-effects model with group fixed effect performed on natural log-transformed values.
Statistics for Tmax and Tlast: Median and Range (Minimum, Maximum).
Statistics for Clast, t½:, CL, and Vss:Geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s2)-1), where s2 is the observed between-subjects variance on the natural log-scale.
Source: [P010V05: adam-adpp]

Summary Statistics of Tazobactam Plasma Pharmacokinetic Parameters Following the Administration of Single IV Doses of Ceftolozane/Tazobactam to Group 1-6 Subjects, Presented as GM and 95% CI
(PK Population)

	Group 1 (Dose 1.5 g) (N=5)	Group 2 (Dose 18/9 mg/kg) (N=6)	Group 3 (Dose 18/9 mg/kg) (N=3)	Group 3 (Dose 30/15 mg/kg) (N=3)	Group 4 (Dose 18/9 mg/kg) (N=1)
AUC0-inf (h*ug/mL)	17.5 (12.6,24.2)	10.2 (6.68,15.5)	17.8 (11.7,27.0)	28.9 (19.0,43.9)	14.9 (7.21,30.9)
AUClast (h*ug/mL)	17.3 (10.7,27.9)	9.69 (6.27,15.0)	17.6 (9.53,32.7)	28.5 (15.4,52.8)	14.8 (5.08,42.9)
Cmax (ug/mL)	14.0 (8.59,22.9)	9.25 (5.92,14.5)	15.7 (8.36,29.6)	24.8 (13.2,46.6)	11.6 (3.88,34.7)
Tmax (h)	1.00 (0.50,1.10)	1.07 (0.58,1.13)	1.02 (1.02,1.03)	1.03 (1.03,1.12)	1.00 (1.00,1.00)
Clast (ug/mL)	0.232 (52.2)	0.420 (188.6)	0.137 (24.1)	0.327 (62.7)	0.224 (-)
Tlast (h)	4.15 (4.00,6.00)	3.10 (2.02,4.15)	5.85 (4.03,6.08)	5.72 (3.85,5.93)	4.00 (4.00,4.00)
t1/2 (h)	0.702 (38.7)	0.544 (3.1)	0.719 (29.7)	0.770 (34.2)	0.538 (-)
CL (L/h)	28.6 (43.8)	30.8 (36.6)	10.2 (36.0)	8.75 (19.0)	6.54 (-)
CL ((L/h)/kg)	0.556 (53.9)	0.886 (23.1)	0.506 (42.0)	0.519 (44.8)	0.611 (-)
Vss (L)	24.4 (61.3)	25.7 (58.4)	9.85 (27.3)	8.63 (22.2)	4.51 (-)
Vss (L/kg)	0.474 (69.6)	0.740 (30.2)	0.488 (32.0)	0.513 (49.2)	0.421 (-)

Summary Statistics of Tazobactam Plasma Pharmacokinetic Parameters Following the Administration of Single IV Doses of Ceftolozane/Tazobactam to Group 1-6 Subjects, Presented as GM and 95% CI
(PK Population)

	Group 4 (Dose 30/15 mg/kg) (N=5)	Group 5 (Dose 20/10 mg/kg) (N=6)	Group 6 (Dose 12/6 mg/kg) (N=2)	Group 6 (Dose 20/10 mg/kg) (N=3)
AUC0-inf (h*ug/mL)	29.9 (21.6,41.4)	24.9 (18.0,34.4)	77.6 (37.5,161)	22.3 (14.7,34.0)
AUClast (h*ug/mL)	28.9 (18.0,46.6)	21.3 (13.8,33.0)	21.6 (10.2,45.9)	21.9 (11.8,40.6)
Cmax (ug/mL)	22.4 (13.8,36.6)	11.7 (7.48,18.3)	6.87 (3.17,14.9)	12.1 (6.43,22.7)
Tmax (h)	1.05 (0.58,1.95)	1.08 (0.95,1.33)	3.89 (1.03,6.75)	1.07 (1.07,1.18)
Clast (ug/mL)	0.401 (90.5)	0.657 (169.2)	3.66 (57.6)	0.266 (81.3)
Tlast (h)	5.02 (4.02,5.75)	5.95 (2.18,6.10)	6.40 (6.05,6.75)	5.85 (5.72,6.02)
t1/2 (h)	0.815 (85.1)	1.09 (32.0)	3.03 (-)	0.875 (20.4)
CL (L/h)	4.29 (42.1)	1.47 (53.1)	0.114 (-)	1.25 (37.6)
CL ((L/h)/kg)	0.502 (34.7)	0.385 (34.1)	0.0760 (-)	0.452 (24.9)
Vss (L)	4.91 (50.2)	2.55 (25.4)	0.508 (-)	1.85 (19.2)
Vss (L/kg)	0.574 (36.2)	0.668 (19.8)	0.338 (-)	0.667 (29.3)

AUC0-inf = area under the plasma concentration-time curve from time zero extrapolated to infinity, AUClast = area under the plasma concentration-time curve from time zero to last quantifiable concentration, Cmax = maximum concentration, CL = clearance, Clast = last quantifiable concentration, T1/2 = terminal half-life, Tlast = time to last quantifiable concentration, Tmax = time to maximum concentration, Vss = volume of distribution at steady state. "-" = Not applicable. PK parameter values that could not be appropriately determined due to inadequate concentration data were not included in summary.
CL values were presented as weight-normalized ((L/h)/kg) and non-weight normalized (L/h).Vss values were presented as weight-normalized (L/kg) and non-weight normalized (L).
One Group 1 subject, one Group 5 subject, and one Group 6 subject were excluded from the PK population because of a likely sample switch, improper drug administration, and insufficient plasma volume, respectively.
One Group 4 (Dose 30/15 mg/kg) subject had a prolonged infusion time of ~2 hours due to loss of intravenous access. One Group 5 subject received a lower dose of C/T due to use of a different screening weight of the subject.
Statistics for AUC0-inf, AUClast, and Cmax: Geometric least-squares mean and confidence interval based on back-transformed least-squares mean and confidence interval from linear mixed-effects model with group fixed effect performed on natural log-transformed values.
Statistics for Tmax and Tlast: Median and Range (Minimum, Maximum).
Statistics for Clast, t½:, CL, and Vss:Geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s2)-1), where s2 is the observed between-subjects variance on the natural log-scale.
Source: [P010V05: adam-adpp]

Assessor's comments:

For ceftolozane's interim analyses an AUC target of 130-175 µg*h/mL was used, which covers the range of AUCs reported in adult healthy volunteers, patients with cUTI and cIAI. An AUC target of 24 µg*h/mL was chosen for the interim analyses of tazobactam.

Interim analyses in older children from Group 1 (ages ≥12 to <18 years) and Group 2 (ages ≥7 to <12 years) determined that the dose exposures of ceftolozane and tazobactam were similar to those in adults and thus no adjustment to the initial dosing was made. However, it is noted that in the final analysis for Group 2, geometric mean AUCs (0-∞) were below the AUC target range for both ceftolozane and tazobactam. In this group, the low geometric mean Tazobactam AUC could be

explained by incomplete PK sampling in 3 patients that resulted in the AUC not being calculated for these patients. In contrast, the PK samples for ceftolozane were sufficient for all 6 patients in this cohort. From Groups 3 to 6, higher dosing adjustments led to changes in PK parameters of both ceftolozane and tazobactam that were almost dose proportional and comparable to exposures in adults.

Ceftolozane's CL and Vss increased with increasing age, and a similar trend was also observed for tazobactam. However, there are variabilities with the tazobactam data. For 16 subjects across all age groups, tazobactam concentrations measured at 6-hours post administration were below the limit of quantification. In addition, the concentration time profiles and Vss were variable in the youngest cohorts (Groups 5 and 6). Therefore, the assessment of the tazobactam PK parameters across age cohorts is confounded by these factors.

Regarding the PK of pharmacologically inactive, tazobactam metabolite (M1), the terminal elimination phase extended beyond the accepted 6-hour sampling window. Furthermore, 2 subjects from Group 2 were given piperacillin/ tazobactam just over 24 hours prior to enrolment to the study and had pre-dose M1 concentrations. Both factors are associated with the longer half-life of M1 and as such, precluded robust PK assessment of this metabolite. Although the timing of piperacillin/ tazobactam administration (>24 hours before enrolment) in these two patients did not meet the study's exclusion criteria per se, the pre-dose M1 results suggest that a longer exclusion period between administration of tazobactam containing antibiotics and the study drug might have been more appropriate. However, no pre-dose tazobactam levels were detected in these subjects to suggest that the timing of previous piperacillin/ tazobactam administration also affected the PK analyses of tazobactam.

Conclusion:

These data demonstrate an approximate dose proportional increase in PK of tazobactam and ceftolozane when doses were adjusted after interim analyses. There is also an observed increase in the CL and Vss for both antibiotics with increasing age. With regards to the youngest age groups, the observed decrease in clearance for both ceftolozane and tazobactam was expected given the immaturity of the renal system in this cohort and given that both products are cleared by the kidney.

This study provides preliminary data on the single dose PK profile of ceftolozane/ tazobactam in children and will be used to inform the paediatric dosing strategy in the planned (pivotal) paediatric studies. Whilst it is acknowledged that there are some limitations of these data, they are sufficient to support further paediatric development of this product. Therefore, the MAH's overall conclusions are acceptable.

2.3.3. Discussion on clinical aspects

Ceftolozane/tazobactam has a favourable benefit-risk profile based on well-characterized efficacy and safety data in adult patients. Single doses of ceftolozane/tazobactam have now been studied in paediatric subjects from birth (7 days postnatal) to <18 years receiving concurrent standard of care antibiotic therapy for treatment of proven or suspected gram-negative infection or perioperative prophylaxis. Study CXA-PEDS-13-08 (P010) evaluated the PK and safety of single doses of IV ceftolozane/tazobactam to determine appropriate paediatric dosing that achieves the efficacious and safe exposure levels observed in adults.

From this completed Phase I study no assessment or conclusion regarding the efficacy of ceftolozane/ tazobactam in the paediatric population can be made.

Ceftolozane and tazobactam PK parameters after a single dose were generally comparable across Groups 1-4 (ages 3 months to <18 years). Subjects in Groups 5 and 6 had lower CL than older subjects, and this is likely due to the immature renal function of the younger subjects. In paediatric patients aged ≤32 weeks gestation, 7 days postnatal to <3 months (Group 6), those who received 12/6 mg/kg ceftolozane/tazobactam had the lowest ceftolozane and tazobactam CL amongst all subjects in the trial, which is consistent with the lower CrCL in this age group. The MAH notes that the initial dose selection for each age group and dose changes as determined by interim analyses mitigated the effect of decreased CL on exposure. Thus, once dose adjustments were made for Groups 3 and 4, exposures were generally comparable across all age groups.

A single dose of IV ceftolozane/tazobactam in paediatric subjects from birth (7 days postnatal) to <18 years of age was well tolerated. Overall, the reported adverse events (AE) were consistent with the trial population of hospitalized paediatric subjects with gram-negative infections. There were no deaths and no SAEs related to the study drug. In addition, no severe TEAEs or TEAEs leading to study drug or study discontinuation were reported. No clinically significant laboratory abnormalities or changes in ECGs were observed after administration of study drug, and no safety concerns were identified with administration of ceftolozane/tazobactam to paediatric subjects in this trial. The adverse effects observed were in keeping with those described in adults. Thus, the MAH concludes no new safety concerns were identified. These conclusions are endorsed.

The MAH states that data from this study have been included in modelling and simulation studies to inform the dosing strategy for the planned treatment studies for cIAI and cUTI in paediatric subjects. Therefore, the results of this study support continued development of ceftolozane/ tazobactam in the paediatric population. This is acceptable.

3. Rapporteur's overall conclusion and recommendation

This study provides preliminary PK and safety data based on single-dose ceftolozane/ tazobactam administration in children. Although there are some limitations with these data, they are adequate to support further paediatric development of this product. However, at this stage of paediatric development, these data do not fully determine the benefit: risk in the paediatric population.

☒ 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 should commit to submit this variation application by 12/21.

4. Additional clarification requested

Not applicable.

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

The studies should be listed by chronological date of completion:

Non-clinical studies

Product Name: Zerbaxa Active substance: Ceftolozane/Tazobactam

Study title	Study number	Date of completion	Date of submission of final study report
Single dose study to assess the pharmacokinetics of ceftolozane and tazobactam in juvenile rats	CX.101.PK.003	04-April-2013	Submitted in initial MAA, 25-July-2014
14-Day dose ranging study in juvenile rats to assess toxicological potential of ceftolozane in combination with tazobactam and to provide information on dose selection	CX.101.TX.033	30-August-2013	Submitted in initial MAA, 25-July-2014
28-Day study in juvenile rats to assess toxicological potential of ceftolozane in combination with tazobactam	CX.101.TX.038	31-March-2014	Submitted in initial MAA, 25-July-2014

Clinical studies

Product Name: Zerbaxa Active substance: Ceftolozane/Tazobactam

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, single dose study to evaluate the pharmacokinetics and safety of ceftolozane/ tazobactam in children (0-18 years) with proven or suspected Gram-negative infection receiving standard antibiotic therapy	CXA-PEDS-13-08 MK-7625A PN010	15-June-2017	14-December-2017
Double-blind, randomised, active controlled study to evaluate safety, tolerability and efficacy of ceftolozane/ tazobactam in children (0-18 years) with complicated urinary tract infection (cUTI)	MK-7625A PN034	On-going	To be submitted
Double-blind, randomised, active controlled study to evaluate safety, tolerability and efficacy of ceftolozane/ tazobactam in children (0-18 years) with complicated intra-abdominal infection (cIAI)	MK-7625A PN035	On-going	To be submitted