23 June 2022
EMA/644705/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zerbaxa

International non-proprietary name: ceftolozane / tazobactam

Procedure No. EMEA/H/C/003772/0000

Note

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

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Table of contents

List of abbreviations

% fT>MIC	Percent time of the dosing interval during which the free concentration in plasma exceeds the minimum inhibitory concentration
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AmpC	Class C β-lactamase
AP	Acute pyelonephritis
APaT	All participants as treated
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BL	β-lactam
BLI	β-lactamase inhibitor
BLQ	Below-limit-of quantification
C/T	Ceftolozane/tazobactam (ZERBAXA™; MK-7625A)
CDAD	Clostridioides difficile-associated diarrhea
CE	Clinically evaluable
Ceoi	Concentration at the end of infusion
cIAI	Complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
cLUTI	Complicated lower urinary tract infection
C_{max}	Maximum (peak) observed drug plasma concentration
C_{min}	Minimum observed drug plasma concentration
CSR	Clinical Study Report
cUTI	Complicated urinary tract infection
CYP	Cytochrome P450 enzyme
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	drug monitoring committee
EBE	empirical Bayes estimates
ECI	Event of Clinical Interest
eGFR	Estimated glomerular filtration rate
ELF	Epithelial lining fluid
EOIV	End of IV treatment (visit)
EOT	End of treatment (visit)
ESBL	Extended-spectrum β-lactamase

ESRD	End-stage renal disease
EU	European Union
FDA	Food and Drug Administration
Fpen	Market penetration factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
HA(B)P	Hospital-acquired (bacterial) pneumonia
ISR	Incurred sample reanalysis
ISS	Integrated Summary of Safety
IV	Intravenous
LOQ	Limit of Quantitation
MAA	Marketing Authorisation Application
MDR	Multi-drug resistant
ME	Microbiologically evaluable
MERO	Meropenem
MIC	Minimum inhibitory concentration
MITT	Modified intent-to-treat
mMITT	Microbiological modified intent-to-treat
MTZ	Metronidazole
NEC	Necrotizing enterocolitis
NOAEL	No Observed Adverse Effect Level
NP	Nosocomial pneumonia
OAT	Organic anion transporter
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PND	Postnatal day
PTA	Probability of target attainment
q8h	Every 8 hours
SAE(s)	Serious adverse event(s)
Sc	subcutaneous
SOC	System organ class
TOC	Test of cure (visit)
UTI	Urinary tract infection
VA(B)P	Ventilator-acquired (bacterial) pneumonia

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 28 June 2021 an application for a variation.

The following changes were proposed:

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

Extension of indication to include treatment of paediatric patients aged birth to less than 18 years for Zerbaxa, based on final results from studies MK-7625A-034 (A Phase 2, Randomized, Active Comparator-Controlled, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam Versus Meropenem in Paediatric Subjects with Complicated Urinary Tract Infection and Acute Pyelonephritis) and MK-7625A-035 (A Phase 2, Randomized, Active Comparator-Controlled, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam Plus Metronidazole Versus Meropenem in Paediatric Subjects with Complicated Intra-Abdominal Infection).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0436/2020 and P/0277/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0436/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0436/2020 within procedure EMEA-C-001142-PIP01-11-M04.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

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

Extension of indication to include cIAI, AP and cUTI treatment of paediatric patients aged birth to less than 18 years for Zerbaxa, based on final results from studies MK-7625A-034 (A Phase 2, Randomized, Active Comparator-Controlled, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam Versus Meropenem in Paediatric Subjects with Complicated Urinary Tract Infection and Acute Pyelonephritis) and MK-7625A-035 (A Phase 2, Randomized, Active Comparator-Controlled, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam Plus Metronidazole Versus Meropenem in Paediatric Subjects with Complicated Intra-Abdominal Infection).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Version 4.0 of the RMP is approved with this procedure.

is recommended for approval.

Amendments to the marketing authorisation

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

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'EMEA/H/C/003772/II/0036'.

4. Scientific discussion

4.1. Introduction

Infections due to resistant Gram-negative bacteria are increasingly common also in paediatric patients.

Beta-lactamases are a major cause of resistance to beta-lactam antibacterial agents in infections caused by Gram-negative pathogens. The increasing resistance has significantly limited treatment options in patients with suspected extended-spectrum β-lactamases (ESBL) infections and often only carbapenems have sufficient coverage for empiric use in these cases.

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

Zerbaxa – Ceftolozane/tazobactam (C/T) - is a fixed drug combination that has been developed as an intravenously administered compound.

- Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death.

- Tazobactam is a beta-lactam structurally related to penicillins. It is an irreversible inhibitor of some beta-lactamases (e.g., certain penicillinases and cephalosporinases), and can bind covalently to some chromosomal and plasmid-mediated bacterial beta-lactamases. Tazobactam has little antibacterial activity in itself.

At the time of this application, Zerbaxa was approved for adults in complicated intra-abdominal infections (cIAI), acute pyelonephritis (AP), complicated urinary tract infections (cUTI) and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

This application was submitted for ceftolozane/tazobactam in order to expand the age range for the treatment of AP, cUTI and cIAI to include use in paediatric patients from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age.

In support of the application, results from 3 clinical studies listed in the agreed paediatric investigation plan (PIP) were submitted; 2 completed Phase 2 studies in AP/cUTI and cIAI (P034 and P035, respectively, both completed in 2021) and 1 completed Phase 1 study (P010, completed in 2017, studying safety and PK of a single-dose of Zerbaxa).

4.1.1. General comments on compliance with GCP

The MAH provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. Furthermore, the MAH declared in the study reports that studies were "conducted in accordance with local and/or national regulations (including all applicable data protection laws and regulations), ICH GCP and with the ethical principles that have their origin in the Declaration of Helsinki regarding IEC review, informed consent and the protection of human participants in biomedical research (MSD Code of Conduct for Interventional Clinical Trials)."

4.2. Non-clinical aspects

No new non-clinical pharmacology, pharmacokinetic, or toxicology studies were conducted to support the paediatric indication for C/T treatment of paediatric patients, from birth to <18 years of age, with cUTI (including pyelonephritis), or cIAI. However, in the non-clinical dossier submitted with the initial application for marketing authorisation for Zerbaxa EMEA/H/C/3772 (AP/cUTI and cIAI in adults), studies in juvenile rats were included. These studies are listed as Non Clinical measures in the agreed PIP (EMEA-001142-PIP01-11-M03). The MAH submitted an updated overview and assessment of these relevant data, focusing on safety aspects related to use in paediatric patients from birth to < 18 years of age. In line with this, an updated assessment of non-clinical paediatric data is included below.

4.2.1. Introduction

Summary of general toxicity profile for ceftolozane and tazobactam

Ceftolozane's pharmacology, pharmacokinetics, and toxicity, both alone and in combination with tazobactam, have been well characterized in a comprehensive series of *in vitro* and *in vivo* non-clinical studies, including GLP-compliant IV repeat dose toxicity studies of up to 4 weeks duration.

Ceftolozane-related effects in rats and dogs were limited primarily to non-adverse microscopic presence of reversible hyaline droplets in proximal tubular cells in renal cortex in rats and dogs, in parallel with accumulation of ceftolozane in renal tissue following repeated dosing. The occurrence of hyaline droplets within the proximal tubular epithelium of the kidney represents lysosomes containing drug and membrane remnants and has been described also for other cephalosporins. Reversible decreased total bilirubin and increased ALAT, changes in liver weight and histological changes, were noted in dogs administered ceftolozane.

No repeat-dose toxicity studies were conducted with tazobactam alone. A well-known tazobactam-related effect evident in animals is a reversible accumulation of glycogen in the cytoplasm of hepatocytes.

No new effects or unexpected toxicities were observed in adult rat or dog when ceftolozane was combined with tazobactam for 2 to 4 weeks. Non-adverse, reversible changes evident in the kidney and liver were consistent with findings noted in studies with either compound alone. See Table 1 for NOAELs, corresponding exposure data and safety margins calculated based on a clinical AUC of 345/82.8 µg.h/mL in cIAI patients. In the lack of severe toxicity, the margins of safety were considered acceptable.

Table 1: *NOAELs, exposure data and safety margins from ceftolozane + tazobactam repeat dose toxicity studies in rat and dog*

Study	**NOAEL (C/T) mg/kg/day**	**C/T AUC at NOAEL (µg.h/mL)**	**AUC based safety margins at NOAEL[a]**
CXA201-T-001 **SD Rat, 4 weeks**	250/125 (mid dose)	389/46 (AUC0-8)	1.1/0.6
CXA201-T-005 **Beagle dog, 2 weeks**	300/150 (high dose)	1868/550 (AUC0-24)	5.4/6.6

[a]: cIAI

The weight of evidence suggests that ceftolozane alone and in combination with tazobactam has a low potential for genotoxicity. Ceftolozane showed a potential for local tolerance effects in rodents, a low

potential for antigenicity and reproductive effects, and no potential for phototoxicity, immunotoxicity, or hemolytic activity.

During the initial MAA assessment, the clinical relevance of a decrease in auditory startle response observed in postnatal day (PND) 60 male and female F1 rats at maternal ceftolozane doses of 300 and 1000 mg/kg/day during pregnancy and lactation was discussed. Although not confirmed in juvenile rat studies, a clinical relevance in the setting of *in utero* exposure could not be excluded and relevant information was included in Section 4.6 of the SmPC.

4.2.2. Pharmacology

Not Applicable

4.2.3. Pharmacokinetics

A non-GLP subcutaneous pharmacokinetic study of ceftolozane and tazobactam in post-natal day (PND) 4 Sprague Dawley rats

Following a single subcutaneous administration of ceftolozane in combination with tazobactam in a 2-to-1 dose ratio to post-natal day (PND) 4 male and female Sprague-Dawley rats, the achieved systemic exposures of ceftolozane and tazobactam were demonstrated to be approximately dose proportional, with similar exposures observed in both male and female neonate animals. See Table 2 and Table 3.

Table 2: *Key plasma pharmacokinetic parameters of ceftolozane in male and female PND4 neonatal Sprague Dawley rats following a single subcutaneous administration in combination with tazobactam*

			CXA-101					
Group	Dose	Gender	C_{max}	T_{max}	C_{max}/Dose	AUC_{inf}	AUC_{inf}/Dose	$T_{1/2}$
	mg/kg		µg/mL	hr	kg*µg/mL/mg	µg*hr/mL	hr*kg*µg/mL/mg	hr
1	100	Female	183	1.0	1.83	429	4.29	1.4
1	100	Male	140	1.0	1.40	386	3.86	1.1
2	300	Female	435	1.0	1.45	1340	4.48	1.3
2	300	Male	406	1.0	1.35	1250	4.16	1.2
3	600	Female	931	1.0	1.55	2780	4.64	1.5
3	600	Male	781	1.0	1.30	2100	3.5	1.5

Table 3: *Key plasma pharmacokinetic parameters of tazobactam in male and female PND4 neonatal Sprague Dawley rats following a single subcutaneous administration in combination with ceftolozane*

			Tazobactam					
Group	Dose	Gender	C_{max}	T_{max}	C_{max}/Dose	AUC_{inf}	AUC_{inf}/Dose	$T_{1/2}$
	mg/kg		µg/mL	hr	kg*µg/mL/mg	µg*hr/mL	hr*kg*µg/mL/mg	hr
1	50	Female	55.3	0.25	1.11	86.7	1.73	1.3
1	50	Male	53.1	0.25	1.06	83.5	1.67	0.75
2	150	Female	208	0.50	1.39	348	2.32	0.92
2	150	Male	171	0.50	1.14	281	1.88	0.87
3	300	Female	295	0.50	0.982	621	2.07	1.4
3	300	Male	296	0.50	0.987	595	1.98	1.1

4.2.4. Toxicology

Reproduction toxicity

A subcutaneous 14-day dose range finding juvenile toxicity and toxicokinetic study in postnatal day (PND) 4 SD rats

Neonatal (PND 4) SD rats (6/sex/group) were administered ceftolozane/tazobactam at 0 (vehicle control), 50/25, 300/150 and 1000/500 mg/kg/day (sc) for 14 days. An additional 18 PND4 rats/sex/group were utilized to determine toxicokinetics of the test articles. Parameters included mortality and moribundity, cageside observations, body weights, haematology, clinical chemistry, toxicokinetics on PND17, gross necropsy, organ weights, femur length, and histopathology on selected tissues.

No test article-related mortalities occurred and no effects on body weights, femur length, haematology, clinical chemistry, or gross necropsy were noted. Adverse clinical signs related to ceftolozane/tazobactam included decreased motor activity, lost or impaired righting reflex, and ataxia in the 1000/500 mg/kg/day dose group between PND 12 through 16. These effects generally occurred on a single day. Non-adverse red and/or purple discoloration was noted at the injection site in 17 of 18 male and female toxicokinetic rats on PNDs 4, 5, and/or 6 at 1000/500 mg/kg/day.

A non-adverse, dose dependent increase in absolute liver and kidney weights were noted at dose levels $\geqslant$ 300/150 mg/kg/day. Liver weights were 6% to 8% higher than controls in the 300/150 mg/kg/day dose group and 11% to 17% higher in the 1000/500 mg/kg/day dose group. Paired kidney weights were 7% to 12% higher than controls in the 300/150 mg/kg/day dose group and 21% to 24% higher in the 1000/500 mg/kg/day dose group. Increased liver and kidney weights correlated with microscopic findings (mild centrilobular hepatocellular hypertrophy) in five male rats and a single female rat at 1000/500 mg/kg/day and in a single male rat at 300/150 mg/kg/day. The degree of hypertrophy seen in these animals was unlikely to be clinically significant, and no associated necrosis was present. Cortical tubular vacuolation and basophilia, and minimal to mild cortical fibrosis were seen in the kidney of both male and female rats in the 1000/500 mg/kg/day dose group. Cortical tubular vacuolation was noted in four of six female rats in the 300/150 mg/kg/day dose group. Hyaline droplets were also present in the proximal convoluted tubular epithelium of two male rats in the 1000/500 mg/kg/day dose group. No epithelial cell necrosis was identified in the renal tubules, but the presence of tubular basophilia is consistent with recent cell loss that may have occurred during the dosing phase and subsequent regenerative activity. Foci of renal cortical fibrosis are also suggestive of previous tubular damage that possibly occurred during the dosing phase.

NOAEL for sc administration of ceftolozane/ tazobactam to male and female neonatal SD rats from PND 4 through 17 was considered to be 300/150 mg/kg/day, which correlated with mean PND 17 AUC0-∞ and Cmax values of 657/145 µg.h/mL and 416/184 µg/mL, respectively. The AUC based safety margins for AP/cUTI and cIAI in paediatric patients are 1.3 and 1.2 for ceftolozane and tazobactam, respectively.

28-day subcutaneous toxicity study including toxicokinetics with a 28-day recovery period in neonatal SD rats

Neonatal (PND 4) SD rats (20/sex/group) were administered ceftolozane/tazobactam at 0 (vehicle control), 50/25, 300/150 and 1000/500 mg/kg/day (sc) for 28 days. The reversal of potential ceftolozane effects was examined following a 4-week recovery period (10/sex/group). Parameters evaluated during the study included morbidity/mortality, clinical signs of toxicity, body weights, food consumption, toxicokinetics, ophthalmology, sexual maturation, acoustic startle response, functional observational

battery, motor activity, femur length, haematology, coagulation, blood chemistry, urinalysis, gross pathology, organ weights, and histopathology.

No mortalities related to ceftolozane/tazobactam were observed. Administration at doses up to 1000/500 mg/kg/day was not associated with any effects on body weights, food consumption, ophthalmology, sexual maturation, femur length, acoustic startle, functional observational battery, motor activity, coagulation, blood chemistry, or urinalysis, or gross pathology. Ceftolozane/tazobactam-related adverse clinical signs of decreased motor activity and/or impaired righting reflex occurred at ⩾300/150 mg/kg/day and were considered adverse at 1000/500 mg/kg/day. The decreased motor activity and impaired righting reflex generally occurred simultaneously, shortly after dose administration and were generally resolved within 1- to 2-hour post-dose observation. These effects were not observed at any dose level following the 28-day recovery period.

The weights of the paired kidneys and the ratios of the paired kidney weights to the terminal body weight and the brain weight were increased (from 8% to 30% above control) in males and females at ⩾ 300/150 mg/kg/day on PND 32.

Values for erythrocytes, haemoglobin and haematocrit were significantly reduced (7% -10%) at 1000/500 mg/kg/day on PND 32, but because they were of a small magnitude and within the historical control range, they were not considered adverse. Centrilobular hypertrophy of hepatocytes, characterized by increased cytoplasmic volume and translucency of affected cells, was observed at 1000/500 mg/kg/day. This is consistent with the cytoplasmic alteration that has been described previously in association with tazobactam. In the absence of effects on liver weight and clinical chemistry, these changes were considered to be adaptive and non-adverse. Centrilobular hypertrophy was also observed at the end of the recovery period; however, there was a trend toward lesser severity at that time point, suggestive of ongoing resolution.

Based on the adverse clinical signs observed at 1000/500 mg/kg/day, the NOAEL for this study was 300/150 mg/kg/day. The TK data for ceftolozane and tazobactam are presented in Table 4.

The highest mean AUC across the paediatric age groups of both the AP/cUTI and cIAI indications studied in the paediatric clinical trials were used to calculate margins for ceftolozane and tazobactam. The PND 31 AUC based safety margins are 0.59 and 0.26 for ceftolozane and tazobactam, respectively.

Table 4: *Mean tazobactam Cmax and AUC values in juvenile male and female Sprague Dawley rats following daily sc administration of ceftolozane/tazobactam for 4 weeks*

Dose (ceftolozane/tazobactam)	Day 1				Day 28			
	C_{max} (µg/mL)		AUC_{last} (mg·h/mL)		C_{max} (mg/mL)		AUC_{last} (mg·h/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
0/0 mg/kg/day								
Ceftolozane	-	-	-	-	-	-	-	-
Tazobactam	-	-	-	-	-	-	-	-
50/25 mg/kg/day								
Ceftolozane	103	90.9	289	263	42.0	51.5	44.2	50.7
Tazobactam	31.8	37.4	61.4	58.5	10.2	10.8	7.28	5.95
300/150 mg/kg/day								
Ceftolozane	532	517	1470	1580	287	300	312	280
Tazobactam	291	224	437	416	54.4	65.1	33.9	32.2
1000/500 mg/kg/day								
Ceftolozane	1370	1490	5950	6410	728	849	951	1050
Tazobactam	730	723	2250	2470	248	266	153	157

4.2.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment was included as part of this extension of indication application for Zerbaxa on the grounds that the predicted environmental concentrations of ceftolozane and tazobactam are not expected to increase.

An extension of indication to include paediatric patient groups can potentially increase the total consumption of Zerbaxa, and consequently the environment exposure of ceftolozane and tazobactam. It was, however, acknowledged by the CHMP that in a previous application that led to extending the indication to treatment of hospital-acquired pneumonia in adults (EMEA/H/C/003772/II/0020), predicted environmental concentration (PEC) and risk quotient (RQ) values were updated for surface water, groundwater and wastewater treatment facilities, based on a maximum daily dose of 6 g ceftolozane and 3 g tazobactam and a default market penetration factor (Fpen) of 0.01. All RQs for tazobactam were under the threshold of 1, indicating no risk to the environment. For Ceftolozane a risk for surfacewater was indicated, which was confirmed after refinement of Fpen. Considering use of default Fpen, that environmental risk assessment covers also this application for extension of indication. Section 6.6 of the SmPC for ZERBAXA includes the following statement:

One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment (see section 5.3). Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed in accordance with local requirements. These measures will help protect the environment.

Considering the above, the CHMP considered that Zerbaxa should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

4.2.6. Discussion on non-clinical aspects

Juvenile toxicity

In GLP-compliant repeat dose toxicity studies performed in adult rat and dog, effects associated with ceftolozane and tazobactam treatment alone were limited to non-adverse changes in the kidney and liver, respectively. Studies in juvenile animals were justified by the need to evaluate potential increased sensitivity to toxicity in immature and developing organs. Rat appeared to be more sensitive than dog and was appropriately selected as species for juvenile animal testing. The juvenile animal studies performed are in compliance with the approved PIP. Sc administration was selected for practical reasons given the young age of the rats. Juvenile rats were treated from PND 4, which would support children from gestation week 32 or later since both liver and kidneys are immature in PND 4 rats (Ref. ICH S11).

Notable findings in the non-GLP 14-day range-finding and the definitive 28-day GLP studies in juvenile rats included:

- adverse clinical signs (decreased motor activity, lost/impaired righting reflex, ataxia) at 1000/500 mg/kg/day. The signs occurred shortly after dosing, but they resolved quickly indicating they were not a developmental consequence and appeared to be Cmax-related. These clinical signs were not associated with findings in the functional observational battery in rats, were seen at high multiples to the clinical plasma Cmax, did not have a histopathological correlate, and are clinically monitorable and reversible. As such, these clinical signs were considered of limited concern for clinical safety.
- adverse renal effects in the non-GLP study, suggestive of possible renal tubular degeneration that may have occurred earlier in the study. However, these possible adverse renal effects did not

replicate in the definitive rat GLP 28-day (PND 4-31) toxicity study that utilized the same doses and a longer dosing period and larger group sizes. Due to the absence of findings in the definitive rat GLP 28-day (PND 4-31) toxicity study initiated in rats at an age equivalent to pre-term infants, the possible renal findings in the range-finding study are considered of limited significance.

- other findings reported in the definitive 28-day juvenile toxicity study (decreases in erythrocytes, hemoglobin, and hematocrit and centrilobular hypertrophy of hepatocyte histomorphologically, only at the highest dose) were non adverse and either reversed or were in the process of reversing following a 28-day recovery period.

Overall, the toxicity profile in neonatal and juvenile rats does not indicate developmental toxicity or more severe effects compared to older rats. Furthermore, juvenile rats do not appear to be significantly more sensitive to toxicity. The decrease in auditory startle response observed in PND 60 male and female F1 rats in a previous peri-post natal rat study (initial MA procedure) was not confirmed in juvenile rat studies. The information included in SmPC section 4.6 is, however, still considered appropriate and relevant in the setting of *in utero* exposure.

Together with clinical safety data, the study results support the safe use of Zerbaxa for the treatment of AP/cUTI and cIAI in paediatric patients from birth to less than 18 years of age.

4.2.7. Conclusion on the non-clinical aspects

Paediatric data on non-clinical aspects

The toxicity profile in neonatal and juvenile rats does not indicate developmental toxicity or more severe effects compared to older rats. Furthermore, juvenile rats do not appear to be significantly more sensitive to toxicity. The decrease in auditory startle response observed in PND 60 male and female F1 rats in a previous peri-post natal rat study (initial MA procedure) was not confirmed in juvenile rat studies. The information included in SmPC section 4.6 is however still considered appropriate and relevant in the setting of in utero exposure.

Together with clinical safety data, the study results support the safe use of Zerbaxa for the treatment of AP/cUTI and cIAI in paediatric patients from birth to less than 18 years of age.

4.3. Clinical aspects

4.3.1. Introduction

GCP

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

- **Tabular overview of clinical studies**

Table 5: *Table of the submitted clinical trials P034 (AP/cUTI) and P035 (cIAI)*

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
MK-7625A-034 [Ref. 5.3.5.1: P034MK7625A]	2	Greece Hungary Mexico Poland Russia Turkey Ukraine USA	A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Versus Meropenem in Pediatric Subjects with Complicated Urinary Tract Infection (cUTI), Including Pyelonephritis	Randomized, active comparator-controlled, multicenter, double-blind study	**Group 1 (Age 12 to <18 years,):** Ceftolozane 1 g and tazobactam 0.5 g IV every 8 hrs OR Meropenem 20 mg/kg (max 1 g/dose) IV every 8 hrs **Group 2 (Age 6 to <12 years,):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (max ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hrs OR Meropenem 20 mg/kg (max 1 g/dose) IV every 8 hrs **Group 3 (Age 2 to <6 years):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (max ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hrs OR Meropenem 20 mg/kg (max 1 g/dose) IV every 8 hrs **Group 4 (Age 3 months to <2 years):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (max ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hrs OR Meropenem 20 mg/kg (max 1 g/dose) IV every 8 hrs **Group 5 (Ages birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (max ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hrs OR Meropenem 20 mg/kg (max 1 g/dose) IV every 8 hrs Treatment duration: 7-14 days	Males/females Age: birth to <18 years Participants with cUTI, including pyelonephritis	Ceftolozane/ tazobactam Group 1: 15 Group 2: 24 Group 3: 22 Group 4: 24 Group 5: 15 Meropenem: Group 1: 5 Group 2: 8 Group 3: 7 Group 4: 7 Group 5: 6

Study ID	Phase	Country/ Region	Study Title	Study Design	IV Dosing Regimen [a]	Study Population	Participant Exposure
MK-7625A-035 [Ref. 5.3.5.1: P035MK7625A]	2	Brazil, Hungary, Lithuania, Malaysia, Mexico, Russia, South Africa, Spain, Turkey, Ukraine, USA	A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Plus Metronidazole Versus Meropenem in Pediatric Subjects with Complicated Intra-Abdominal Infection (cIAI)	Randomized, active comparator-controlled, multicenter, double-blind study	**Group 1 (Age 12 to <18 years):** Ceftolozane 1 g and tazobactam 0.5 g + metronidazone (MTZ) 10 mg/kg OR Meropenem (MERO) 20 mg/kg **Group 2 (Age 6 to <12 years):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg + MTZ 10 mg/kg OR MERO 20 mg/kg **Group 3 (Age 2 to <6 years):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg + MTZ 10 mg/kg OR MERO 20 mg/kg **Group 4 (Age 3 months to <2 years):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg + MTZ 10 mg/kg OR MERO 20 mg/kg **Group 5 (Ages birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months):** Ceftolozane 20 mg/kg and tazobactam 10 mg/kg + • >28 days of age: +MTZ 10 mg/kg every 8 hours • ≤28 days of age and ≤2 kg: +MTZ 15 mg/kg loading, then 7.5 mg/kg every 12 hours • ≤28 days of age and >2 kg: +MTZ 15 mg/kg loading, then 10 mg/kg every 8 hours OR MERO 20 mg/kg Treatment duration: 7-14 days	Males/females Age: birth to <18 years Participants with cIAI	Ceftolozane/ tazobactam Group 1: 16 Group 2: 30 Group 3: 22 Group 4: 1 Group 5: 1 Meropenem: Group 1: 5 Group 2: 9 Group 3: 7 Group 4: 0 Group 5: 0

[a] All regimens were IV doses administered every 8 hours unless otherwise specified.
Maximum ceftolazone dose: 1 g/dose; maximum tazobactam dose=0.5 g/dose; maximum metronidazole dose: 1.5 g/day; maximum meropenem dose=1 g/dose

4.3.2. Pharmacokinetics

The original marketing application for ceftolozane/tazobactam (C/T) included data from 13 studies (2 Phase 3, 2 Phase 2, and 9 Phase 1). The Phase 1 studies characterized the clinical pharmacology profile of C/T by defining the general pharmacokinetic (PK) characteristics of C/T or ceftolozane alone, effects of intrinsic factors (eg, renal impairment), effects of extrinsic factors (eg, DDIs), tissue distribution (e.g., ELF), and pharmacodynamics (PD) (eg, QT/corrected QTc interval). These studies were performed to support the initial marketing application for the use of Zerbaxa 1.5 g (C/T) powder for concentrate for infusion in the treatment of adult patients with complicated urinary tract infection (cUTI), including pyelonephritis and complicated inter-abdominal infections (cIAI) (EMEA/H/C/3772). The indication was later extended to include Nosocomial pneumonia (NP) including HA(B)P/VA(B)P (EMEA/H/C/003772/II/0020) with the dosing regimen 3 g C/T q8h. That extension of indication application included 3 additional studies (2 Phase 1 and one Phase 3 study) to support the new adult NP indication and dose regimen. Table 6 shows the key PK characteristics of Zerbaxa established in previous procedures.

Table 6: *Brief overview of key PK characteristics of adult population*

Absorption	• Intra venous administration • Not significantly affected by concomitant food
Distribution	• 16-21% (ceftolozane) and ~30% (tazobactam) protein bound in human plasma • Steady state volume of distribution (V_{SS}): 13.5 L (ceftolozane) and 18.2 L (tazobactam) • Active transport: Not substrate for P-gp or BCRP (ceftolozane) • Not substrate for OCT2, substrate for OAT1 and OAT3 (tazobactam)
Elimination	• Ceftolozane undergoes minimal metabolism. Predominantly eliminated by renal excretion. • Tazobactam is metabolised by hydrolysis of the β-lactam ring to M1 metabolite. Tazobactam and tazobactam M1 are eliminated by renal excretion • Excretion following single IV dose of 1g/0.5g C/T: o Ceftolozane: 95% unchanged in urine o Tazobactam: >80% unchanged in urine, the remaining amount as single tazobactam M1 metabolite • Apparent clearance (CL/F): 16.2 L/h • T1/2 (healthy adults) = 2-3 hours (ceftolozane) and 1 hour (tazobactam)
Metabolism	• Primary metabolic pathway: Carboxylesterase-catalysed amide hydrolysis to a major inactive metabolite, M1 (tazobactam).
Dose proportionality	• Established from 250 mg to 3 g (ceftolozane) and 500 mg to 1.5 g (tazobactam) • No notable accumulation after multiple 1h IV infusion of 1g/0.5g C/T or 2g/1g C/T administered every 8h for up to 10 days

Overview of new pharmacokinetics data

This application to extend the cUTI, AP and cIAI indications to children and adolescents from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years is supported by one phase 1 (P010: **P010MK7625A**) and two phase 2 studies;

- P034: **P034MK7625A** (Please note that the patient population in this study is called **cUTI** in the clinical pharmacology report, but is comprised of both patients with cUTI and AP)
- P035: **P035MK7625A** (patients with **cIAI**).

In study **P010**, extensive PK data were collected from patients ≥3 months of age and sparse samples were collected for patients <3 months of age. Sparse PK data was collected from patients in **P034 and**

P035. These PK data were used to develop a paediatric population PK model based on prior information from established adult population PK (population-PK) models and re-investigate covariates impacting the PK of C/T in paediatric patients. Furthermore, the population-PK model was used to derive individual PK exposure metrics, which in turn were used to explore exposure-response relationships of Zerbaxa in children and adolescents with AP/cUTI or cIAI, as well as a joint PTA analysis to support the paediatric dose recommendations. After a request from the CHMP, the population PK models of ceftolozane and tazobactam were also used to perform additional simulations to provide dosing recommendation in paediatric patients (2 to <18 years) with renal impairment category (moderate and severe). Further to additional questions by the CHMP, the MAH withdrew the initial proposals for dosing recommendations in paediatric patients aged 2 to <18 years of age with moderate or severe renal impairment (see section Special populations - Paediatric patients with impaired or immature renal function). Table 7 shows the design of the studies supporting the application.

There are no expected differences in the mechanism of action of C/T based on age as both ceftolozane and tazobactam exert their effects by acting on the causative pathogen, and the Gram-negative causative pathogens are similar in adults and children, and the same joint PK/PD targets would be relevant to dose setting in paediatric patients. Thus, the aim of the dose selection was to achieve comparable exposures to those calculated for adult patients with cIAI and AP/cUTI.

The initial dose in study **P010** was subject to change based upon the interim analysis of PK and safety data, resulting in the following dosing regimen in the two Phase 2 studies (**P034** and **P035**);

- Group 1 (12 to <18 years): 1 g ceftolozane and 0.5 g tazobactam
- Group 2-5 (birth to <12 years): 20 mg/kg ceftolozane and 10 mg/kg tazobactam (maximum ceftolozane 1 g and tazobactam 0.5 g/dose).

In the Phase 2 studies (**P034** and **P035**), one of the exclusion criteria was CrCL <50 mL/min/1.73 m^2. In study **P010** estimated renal function was also an inclusion criteria (Groups 1 through 4 needed CrCL ≥80 mL/min/1.73m^2, Group 5 needed CrCL ≥50 mL/min/1.73m^2, Group 6 needed CrCL ≥20 mL/min/1.73m^2). Creatinine clearance estimated in the clinical trials (CrCL) was calculated by the Bedside Schwartz equation.

In this application, the proposed posology in children and adolescents from birth to <18 years with AP/cUTI or cIAI and with eGFR>50 mL/min/1.73 m^2 is 30 mg/kg (20 mg/kg ceftolozane and 10 mg/kg tazobactam) up to a maximum dose of 1.5 g (1 g ceftolozane and 0.5 g tazobactam for ≥50 kg body weight) administered every 8^{th} hour by IV infusion over 1 hour. As can be seen, this is a simplified dosing regimen compared to the age-based dose regimen that was administered in the Phase 1 and Phase 2 studies (Table 7 shows the dosing regimens in the Phase 1 and Phase 2 studies).

No new formulation was developed for use in the paediatric AP/cUTI and cIAI indications, and no new biopharmaceutical studies were conducted to support this variation application. The formulation used in the paediatric studies submitted with this application is the intended formulation for use in paediatric patients and was identical to the currently marketed formulation approved for use in adults.

Table 7: *Summary of Designs of Studies Included in the Population PK Analyses.*

Study	Number of subjects	Population	Dosing regimen	PK measurements
CXA-PEDS-13-08 (P010)	35	Pediatric patients receiving standard of care antibiotic therapy for proven or suspected gram-negative infection or for perioperative prophylaxis Group 1 :12 to <18 years Group 2: 7 to < 12 years Group 3: 2 to < 7 years Group 4: 3 months to < 2 years Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months* Group 6 birth [≤ 32 weeks gestation, 7 days postnatal] to < 3 months*	C/T administered as 1-hour infusion every 8 hours. Group 1 (n = 6): 1.5g C/T Group 2 (n = 6): 27 mg/kg C/T Group 3 (n = 6,): 27 mg/kg CT; and 45 mg/kg C/T Group 4 (n = 6): 27 mg/kg C/T; and 45 mg/kg C/T Group 5 (n = 6): 30 mg/kg C/T Group 6 (n = 5): 30 mg/kg C/T (if eGFR > 50 mL/min/1.73 m^2); and 18 mg/kg C/T (if eGFR ≤ 50 mL/min/1.73 m^2)	For Groups 1 - 4, plasma samples were collected at 0, 0.5 (optional), 1, 2, 4, and 6 hours after start of infusion For Groups 5 - 6, plasma samples were collected at 1, 2, and 6 hours after start of infusion
MK-7625A-034	133	Pediatric subjects with cUTI, including pyelonephritis Group 1 :12 to <18 years Group 2: 7 to < 12 years Group 3: 2 to < 7 years Group 4: 3 months to < 2 years Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months*	C/T administered as 1-hour infusion every 8 hours. Group 1 (n = 20, 50 in combination with Group 2): 3:1 randomization to 1.5g C/T or 20 mg meropenem Group 2 (n = 32, 50 in combination with Group 2): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem Group 3 (n = 29): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem Group 4 (n = 31): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem Group 5 (n = 21): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem	After administration of at least 6 doses. Plasma samples were collected at end of infusion, between 3-4 hours and 6-7 hours (pre-next dose) after end of infusion
MK-7625A-035	91	Pediatric subjects with cIAI Group 1 :12 to <18 years Group 2: 7 to < 12 years Group 3: 2 to < 7 years Group 4: 3 months to < 2 years Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months*	C/T administered as 1-hour infusion every 8 hours. Group 1 (n = 21, 50 in combination with Group 2): 3:1 randomization to 1.5g C/T + 10 mg/kg metronidazole or 20 mg meropenem Group 2 (n = 39, 50 in combination with Group 2): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem Group 3 (n = 29): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem Group 4 (n = 1): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem Group 5 (n = 1): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem	After administration of at least 6 doses. Plasma samples were collected at end of infusion, between 3-4 hours and 6-7 hours (pre-next dose) after end of infusion
*Age definition per individual protocol				

Source: M&S ANALYSIS REPORT, 082HY8, page 56-57

Methods

- **Analytical methods**

Bioanalysis

In all studies ceftolozane and tazobactam were analysed using LC-MS/MS methods but the laboratories that performed the analyses varied. According to the MAH, the bioanalytical methods used for determination of concentrations of ceftolozane, tazobactam and tazobactam M1 in plasma samples from clinical studies are the same as those previously described and assessed in the initial procedure (EMEA/H/C/3772).

In study **P010,** plasma concentrations of ceftolozane, tazobactam and tazobactam M1 in subject samples were measured using the validated LC-MS/MS method **MN14014**. In the studies **P034 and P035**, plasma concentrations of ceftolozane and tazobactam in subject samples were measured using the validated LC-MS/MS method **PMRI-1756-18 v.00**. While tazobactam M1 were measured using the

validated LC-MS/MS method **PMRI-1757-18 v.00**. The analytical ranges were the same in all studies (0.25 to 150 µg/mL, 0.10 to 60.0 µg/mL, and 0.05 to 30.0 µg/mL for ceftolozane, tazobactam, and tazobactam M1, respectively).

The CHMP considered that the described validation of the bioanalytical assays for quantification of ceftolozane, tazobactam and tazobactam M1 in human plasma to be acceptable in the initial MAA procedure (EMEA/H/C/3772).

The acceptance criteria used for the in-study validation was in accordance with the CHMP *Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)*, and the within-study validation of the studies **P010**, **P034** and **P035** was successful. The previously established sample storage stability covered the storage period of the study samples.

Incurred sample reproducibility was assessed for >10% of samples in study **P034** and **P035**, and ~10% (9.6%) of samples in study **P010**. The ISR met acceptance criteria *i.e.* at least 2/3 of all the analysed ISR samples had no more than a ±20.0% difference when compared to the original analysis results, which is in accordance with CHMP *Guideline on bioanalytical method validation*, and thus considered acceptable by the CHMP.

Database

The population PK analysis included paediatric data from two Phase 2 studies [AP/cUTI (P034) and cIAI (P035)] and one Phase 1 PK study (P010). P010 was conducted in patients with proven or suspected gram-negative infections, whereas P034 and P035 were conducted in patients with AP/cUTI or cIAI, respectively. The studies are described under the section on Special populations in this assessment report.

A total of 194 subjects from the three clinical studies were included in the analysis dataset, and 3 subjects were excluded due to unreasonable PK profiles. A total of 191 subjects were included in the final dataset: 35 (18.3%) from PN010, 89 (46.6%) from PN034, and 65 (35.1%) from PN035. There were 596 ceftolozane and 594 tazobactam samples in total; of which, 2 samples were BLQ for ceftolozane and 98 samples BLQ for tazobactam. 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.

Characteristics of participants in all three studies, including covariates of interest, are summarized in Table 8 and data disposition for ceftolozane and tazobactam is summarized in Figure 1**Error! Reference source not found.**.

Table 8: *Summary of Characteristics of Participants in Paediatric Studies Included in the Modeling Dataset*

	Overall, n = 191 [a]	Group 1 (12y, 18y), n = 36[a]	Group 2 (7y, 12y), n= 48 [a]	Group 3 (2y, 7y), n= 53 [a]	Group 4 (3m, 2y), n = 28 [a]	Group 4 (birth, 3m), n = 21 [a]	Group 5 (0, 3m), n = 5 [a]
STUDY							
MK-7625A-010	35 (18%)	6 (17%)	6 (12%)	6 (11%)	6 (21%)	6 (29%)	5 (100%)
MK-7625A-034	89 (47%)	14 (39%)	15 (31%)	24 (45%)	22 (79%)	14 (67%)	0 (0%)
MK-7625A-035	67 (35%)	16 (44%)	27 (56%)	23 (43%)	0 (0%)	1 (4.8%)	0 (0%)
AGE (Years)	6.3 (5.3) 0.0 -- 17.5	14.8 (1.7) 12.0 -- 17.5	8.8 (1.4) 7.0 -- 11.0	4.0 (1.4) 2.0 -- 6.6	0.9 (0.4) 0.2 -- 1.7	0.1 (0.0) 0.0 -- 0.2	0.1 (0.1) 0.1 -- 0.2
SEX							
Female	95 (50%)	18 (50%)	25 (52%)	31 (58%)	14 (50%)	4 (19%)	3 (60%)
Male	96 (50%)	18 (50%)	23 (48%)	22 (42%)	14 (50%)	17 (81%)	2 (40%)
WEIGHT (Kg)	25.3(19.1) 1.1 -- 90.0	55.2 (13.2) 33.0 -- 90.0	32.8 (9.9) 19.8 -- 75.3	17.5 (4.8) 11.8 -- 36.0	8.6 (1.8) 5.2 -- 11.9	4.4 (1.0) 2.6 -- 6.2	2.2 (1.0) 1.1 -- 3.7
eGFR (mL/min/1.73 m^2)	147.6(65.3) 30.2 -- 561.0	155.6 (59.6) 46.2 -- 366.3	165.0 (41.1) 86.3 -- 293.7	163.6 (77.6) 75.4 -- 561.0	138.1 (68.1) 55.0 -- 427.8	83.8 (28.0) 55.8 -- 139.5	73.8 (37.8) 30.2 -- 113.7
RACE							
Asian	3 (1.6%)	0 (0%)	0 (0%)	2 (3.8%)	1 (3.6%)	0 (0%)	0 (0%)
Black	12 (6.3%)	2 (5.6%)	4 (8.3%)	1 (1.9%)	0 (0%)	1 (4.8%)	4 (80%)
Other	5 (2.6%)	0 (0%)	1 (2.1%)	1 (1.9%)	2 (7.1%)	0 (0%)	1 (20%)
White	171 (90%)	34 (94%)	43 (90%)	49 (92%)	25 (89%)	20 (95%)	0 (0%)
INFECTION TYPE							
cIAI	67 (35%)	16 (44%)	27 (56%)	23 (43%)	0 (0%)	1 (4.8%)	0 (0%)
cUTI	89 (47%)	14 (39%)	15 (31%)	24 (45%)	22 (79%)	14 (67%)	0 (0%)
Other	35 (18%)	6 (17%)	6 (12%)	6 (11%)	6 (21%)	6 (29%)	5 (100%)
Pyelonephritis	75 (39%)	14 (39%)	9 (19%)	19 (36%)	18 (64%)	15 (71%)	0 (0%)
Appendicitis	66 (35%)	14 (39%)	27 (56%)	25 (47%)	0 (0%)	0 (0%)	0 (0%)

[a]Statistics presented: n (%); Mean (SD); Minimum – Maximum
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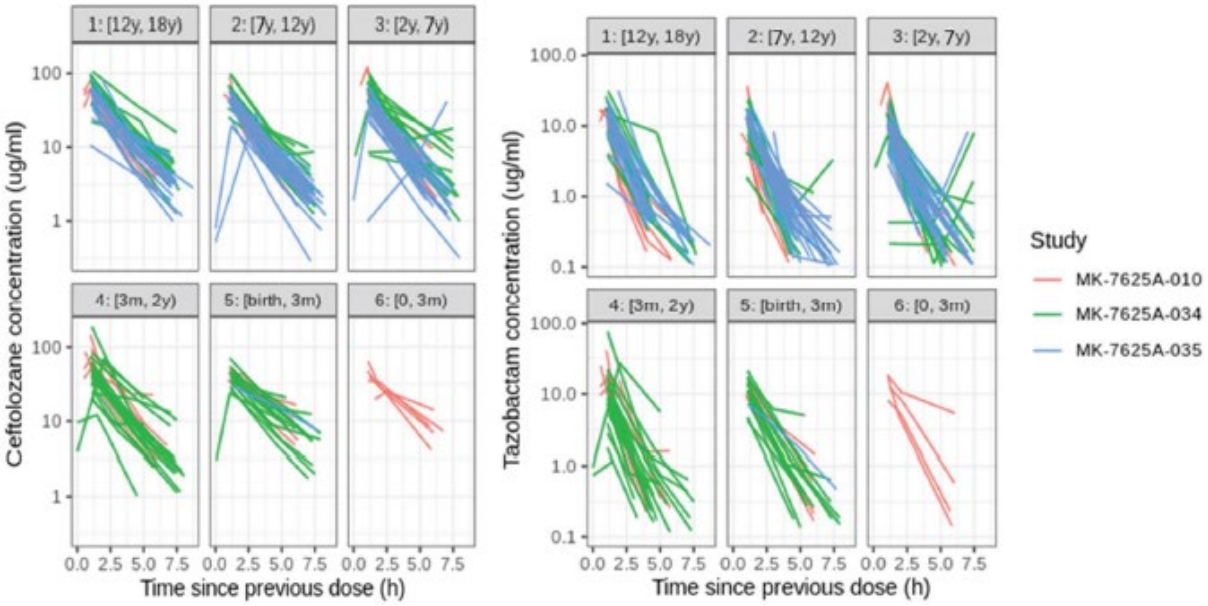
Figure 1: *Plasma Ceftolozane (Left Panel) and Tazobactam (Right Panel) Concentration-Time Profiles in Paediatric Participants in P010, P034 and P035 (Linear-Log Plots) By Age Groups*



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The CHMP noted that the PK analysis dataset consists of sparse samples from 191 paediatric patients. All relevant studies were included in the data base and raw data have been presented. The potential sources of variability investigated was mainly related to demographic factors: age, weight, gender and race. Renal function and infection type is known to affect the PK of C/T and both was tested in the paediatric models.

The dataset spans across the full age range, albeit with few patients in the lower age ranges. Accordingly, there are also few patients at the lower end of the weight and renal function ranges. Only one patient below 2 years of age with cIAI was included in the studies. The inclusion/exclusion criteria were set to only include most patients with eGFR above 50 mL/min/1.73 m^2. A few patients with eGFR below 50 mL/min/1.73 m^2 were included in the study (see section Special populations on Paediatric patients with impaired or immature renal function). The full range of renal function values expected from birth (term/preterm) have thus not been covered. Adjustments were made in the dosing recommendation during the phase 1 PK study, by simplifying the dosing to mg/kg to all patients (with cap at the adult dose). The limitations in the observed data impact the ability to validate the model predictions at low weight, low renal function and for the cIAI indication. Furthermore, a high proportion of the tazobactam samples were below the Limit of Quantitation (LOQ). This mostly relates to the pre-dose and the samples taken 6 to 7 hours after dosing, even though some additional time points are affected for a few patients. The samples that were below LOQ were excluded from the dataset.

Model diagnostics

The final models were evaluated using all diagnostic plots mentioned in the model analysis plan.

- Visual predictive checks (VPCs) of concentration versus time were constructed.
    - VPCs were performed manually using R 3.6.1. Simulated data distributions were based on a minimum of 500 replicates. The mean and 90% prediction interval of the simulated data were plotted, and the observed data were overlaid together with the observed median, 5^{th}, and 95^{th} percentile. In response to the first request of supplementary information, the MAH also provided prediction corrected VPCs (pcVPC) as requested by CHMP.

- To evaluate model performance across the population, VPCs and pcVPCs were stratified by key factors of interest, such as age group. Consistency of simulated and observed quantiles qualifies the model as suitable to predict concentration-time profiles.

- Parameter precision for the final Population-PK model were evaluated using the standard errors calculated from NONMEM.

- Ceftolozane

The final PK model parameters of ceftolozane is given in Table 9.

Table 9: *Final pharmacokinetic model parameter estimates for Ceftolozane*

Parameters	Fixed effect (%RSE)	IIV %CV (%RSE)
CL (L/h): Systemic Clearance	8 (2.88)	33.2 (13.3)
~eGFR [power model]	0.11 (44.1)	--
~Infection (cUTI)	1.03 (269)	--
~Infection (cIAI)	1.21 (39.3)	--
V1 (L): Central Volume	13 (4.4)	46.4 (24)
~Infection (cUTI)	1.42 (32.1)	--
~Infection (cIAI)	1.43 (33.1)	--
V2 (L) : Peripheral Volume	4.23 (15.6)	--
Q (L/h): Intercompartmental Clearance	6.35 (6.01)	--
Residual variability (%)	22.2 (9.74)	--

Source: Model_Summary_CEF.docx

The MAH provided graphical presentations of ceftolozane and tazobactam steady-state exposure metrics (Ceoi and AUC) versus body weight, on a continuous scale. In addition, both ceftolozane and tazobactam exposure measures (Ceoi and AUC) versus age were also depicted in separate figures focused on children 0 – 1 year of age (see section Special populations - Paediatric patients with impaired or immature renal function). As infection type was shown to be a covariate of ceftolozane and tazobactam PK in the models, separate panels for cIAI and cUTI were provided in each figure. In order to allow assessment of dosing-adequacy for body weight and age, 2000 paediatric subjects per age category from the virtual paediatric population database were simulated using the paediatric population PK model of ceftolozane and tazobactam. The results of the simulations were illustrated graphically by superimposing the distribution of simulated paediatric exposure (Ceoi and AUC) values (median and 90% prediction interval) on the adult reference range, together with the predicted paediatric exposure (Ceoi and AUC) values for the individual paediatric patient using the empirical Bayes estimates (EBEs) from the final population PK model.

The CHMP considered that, overall, the model diagnostics indicate that the ceftolozane population-PK model fit the paediatric data well. As part of the assessment, the MAH was requested by the CHMP to provide prediction corrected VPCs (pcVPS) to allow detecting potential misspecifications (Bergstrand et al. 2011). These were provided and indicated reasonable fit of the population-PK model to the paediatric data.

Due to the rather sparse dataset, the MAH was also requested to discuss whether other data could be presented to better understand the adequacy of the dosing recommendations in the lowest age range (<3mo). Furthermore, the MAH was requested to present plots of observed data vs simulated to better understand the ceftolozane exposures at the end of the dosing interval. Additionally, graphical presentations of exposure metrics (Css, Cmax, Cmin) versus body weight, age and renal function on continuous scales for the full paediatric populations with additional separate plot focused on the children 0

– 1 year of age were requested. The graphical presentations of simulated exposure metrics by age and body weight have been provided for AUC and Ceoi. Since in smaller children there is a risk that similar AUC may be observable, while Cmax may be higher and Cmin lower (which may affect the PTA simulations), presentations with Cmax and Cmin would have been preferable. However, this was not further pursued, as it is not expected to further inform the conclusion on the dosing recommendations in the lowest age range (<3 months). AUC and Ceoi vs. weight have been provided for the whole age range, but a closer look at the lower weight ranges would have been preferable.

The simulations of ceftolozane exposures in moderate and severe renal impairment submitted by the MAH in response to the first request for supplementary information indicated that the paediatric model for ceftolozane did not adequately describe the influence of renal function. The CHMP considered that a potential explanation for this could be that the co-variate on renal function was overfit with the observed paediatric data and consequently lost predictive ability on the impact of renal function (see also section *Paediatric patients with impaired or immature renal function* for assessment). Hence, in the second request for supplementary information further questions were posed regarding paediatric patients with impaired or immature renal function, especially those <2 years of age. To better understand the adequacy of the dosing recommendations in the lowest age range (<3 months) and in paediatric patients with reduced renal function and low weight, the MAH was requested to provide graphical presentations of observed and simulated ceftolozane exposure metrics by continuous renal function (all age ranges) and weight (focused on children 0 – 1 year of age, all age ranges already provided). As requested, the MAH provided graphical presentations of ceftolozane steady-state exposure metrics (AUC and Ceoi) versus the continuous measure of renal function (eGFR) for all age ranges and for 0 – 1 year-olds. See the Special Populations section on *Paediatric patients with impaired or immature renal function* for further discussion of dosing recommendations in this patient population.

- Tazobactam

The final PK model parameters of tazobactam were provided. The MAH also provided graphs of the observed and individual predicted versus predicted, pcVPCs. Overall, by age, by infection type, by weight and by eGFR. Etas versus co-variates and CWRES vs Time were also provided.

The evaluation of the various provided parameters seemed to indicate model mis-specifications for tazobactam, with bias observed in both CWRES versus predicted and CWRES versus time since last dose. Attempts to improve the model were made by relaxing the priors on some of the thetas (CL, V), relaxing the omega prior, removing the random effect on V2 and testing a block structure for CL and V1 covariance (omega), however these runs either failed to converge or lead to no improvement in model fit. No indications of outliers were reported. Shrinkage was reported as low, except from V2 (40.9%). No attempts were made to test methods for handling the BLOQ values (such as handling BLOQs as censored data along the lines discussed in Ahn et al. 2008) or test simplifications in model structure to account for the limitations in the paediatric database. Due to the low number of patients in the lower age ranges, the VPC plots initially provided were not well fit for evaluating the goodness of fit in these age categories.

In response to the first request for supplementary information, the MAH provided pcVPCs for the tazobactam model. As well as graphical presentations of the exposure metrics AUC and Ceoi versus body weight and age on continuous scales for the full paediatric populations with additional separate plot focused on the children 0 – 1 year of age. The provided overall pcVPC indicated no major mis-specification in the model, and overall, the additional presentations submitted indicated that the tazobactam population-PK model fit to the paediatric data reasonably well, also at the lower age range. Still the model is considered as of low credibility, particularly for the lowest age ranges (below 3 months for AP/cUTI and below 2 years for cIAI), and some aspects still bring uncertainties to the joint PTA

analysis. Please refer to the section on *special population* for the discussion of the observed tazobactam data.

As for ceftolozane, to better understand the adequacy of the dosing recommendations in the lowest age range (<3 months) and in paediatric patients with reduced renal function and low weight, the MAH was requested to provide graphical presentations of observed and simulated tazobactam exposure metrics by continuous renal function (all age ranges) and weight (focused on children 0 – 1 year of age, all age ranges already provided). The requested presentations of tazobactam steady-state exposure metrics (AUC and Ceoi) versus the continuous measure of renal function (eGFR) for all age ranges and for the 0 – 1 year-old were provided by the MAH.

Special populations

- **Paediatrics**

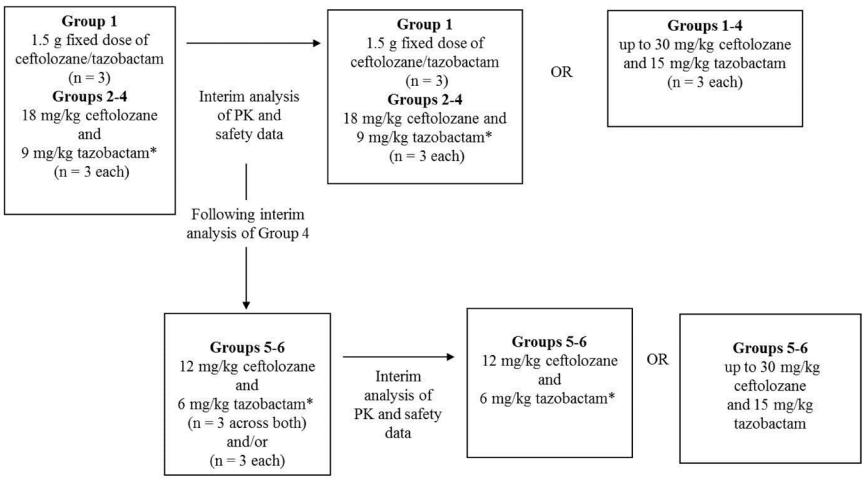
AP/cUTI and cIAI

*- Study **P010** – Non-compartmental analysis*

This was a Phase 1, single-dose, non-comparative, open-label trial to evaluate the pharmacokinetics (PK) and safety of C/T 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. In December 2017, the MAH submitted the completed paediatric study for C/T (**P010**), in accordance with Article 46 of Regulation (EC) No1901/2006 (EMEA/H/C/003772/P46/002).

Since the study was already assessed by CHMP, only a shorter summary is provided in this report. An evaluation of the results from study **P010,** together with results from study **P034** and **P035**, are made in light of this application for extension of indications.

Included subjects received a single age-based intravenous (IV) dose of C/T 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 C/T) based upon interim analysis of PK and safety data. Trial design including interim analysis is shown in Figure 2.



* The initial dose is 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 of previous groups

Figure 2: *Trial design P010.*

Treatment groups and actual treatment received are shown in Table 10. Among the inclusion criteria was estimated renal function where Groups 1 through 4 needed CrCL ≥80 mL/min/1.73m^2, Group 5 needed CrCL ≥50 mL/min/1.73m^2 and Group 6 needed CrCL ≥20 mL/min/1.73m^2. CrCL estimated in the clinical trials was calculated by the Bedside Schwartz equation. In addition, in Groups 1 through 5, patients with height or weight outside of the 5th to 95th percentile was excluded.

Table 10: *Treatment Groups with Actual Treatment Received and proposed posology*

Age group	P010	P034/P035	Proposed posology
Group 1 *≥12 to <18 years*	Single IV dose, 1.5 g fixed dose of C/T (comprising 1000 mg ceftolozane and 500 mg tazobactam) 6 Participants	1 g ceftolozane and 0.5 g tazobactam	Children and adolescents from birth to <18 years with cUTI or cIAI and with eGFR>50 mL/min/1.73 m^2 is 30 mg/kg (20 mg/kg ceftolozane and 10 mg/kg tazobactam) up to a maximum dose of 1.5 g (1 g ceftolozane and 0.5 g tazobactam for ≥50 kg body weight) administered every 8th hour by IV infusion over 1 hour.
Group 2 *≥7 to <12 years*	Single IV dose, 18 mg/kg ceftolozane and 9 mg/kg tazobactam 6 Participants	20 mg/kg ceftolozane and 10 mg/kg tazobactam (maximum ceftolozane 1 g and tazobactam 0.5 g/dose).	
Group 3 *≥2 to <7 years*	Single IV dose, 18 mg/kg ceftolozane and 9 mg/kg tazobactam 3 Participants		
	Single IV dose, 30 mg/kg ceftolozane and 15 mg/kg tazobactam 3 Participants		
Group 4 *≥3 months to <2 years*	Single IV dose, 18 mg/kg ceftolozane and 9 mg/kg tazobactam 1 Participant		
	Single IV dose, 30 mg/kg ceftolozane and 15 mg/kg tazobactam 5 Participants		
Group 5 *Birth (>32 weeks gestation, 7 days postnatal) to <3 months*	Single IV dose, 20 mg/kg ceftolozane and 10 mg/kg tazobactam 7 Participants		
Group 6 *Birth (≤32 weeks gestation, 7 days postnatal) to <3 months*	Single IV dose, 12 mg/kg ceftolozane and 6 mg/kg tazobactam 2 Participants	*Participants ≤32 weeks gestation were not included in P034 or P035*	*For Birth (≤32 weeks gestation, 7 days postnatal) there is no posology proposed.*
	Single IV dose, 20 mg/kg ceftolozane and 10 mg/kg tazobactam 4 Participants		

A summary of ceftolozane and tazobactam plasma PK parameters in Group 1-6 is presented below in Table 11 and in Table 12 respectively.

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 C/T. 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 pre-dose tazobactam M1 concentrations.

Table 11: *Summary Statistics of Ceftolozane Plasma Pharmacokinetic Parameters Following the Administration of Single IV Doses of C/T 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 (-)

	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]

Table 12: *Summary Statistics of Tazobactam Plasma Pharmacokinetic Parameters, Following the Administration of Single IV Doses of C/T 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 (-)

	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]

The CHMP considered that the aim of the dose selection in study P010 was to achieve comparable exposures to those calculated for adult patients with cIAI and AP/cUTI. For ceftolozane, an AUC target of 130-175 µg*h/mL was used, which covers the range of AUCs reported in adult healthy volunteer, in patients with AP/cUTI and in patients with cIAI (130, 158 and 175 µg*h/mL respectively). Hence, the selected exposure target for ceftolozane seems appropriate. An AUC target of 24 µg*h/mL was chosen for the interim analyses of tazobactam.

The ceftolozane geometric mean $AUC_{0-\infty}$ ranged from 99.4 to 202 µg*h/mL across Groups 1-6. 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 geometric mean $AUC_{0-\infty}$ of approximately 1.9-fold in Group 3, suggesting that the PK of ceftolozane is approximately dose-proportional.

The ceftolozane PK parameters were generally comparable across Groups 1-4, but the ceftolozane and tazobactam CL appeared to be lower in subjects aged birth to <3 months (Groups 5 and 6). Ceftolozane and tazobactam geometric mean Vss also trended lower with decreasing age. After accounting for weight, the ceftolozane geometric mean Vss and CL was comparable across most age groups with a slight trend in increased Vss in subjects aged birth (7 days postnatal) to <3 months (Groups 5 and 6 subjects) and a lower weight corrected CL in patients in Group 6 with CrCL <50 mL/min/1.73m^2 (these patients received

a lower dose of C/T). The MAH points out that renal function matures through infancy with clearance values reaching adult values around the second year of life. Thus, renal clearance of drugs, including those that are governed by glomerular filtration and/or tubular secretion (as in the case of ceftolozane and tazobactam), increases with increasing gestational age and body weight. Therefore, the lower CL observed in infants and neonates is likely due to their immature renal function. This was supported by the CHMP.

Two subjects in Group 6 had CrCL between 20 and 49 mL/min/1.73m^2. They received a dose of 12 mg/kg ceftolozane and 6 mg/kg tazobactam to take into account the lower CrCL in these subjects. These patients had a geometric mean ceftolozane $AUC_{0-\infty}$ of 165 µg*h/mL, with individual measures 134 and 204 µg*h/mL). See the section *Paediatric patients with impaired renal function*, for further assessment of C/T treatment in paediatric patients with reduced renal function.

As was pointed out previously during the assessment of procedure EMEA/H/C/003772/P46/002, CHMP 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.

*- Study **P034** and **P035***

A total of 228 participants were enrolled and randomized across the two Phase 2 studies (134 participants in **P034** and 94 participants in **P035**). In these studies, the evaluation of PK of ceftolozane and tazobactam was only an exploratory objective. In the two studies, the paediatric patients were divided into five age groups, Group 1 (12 to <18 years), Group 2 (6 to <12 years), Group 3 (2 to <6 years), Group 4 (3 months to <2 years) and Group 5 (birth to <3 months). The PK data generated from the Phase 2 studies were integrated in the population-PK modelling and PTA analysis.

Study **P034** was a Phase 2, randomized, active comparator-controlled, multicenter, double-blind study evaluating the safety and efficacy of ceftolozane/tazobactam (C/T) versus meropenem (MERO) in paediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cUTI, including pyelonephritis.

Study **P035** was a Phase 2, randomised, active comparator-controlled, multicenter, double-blind study conducted in paediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cIAI of sufficient severity requiring hospitalisation and treatment with intravenous (IV) antibiotics. In study **P035**, one patient was enrolled in Group 4 in the C/T arm but discontinued before the day of PK sample collection, hence no PK data are available from patients with cIAI in the age range 3 months to <2 years of age. One participant was enrolled for Group 5 in the C/T arm with estimated steady-state ceftolozane PK parameter values: AUC_{0-8}=173 µg*h/mL; C_{eoi}=43.4 µg/mL; and with estimated tazobactam PK parameter values: AUC_{0-8}=69.9 µg*h/mL; C_{eoi}=30.5 µg/mL.

See Figure 12 and Figure 13 for study design and dose regimens and sections 4.4 and 4.5 for additional details of the studies, endpoints and included patients. In both the Phase 2 studies (**P034** and **P035**), one of the exclusion criteria was CrCL <50 mL/min/1.73 m^2.

Population-PK

Individual model-predicted exposures

In the population-PK model, body weight, eGFR (as a renal function estimate), and age were identified as significant covariates for both compounds. Infection types (cUTI and cIAI) were identified as additional significant covariates for ceftolozane; but not for tazobactam.

Individual model predicted exposures in paediatric patients from the two Phase 2 studies (**P034** and **P035**) are presented below in Table 13 (cUTI) and Table 14 (cIAI).

Table 13: *Summary of Steady-State Ceftolozane and Tazobactam Plasma PK Parameter Values (GM and GCV%) Estimated by Population PK Model in Paediatric cUTI Participants in P034 Versus Adult (Phase 2/3) Studies*

Parameters	**Group 1 12 to <18 y n=14**	**Group 2 7 to <12 y n=15**	**Group 3 2 to <7 y n=24**	**Group 4 3 mo to <2 y n=22**	**Group 5 Birth to <3 mo n=14**	**Adult cUTI patients n=156**
Ceftolozane						
Ceftolozane/ tazobactam dose	1000/500 mg	20/10 mg/kg	20/10 mg/kg	20/10 mg/kg	20/10 mg/kg	1000/500 mg
AUC_{0-8}, µg*h/mL	168 (35)	137 (36)	127 (37)	119 (41)	139 (29)	203 (34)
C_{eoi}, µg/mL	65.5 (34)	58.5 (38)	55.5 (40)	46.9 (40)	41.6 (28)	70.6 (30)
$t_{1/2}$, h	2.26 (16)	1.97 (22)	1.8 (25)	1.9 (34)	2.58 (24)	2.73 (29)
CL, L/h	6 (35)	4.7 (44)	2.6 (40)	1.4 (46)	0.7 (48)	4.92 (34)
V_{ss}, L	15 (33)	10.4 (46)	5.4 (41)	3.2 (52)	2.3 (44)	16.1 (31)
Tazobactam						
AUC_{0-8}, µg*h/mL	33.4 (33)	26.3 (32)	25.1 (28)	26.5 (40)	41.7 (41)	31.3 (32)
C_{eoi}, µg/mL	22 (29)	19.3 (40)	18.1 (31)	17.2 (50)	24.3 (39)	19.9 (21)
$t_{1/2}$, h	1.26 (26)	1.16 (29)	1.02 (24)	1.01 (37)	1.08 (42)	1.41 (19)
CL, L/h	15 (32)	12.3 (45)	6.58 (42)	3.15 (52)	1.13 (61)	16.0 (32)
V_{ss}, L	14.9 (40)	8.33 (77)	5.13 (59)	2.79 (85)	1.36 (55)	18.6 (20)

cUTI = Complicated urinary tract infection; AUC_{0-8}=Area under the plasma concentration-time curve in the dosing interval 0 to 8 hours; C_{eoi}=Concentration at the end of infusion; CL= Clearance, $t_{1/2}$= Terminal half-life; V_{ss} = Volume of distribution at steady-state

Source: [Ref. 5.3.5.3: 082HY8]

Table 14: *Summary of Steady-State Ceftolozane and Tazobactam Plasma PK Parameter Values (GM and GCV%) Estimated by Population PK Model in Paediatric cIAI Participants in P035 Versus Adult (Phase 2/3) Studies*

Parameters	Group 1 12 to <18 y n=16	Group 2 7 to <12 y n=27	Group 3 2 to <7 y n=23	Adult cIAI patients n=161
Ceftolozane				
Ceftolozane/ tazobactam dose	1000/500 mg	20/10 mg/kg	20/10 mg/kg	1000/500 mg
AUC_{0-8}, µg*h/mL	115 (43)	113 (28)	95.7 (27)	148 (37)
C_{eoi}, µg/mL	46.7 (50)	51.2 (32)	41.7 (34)	53.8 (37)
$t_{1/2}$, h	2.12 (19)	1.77 (13)	1.69 (16)	2.44 (27)
CL, L/h	8.74 (43)	5.53 (39)	3.58 (33)	6.75 (37)
V_{ss}, L	20.3 (51)	10.7 (44)	7.11 (37)	19.6 (38)
Tazobactam				
AUC_{0-8}, µg*h/mL	28.8 (46)	29.5 (25)	23.2 (28)	27.6 (60)
C_{eoi}, µg/mL	19.7 (48)	20.3 (35)	16.3 (41)	15.4 (33)
$t_{1/2}$, h	1.24 (17)	1.11 (14)	0.991 (19)	1.69 (40)
CL, L/h	17.4 (46)	10.6 (35)	7.39 (35)	18.1 (60)
V_{ss}, L	16.5 (56)	9.46 (58)	6.17 (64)	26.6 (22)

cIAI = Complicated intra-abdominal infection; AUC_{0-8}=Area under the plasma concentration-time curve in the dosing interval 0 to 8 hours; C_{eoi}=Concentration at the end of infusion; CL= Clearance, $t_{1/2}$= Terminal half-life; V_{ss} = Volume of distribution at steady-state
*One participant was enrolled in Group 4 in the C/T arm but discontinued before the day of PK sample collection; one participant was enrolled for Group 5 in the C/T arm with steady-state ceftolozane PK parameter values: AUC_{0-8}=173 µg*h/mL; C_{eoi}=43.4 µg/mL; $t_{1/2}$=3.29 h; CL=0.4 L/h; V_{ss}=1.75 L; and with tazobactam PK parameter values: AUC_{0-8}=69.9 µg*h/mL; C_{eoi}=30.5 µg/mL; $t_{1/2}$=1.44 h; CL=0.5 L/h; V_{ss}=0.95 L.

Source: [Ref. 5.3.5.3: 082HY8]

The CHMP considered that, overall, the exposure of ceftolozane in study **P034** and **P035** estimated by the population-PK model are within the defined target exposure, although some trends were observed in PK measures that deviated from the adult population. The exposure measures are provided in the study description above but are shortly summarised below.

AP/cUTI

The estimated exposure of both ceftolozane and tazobactam (AUC_{0-8} and C_{eoi}) in paediatric AP/cUTI patients trended lower (except Group 1 both ceftolozane and tazobactam which were comparable and Group 5 tazobactam that had elevated exposure compared to adults) compared to that in adults with AP/cUTI. Of particular notice are the lower Ceoi and AUC 0-8 in patients from Group 3 and 4 in study **P034**.

The patient population in study **P034** includes both cUTI and pyelonephritis of sufficient severity requiring hospitalisation and treatment with intravenous (IV) antibiotics. The MAH did not present any specific analysis to investigate potential differences in PK between the AP and cUTI patients. However, there is no expected difference in pharmacokinetics between cUTI and AP based on adult PK data, and it was considered that the paediatric PK data is representative for both cUTI and AP.

cIAI

The estimated AUC_{0-8} of both ceftolozane and tazobactam in paediatric patients with cIAI also trended lower compared to adults with cIAI. While ceftolozane C_{eoi} was comparable to adult values, tazobactam values trended higher in paediatric patients.

AP/cUTI and cIAI

Although some trends were observed in the steady-state ceftolozane and tazobactam plasma PK parameter values estimated by population-PK modelling, the presented data are still within the range of observations in the adult participants with AP/cUTI and cIAI. Of note, there are few patients included in each age group, especially in the lower age groups which brings uncertainties to the estimates. Still, the provided data are considered sufficient in support of extension of indication to the paediatric AP/cUTI patients and cIAI patients ≥2 years.

The graphical presentations provided in response to the request by the CHMP shows simulated ceftolozane exposures (AUC and Ceoi) mainly within the range observed for adult patients, slightly lower AUC for AP/cUTI patients between 6 months and 1 year. Similarly, the simulations of the tazobactam exposures (AUC and Ceoi) are mainly within the range observed for adult patients, but the Ceoi seems to be higher in the youngest patients with cIAI. Of importance, there only exists PK data from one single patient <1 year with cIAI, consequently the provided simulations need to be interpreted with caution.

Extrapolation of PK to paediatric patients <2 years of age with cIAI

Despite the lack of PK data from paediatric patients <2 years of age, the MAH argued that the proposed dosing regimens can be extended to these age groups in cIAI based on extrapolation from modelling and simulations. The MAH did not provide a thorough discussion concerning the scientific rationale for extrapolating PK from the AP/cUTI population <2 years of age to the cIAI population <2 years of age. According to the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/CHMP/187859/2017)*, it may not be necessary to obtain pharmacokinetic data from all age subgroups in which use is to be proposed. In some circumstances, modelling and simulation of adult data may be sufficient to support dosing recommendations for certain age subgroups (e.g., adolescent subjects). On the other hand, pharmacokinetic data will need to be generated in neonates in almost all cases owing to the rapid developmental changes in absorption, distribution, metabolism and excretion. Furthermore, according to the *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)*, pharmacokinetic information from one indication can be extrapolated to another indication if it can be assumed that the diseases and commonly used concomitant medications are not affecting the pharmacokinetics of the drug. In the submitted population-PK model, body weight, renal function (eGFR) and age were identified as significant covariates for ceftolozane and tazobactam, while infection types (cUTI, cIAI and NP) were identified as significant covariates for ceftolozane, but not for tazobactam. Of note, the expected difference in exposure between the two infection types are not large and does not lead to adjustments in the dosing regimen for adults or children.

The single patient <3 months of age with cIAI had estimated exposures of ceftolozane comparable to the patients <3 months of age with AP/cUTI in study **P034**, while the estimated tazobactam exposures was higher. Of importance, this is an estimated/predicted measure from one single cIAI patient, the tazobactam exposure distribution in the AP/cUTI patients <3 months of age are wide, and the exposure measures from the patient with cIAI <3 months of age is only slightly higher than the highest estimated values in the AP/cUTI population (69.9 µg*h/mL vs. ~65 µg*h/mL). The observed concentration measurements (C_{eoi}) in the single patient <3 months of age is comparable with the range of observations collected from AP/cUTI patients <3 months of age (cIAI; 29.8 (ceftolozane) and 7.12 (tazobactam),

AP/cUTI; 23.7-70.4 (ceftolozane) and 4.13-21.5 (tazobactam)). The single patient <3 months of age in study **P035** had estimated ceftolozane AUC higher than the estimated geometric mean AUC in older paediatric cIAI patients (≥2 years) and adults, while C_{eoi} was comparable. The estimated exposure of tazobactam in the single patient <3 months of age was approximately twice the estimated geometric mean exposure observed in older children and adults with cIAI. Still, the estimated measures of AUC and C_{eoi} for the patient <3 months of age with cIAI were within the range of values observed in adults with cIAI. As discussed in the section *model qualification*, the credibility of the tazobactam model is low, particularly for the lowest age ranges (<3 months for AP/cUTI and <2 years for cIAI). The model overpredicts the tazobactam exposures, most prominently at the end of the dosing interval. Even so, considering the target of fraction of time above 1mg/mL at 20%, the observed exposure data indicate that patients are above this limit. Due to the limited PK data available, it is difficult to draw any clear conclusions on the comparison between the cIAI and AP/cUTI populations <3 months of age.

Based on the totality of the data presented, although very limited, the CHMP supported that the proposed dosing regimens can be extended to the age groups <2 years with cIAI based on extrapolation from the modelling and simulations.

NP (Nosocomial Pneumonia)

It was noticed that the MAH provided a report on modelling and simulation concerning dose selection in paediatric NP patients (including HAP/VAP) in the submitted dossier. The analyses described in the report focuses on population-PK modelling for C/T in paediatric patients with confirmed or suspected gram-negative infections enrolled in Study CXA-PEDS-13-08 (**P010**) and simulations to support dose selection for evaluation in paediatric patients with NP. The NP population PK model have not been further assessed as the NP indication is not part of this application. Of note, the approved dose for the NP indication in the adult population is twice that of cIAI and AP/cUTI. According to the paediatric investigational plan (EMA-001142-PIP02), a study investigating PK, tolerability, and safety of C/T in children from birth to <18 years of age with NP is to be completed by July 2023.

- **Paediatric patients with impaired or immature renal function**

In adult AP/cUTI and cIAI patients, ceftolozane dose normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold and 5-fold in subjects with CrCL 51-80 mL/min, 30-50mL/min, and 15- 29 mL/min, respectively, compared to healthy subjects with normal renal function. The respective tazobactam dose normalized geometric mean AUC increased approximately up to 1.3-fold, 2-fold, and 4-fold. Dosage adjustment is required to maintain similar systemic ceftolozane and tazobactam exposures to those with normal renal function.

Published data suggest that renal function, including glomerular filtration rate and tubular secretion, matures with child growth(Zhang et al. 2019). In paediatric AP/cUTI and cIAI patients, maturation of renal function and increase in kidney size with child growth affect the PK of ceftolozane and tazobactam. According to the covariate analysis, both eGFR and maturation factors were found to affect ceftolozane and tazobactam PK. According to the MAH, there is no clinical experience in paediatric patients with eGFR <50 mL/min/1.73 m^2 to inform dose adjustment recommendation.

Two patients with CrCL <50 mL/min/1.73 m^2 (27.69 mL/min/1.73m^2 and 34.12 mL/min/1.73m2) were included in the Phase 1 study (**P010**), they were dosed 12mg/kg and 8mg/kg C/T and had a geometric mean $AUC_{0-\infty}$ of 165 µg*h/mL (with individual measures 134 and 204 µg*h/mL). In study **P035**, one patient in the age range 12 to <18 years with CrCL in the range of ≥30 to <50 mL/min/1.73m^2 was included. According to the MAH, the patient was dosed 1.5 g C/T, and had ceftolozane AUC of 129 µg*h/mL and C_{max} of 57.7 µg/mL, tazobactam AUC of 27.2 µg*h/mL and C_{max} of 14.5 µg/mL (estimated

using the population PK models). A summary of eGFR for paediatric patients less than/equal to 2 years old and greater than 2 years old is shown in Table 15.

Table 15: *Summary of eGFR for Paediatric Subjects Less than/equal to 2 years old and Greater than 2 years old.*

Age Cutoff	EGFR category	n	Median EGFR	Median CrCl	Within Age %
</=2	augmented (>160 mL/min/1.73m2)	12	194.65	57.60693642	18.8
</=2	normal (90-159 mL/min/1.73m2)	28	126.75	29.15722543	43.8
</=2	mild (50-89 mL/min/1.73m2)	22	70.6	10.88150289	34.4
</=2	moderate (30-49 mL/min/1.73m2)	2	33.7	2.230057804	3.1
>2	augmented (>160 mL/min/1.73m2)	59	188.2	120.1572254	45.4
>2	normal (90-159 mL/min/1.73m2)	64	131.25	78.56127168	49.2
>2	mild (50-89 mL/min/1.73m2)	6	85.55	39.34566474	4.6
>2	moderate (30-49 mL/min/1.73m2)	1	46.2	45.93294798	0.8

Units for eGFR are ml/min/1.73m^2 and units for CrCl are ml/min.

Source: MAH's response to second request for supplementary information

- Paediatric patients from 2 years of age with impaired renal function

No dosing recommendations was provided in the submitted dossier for paediatric patients with impaired renal function, despite the renal elimination pathways for both ceftolozane and tazobactam. On request from the CHMP, the MAH conducted additional simulations using the submitted population PK models of ceftolozane and tazobactam to include additional recommended dose adjustments in paediatric patients with moderate and severe renal impairment. As the influence of renal maturation function on ceftolozane and tazobactam PK is expected to be small for paediatric population older than 2 years of age, it was considered feasible to use modelling-based extrapolation to propose dosing regimen for paediatric patients older than 2 years of age with renal impairment, if assuming that the renal impairment categorization in adult patients applies.

The CHMP raised questions in relation to the proposed dosing regimens proposed for paediatric patients 2 years and older. The Committee noticed that the submitted simulations of ceftolozane exposures in moderate and severe renal impairment indicated that the paediatric model for ceftolozane did not adequately describe the influence of renal function. Based on the CHMP remarks, the MAH conducted a thorough review of the submitted population pharmacokinetic (PK) model(s) (Ref. 5.3.5.3: 082HY8), including covariate selection as summarized in the appendix 2 assessment of the applicant's 2nd response to request for supplementary information. The underlying demographics across the paediatric population were evaluated and compared to adults (described by separate population PK models) and guided model assessments. As a result, alternative models were explored with re-evaluations of exposure metrics and probability of target attainment (PTA) from the selected models conducted.

In general, and consistently with the CHMP's observations, the MAH confirmed that the current ceftolozane model appears to be over-parameterized where any ability to resolve an effect of eGFR is limited. In contrast to the adult datasets, a very limited fraction ($\leqslant$ 5%) of paediatric patients over 2 years of age had an eGFR $\leqslant$ 90 mL/min/1.73m2 and could not support the estimation of a meaningful relationship between ceftolozane and eGFR; this also applies to tazobactam. This results in a discrepancy between the exponents of the eGFR power model estimated in the paediatric (0.11) and adult (0.704) models. Based upon further model evaluation, only the effects of weight (fixed allometric scaling exponents of 0.75 for CL and intercompartmental clearance (Q) and 1.0 for central volume (Vc) and peripheral volume (Vp)) and a function describing renal maturation in paediatric patients $\leqslant$ 2 years as described in [Rhodin et al. 2009] appeared to be meaningful and identifiable on CL (ceftolozane and

tazobactam). The effect of eGFR on CL had no or minimal impact on the fit or predictive performance of the models and were removed in reduced models explored in this response.

The proposed dosing adjustments in paediatric patients with moderate and severe renal impairment were informed by the negligible/minimal effects of eGFR in the paediatric model resulting in discordance between existing dose adjustments (for moderate and severe renal impairment) in adults. The submitted model and the reduced (refined) models explored in response to the CHMP questions continue to support dosing recommendations proposed in the SmPC in paediatric patients with normal renal function and mild renal impairment (eGFR > 50 mL/min/1.73m2), with estimates of exposure metrics (AUC and Ceoi) and PTA largely similar across models and no evidence of a systematic bias. As adequate characterization of ceftolozane (and tazobactam) remains credible in paediatric patients with an eGFR > 50 mL/min/1.73 m2, the MAH suggested that no formal update to the current paediatric models (ceftolozane and tazobactam) are necessary at this time. Nor would a model update address the absence of an effect of eGFR applicable to a paediatric population, based upon the current PK data, to inform posology in moderate or severe renal impairment.

According to the MAH, additional data in paediatric patients with nosocomial pneumonia (NP) are expected from an ongoing study (MK-7625A-036) with inclusion of patients from birth to < 3 months of age with an eGFR ≥ 20 mL/min/1.73 m2 and where additional experience in older children with an eGFR between 50 to 90 mL/min/1.73 m2 may be available to inform any effect of eGFR on ceftolozane (and tazobactam) clearance. Together with application and/or integration of existing adult data, including varying degrees of renal impairment, this is expected to mitigate the current limitations of the PK model and potentially support dosing recommendations in moderate and severe renal impairment in paediatric patients as described in Study #3 from EMEA-00114-PIP02-16.

The MAH also stated that the full range of renal function values expected from birth (term/preterm) have not been covered in the analysis datasets due to exclusion of patients with eGFR ≥ 50 mL/min/1.73 m2 from the clinical studies. This prevented the identification of any effect of renal function on PK variability beyond renal maturation and limited the predictive capabilities of the selected model in the setting of renal impairment or immaturity. Although dosing recommendations in patients with moderate and severe renal impairment (eGFR ≥ 50 mL/min/1.73m2) may be desirable, the MAH argued that, consistently with the initial submission of the paediatric extension of indication variation, no dosing recommendations in these subgroups regardless of age could be supported at this time and therefore the initially proposed SmPC dose adjustments for paediatric patients with moderate and severe renal impairment in the response to request for supplementary information were withdrawn by the MAH. However, dosing recommendations in paediatric patients, from birth to < 18 years of age, with an eGFR > 50 mL/min/1.73 m2, is supported, as per Section 4.2 of the SmPC.

- Paediatric <u>patients <2 years of age</u> with impaired or immature renal function

While the population PK models were developed based on ceftolozane and tazobactam plasma concentration data collected in the paediatric studies, the covariate relationships with regard to eGFR in the models and its interplay with renal maturation function cannot be validated for children younger than 2 years of age with eGFR ⩽50 mL/min/1.73 m2, as patients in this category were excluded in the trials and thus no PK data are available. Furthermore, there were no adults with moderate or severe renal impairment (CrCL ⩽50 mL/min) in the global Phase 3 cIAI/cUTI trials, no observed data in this category were available to compare with simulations based on eGFR. Thus, the MAH did not consider it appropriate to propose a dosing regimen based on extrapolation with modeling and simulation alone for children younger than 2 years of age with eGFR ⩽50 mL/min/1.73 m2.

With regards to the suitability of the posology with a cut-off based on eGFR, the CHMP requested the MAH to discuss possible alternatives to the proposed posology including if the youngest paediatric patients should be recommended a lower dose based on age rather than estimated kidney function due to their immature kidney function and the known challenges in estimating kidney function in newborns. The MAH agreed in their response that renal function in newborns is affected by both gestational age as well as post-natal age with rapid increases seen in the first few post-natal weeks. Due to renal immaturity at birth the expected eGFR in the term newborn in the first week of life is expected to be ~20mL/min/1.73m2 increasing to ~40-60 mL/min/1.73m2 in the 2-4 weeks of life. While the MAH agreed that the proposed eGFR cutoff of ⩽50 mL/min/1.73 m2 may exclude a portion of neonates including preterm neonates from receiving ceftolozane/tazobactam, there will be a substantial proportion of neonates, especially term neonates older than 2 weeks post-natal that will have an eGFR >50 mL/min/1.73 m2. This is supported by the fact that in **P010** and **P034** combined there were 5 neonatal participants (⩽28 days old, range 13-28) all of whom had eGFR >50 mL/min/1.73m2 (range 56.0-90.5).

- General Suitability of the posology with a cut-off based on eGFR

The CHMP also noted that the MAH did not initially establish dose recommendations in paediatric patients below 18 years of age with eGFR ≤ 50 mL/min/1.73 m^2 based on the argument that there is no clinical experience in paediatric patients with CrCL <50 mL/min/1.73 m^2. Exclusion criteria in study **P034** and **P035** were moderate or severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the Bedside Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration. Considering that both ceftolozane and tazobactam are renally excreted, dosing recommendations in renal impairment is generally required.

Low GFR is expected in new-born: children born at term is expected to have GFR of approximately 10-20 mL/min/1.73m^2 the first day of life, there after rising up to approximately 30-40 mL/min/1.73m^2 after two weeks, reaching adult levels 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. Hence, this cutoff will most likely exclude a large proportion of the youngest patients born at term and possibly all the youngest preterm patients from treatment with C/T. Further, the estimation of GFR in paediatric patients is challenging, and the proposed posology with a cutoff based on CrCL/eGFR might not be well-suited for clinical practice. In the first request for supplementary information, the MAH was asked to discuss possible alternatives to the proposed posology including if the youngest paediatric patients should be recommended a lower dose based on age rather than estimated kidney function due to their immature renal function and the known challenges in estimating renal function in newborns. The MAH did provide a discussion for not changing the proposed posology; instead, they only recommended a dose regimen in children below 2 years of age with eGFR >50 mL/min/1.73 m2, and did not consider it appropriate to recommend a dosing regimen based on extrapolation with modelling and simulation alone for children younger than 2 years of age with eGFR ⩽50 mL/min/1.73 m2. Further to CHMP concerns that the proposed posology, only with a cut-off based on CrCL/eGFR, would not be well-suited for clinical practice since the estimation of GFR in paediatric patients is challenging, additional data regarding the above mentioned eGFR cut-off was requested.

The Committee agreed with the MAH that clinical experience in paediatric patients <18 years of age with eGFR ≤ 50 mL/min/1.73 m^2 is limited, however some data was collected in paediatric patients with reduced renal function. The MAH was therefore requested to provide an overview of the available data from patients with CrCL <50 mL/min/1.73 m^2, including information of actual doses received. In response to the first request for supplementary information, the MAH provided data from one 12 year-old patient, in study **P035**, that had CrCL <50 mL/min/1.73 m^2 (baseline eGFR 46.2 mL/min/1.73 m^2). The patient received the dose recommended for paediatric patients with CrCL/eGFR >50 mL/min/1.73 m^2, 1 g

ceftolozane and 0.5 g tazobactam q8h. Ceftolozane AUC were approximately within the ceftolozane AUC target of 130 to 175 µg*h/mL, and tazobactam were in accordance tazobactam AUC seen in the cIAI population 12 to <18 years. The two paediatric patients <3 months of age in study **P010** with CrCL <50 mL/min/1.73 m^2, received a lower dose to account for immature renal function and reduced CL of C/T; the two subjects had eGFR of 27.69 and 34.12 mL/min/1.73m^2. They received half the dose, 12mg/kg and 8mg/kg C/T and had AUCs of 134 and 204 µg*h/mL, which is close to the target range, and within range observed in the population studied in **P010**. One of the two patients had especially high AUC measures of tazobactam, in the two subjects the AUC0-∞ was 37.5 and 161 µg*h/mL, while AUC0-last was 10.2 and 45.9 µg*h/mL. Concerning Cmax the values were 3.17 and 14.9 µg/mL, which is slightly lower or similar to the rest of the studied population in **P010**. On request from the CHMP, the MAH provided summaries of eGFR for paediatric patients ≤2 years of age and >2 years of age.

- Paediatric patients from 2 years with impaired renal function

The MAH provided dosing recommendations for paediatric patients with impaired renal function. Very limited C/T PK data are available for paediatric patients with moderate to severe renal impairment, only two patients with moderate renal impairment (whereas one of them with immature renal function) and one patient with severe renal impairment (neonate with immature renal function). Consequently, the proposed dosing recommendations in moderate and severe renal impairment were primarily based on adult PK data. Although not a validated assumption, it is considered reasonable to expect a similar relationship between eGFR/CrCL and C/T clearance in children (aged 2 years and older) and adults when accounting for body weight.

The dosing regimen proposed by the MAH involved a 25% reduction of dose in moderate renal impairment (eGFR 30-50 mL/min/m^2) and 40% reduction in severe renal impairment (eGFR 15-29 mL/min/m^2) for patients 2 to <18 years, which is <u>not</u> comparable to the corresponding dosing recommendation in adults where the dose is reduced by 50% in moderate renal impairment and 75% in severe renal impairment. Consequently, during the second request for supplementary information, the MAH was also requested to discuss the proposed paediatric dosing recommendations in paediatric patients with impaired renal function in the age range 2 to <18 years in the light of the knowledge established in the adult population <u>with impaired renal function</u>. The discrepancy between the adult and paediatric dosing recommendations with renal impairment added to the concern regarding the adequacy of the population PK model.

Simulations of exposures and PTA analysis was provided for patients aged 2 to <18 years with both moderate and severe renal impairment. The simulated plots provided by the MAH indicated that the co-variate for renal function had a very low impact on the exposures of ceftolozane; the predicted exposures were very similar for severe and moderately reduced renal function. Further the predicted exposure of non-adjusted doses of ceftolozane was within the adult range with normal dose, whereas the reduced dose to account for reduced renal function led to predicted exposure levels much below the adult levels for both moderate and severe renal function. The predictions for tazobactam, showed an impact of the co-variate for renal function; the predicted exposures are higher for severe as compared to moderate renal function and the exposures are higher than the adult's exposure levels at normal dose.

The MAH's proposal for adjusted dosing recommendation in moderate/severe renal impairment were believed to be based on tazobactam exposures alone and the aspect that the PTA simulations even at a quite low exposure level of ceftolozane seemed adequate. The MAH did not discuss these aspects. As the impact of renal function on the PK of ceftolozane and tazobactam has been shown to be very similar in the adult data, this indicated that the paediatric model for ceftolozane did not adequately describe the influence of renal function (with the low value of the parameter estimate for the eGFR power model of

0.11, it would appear that the predicted influence of renal impairment is too low). As a Bayesian modelling approach was taken; adjusting adult priors on the co-variate parameters combined with a paediatric dataset with very limited range of observed data on renal function, there is a risk that the co-variate on renal function was overfit with the observed paediatric data and consequently lost predictive ability on the impact of renal function. In addition, the equation for clearance included body weight based allometric scaling, GFR power function and Rhodin maturation and these will all be highly correlated. The MAH was therefore requested to discuss the qualification of the ceftolozane model for predicting renal function and suggest steps to take to mitigate the issue and ensure that the model is credible and further to discuss the adequacy of including allometric scaling, the Rhodin maturation as well as a GFR power function on clearance.

As requested by the CHMP, the MAH rediscussed the proposed paediatric dosing recommendations in paediatric patients aged 2 to <18 years of age with renal impairment in the light of the knowledge established in the adult population with impaired renal function and conducted an additional review of the submitted population pharmacokinetic (PK) model. In addition, the demographics across the underlying paediatric population were evaluated and compared to adults. Based on the additional review, the MAH confirmed that the population PK model submitted was not informative concerning renal function and withdrew the previously proposed dosing recommendations in paediatric patients >2 years of age with impaired renal function.

- Paediatric patients <2 years of age with impaired or immature renal function

After additional investigation and refinements of the submitted population PK model, it was clear that the model is not considered suitable for predicting dosing recommendations for paediatric patients <2 years of age with immature or impaired renal function. Considering the limitations in the data and the lack of a reliable population PK model, no dosing recommendations can be provided for paediatric patients <2 years of age with reduced (moderate or severe) renal function at this time. Furthermore, it is acknowledged that no alternative to the currently proposed dosing recommendations can be provided for neonates with immature renal function and, consequently, alternatives to the proposed posology attempting to avoid the need for determination of eGFR in new-borns is not feasible at this time. A large proportion of the youngest patients born at term and possibly all the youngest preterm patients will not therefore be covered by this approach. The MAH confirmed that in the ongoing study **MK-7625A-036**, data are expected to emerge from patients from birth to <3 months of age with an eGFR ≥ 20 mL/min/1.73 m2 and that additional experience in older children with an eGFR between 50 to 90 mL/min/1.73 m2 may be available to inform any effect of eGFR on ceftolozane and tazobactam. The CHMP decided not to request more information at this stage. However, when the data in paediatric patient with reduced renal function are available it is expected that an application be submitted for a variation to include in sections 4.2 and 5.2 of the SmPC (and other sections as relevant) dosing recommendations to paediatric patients with AP/cUTI or cIAI with immature or impaired renal function, if supported by the data. When submitting this future variation, the MAH is recommended to present full results of updated/relevant population PK model(s).

In the SmPC "from birth" is now defined as >32 weeks gestational age and ⩾7 days postnatal, in both Sections 4.2 and 5.1, reflecting the population actually studied.

In summary, the above issues were not further pursued at this time. The MAH is recommended to submit a variation application to support dosing recommendation in paediatric patients with reduced renal function as described above.

Pharmacokinetic interaction studies

In vivo data for Zerbaxa evaluated in previous procedures indicates that both ceftolozane and tazobactam are eliminated predominantly via renal excretion and are not substrates of CYPs. Thus, clinically relevant DDIs with inhibitors or inducers of CYPs are not expected. Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam is not a substrate for OCT2. Tazobactam is a known substrate for OAT1 and OAT3. Coadministration of tazobactam with the OAT1/OAT3 inhibitor probenecid, has been shown to prolong the tazobactam t1/2 by 71%. Coadministration of C/T with drugs that inhibit OAT1 and/or OAT3 may increase tazobactam plasma concentrations.

Based on *in vitro* data, and a clinical study in adults (P030), C/T is unlikely to perpetrate DDIs related to CYPs or membrane drug transporters.

According to the MAH, the low DDI risk profile based on in vitro studies and clinical data in adults can be extended to paediatric population based on the paediatric exposure distribution and safety profile.

The CHMP noted that no new DDI studies were provided in support of this application. Data from previous procedures indicate a low risk of DDIs during C/T treatment, and it is reasonable that the low DDI potential observed in adults can be extended to the paediatric population. In the two paediatric Phase 2 studies (**P034** and **P035**) submitted for the current application based on the low risk of DDIs related with C/T, no further assessment of concomitant treatment in the two clinical studies (**P034** and **P035**) have been made.

4.3.3. Pharmacodynamics

Primary and secondary pharmacology

The microbiology profile of C/T was extensively described in the original MAA and is reflected in the approved prescribing information for Zerbaxa.

C/T is a β-lactam/β-lactamase inhibitor combination with activity against *P. aeruginosa*, including drug-resistant strains, and other common gram-negative pathogens. Ceftolozane belongs to the cephalosporin class of antibacterial drugs but is less susceptible to hydrolysis by AmpC β-lactamases than other antibiotics in this class. The combination of ceftolozane with β-lactamase inhibitor tazobactam, which is a potent inhibitor of most class A and some class C β-lactamases, improves the coverage of ceftolozane to include ESBL-producing Enterobacterales.

The spectrum of activity for ceftolozane includes many clinically relevant gram-negative respiratory pathogens, including Enterobacterales such as *Escherichia coli* and *Klebsiella pneumoniae* as well as *Pseudomenas aeruginosa* and *Haemophilus influenzae*.

Susceptibility testing

Broth microdilution susceptibility testing of C/T was performed following Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology with a fixed 4-µg/mL concentration of tazobactam and increasing doubling dilutions of ceftolozane.

Breakpoints for AP/cUTI and cIAI

The C/T breakpoints used in **P034** and **P035** were the existing breakpoints for AP/cUTI and cIAI used in adults approved by CLSI 2020 (CLSI M100 Edition 30) Table 16. Current EUCAST breakpoints are shown in Table 17. Provisional breakpoints of S/I/R ≤4/8/≥16 ug/mL were used for both C/T and MERO for any pathogen without current CLSI breakpoints.

Table 16: *CLSI Interpretative Breakpoints.*

	MIC (ug/mL)			Disk diffusion (mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacterales	≤2/4	4/4	≥8/4	≥21	18-20	≤17
P. aeruginosa	≤4/4	8/4	≥16/4	≥21	17-20	≤16
Streptococcus spp. (viridans group)	≤8/4	16/4	≥32/4	-	-	-

Table 17: *EUCAST Interpretative Breakpoints.*

	MIC (mg/L)		Disk diffusion (mm)	
Pathogen	**S**	**R**	**S**	**R**
Enterobacterales	≤2	>2	≥22	<22
P. aeruginosa	≤4	>4	≥24	<24
Streptococcus anginosus group	IE*	IE*	IE*	IE*

*Insufficient Evidence

Source:https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf]

- Baseline Pathogens

In study **P034**, 95 participants (C/T + MERO) were included in the mMITT population. The most common baseline qualifying gram-negative uropathogens were *E. coli* (74.6%), *Klebsiella pneumonia* (8.5%), and *P. aeruginosa* (7.0%). Among the 88 participants with Enterobacterales, 4 (3 in the C/T and 1 in the MERO treatment arms) were ESBL-positive. All 4 of the ESBL-positive isolates were *E. coli*. *P. aeruginosa* was isolated from 7 (7.4%) participants. AmpC-overexpression was not detected in any participants with *P. aeruginosa*.

In study **P035**, 91 participants (C/T+MTZ and MERO) were included in the MITT population. The most common gram-negative pathogens were *E. coli* (67.1%), *P. aeruginosa* (27.1%), and *Bacteroides fragilis* (18.6%). Among all 60 participants with Enterobacterales, 9 (15%) were ESBL-positive. *P. aeruginosa* was isolated from 25 (27.5%) participants and was the second most prevalent pathogen. AmpC-overexpression was detected in 1 (4%) of the participants with *P. aeruginosa*.

- MIC frequency distributions of P034 and P035 isolates compared to surveillance isolates

Global surveillance of C/T *in vitro* activity against *P. aeruginosa* and Enterobacterales was conducted by IHMA Laboratories through SMART in the United States and Europe. During studies, **P034** and **P035**, all aerobic and anaerobic pathogens were tested at a central laboratory, JMI Laboratories (North Liberty, Iowa United States). At JMI Laboratories, each isolate was identified, and susceptibility testing was performed by broth microdilution according to CLSI M07 (2018) guidelines.

The CHMP acknowledged that C/T appears to demonstrate potent *in vitro* activity against Enterobacterales and *P. aeruginosa* isolates collected globally from paediatric patients (2017-2019), regardless of infection site. The overall distribution of C/T MICs among the *P. aeruginosa* clinical trial isolates from study **P034** and **P035** was similar to that of the surveillance study isolates in both the US and EU. The Enterobacterales modal C/T MIC from the surveillance studies seems to be somewhat higher than what is found in the clinical studies. Since this is an application where efficacy data mainly are

extrapolated from adult data to paediatric patients, the surveillance data and MIC distributions is considered more of a descriptive part of the application and was not further assessed.

- PK/PD indices and targets from non-clinical data

No new pharmacodynamics or PK/PD studies were performed to support the paediatric indication in cUTI (including pyelonephritis), or cIAI. The pharmacodynamics or PK/PD studies conducted previously was summarized in the original marketing application for adult patients with AP/cUTI and cIAI and the supplemental marketing application for adult patients with HAP/VAP. Data from neutropenic thigh infection models in mice that supports the PK/PD indices and target values for ceftolozane and tazobactam are summarized below.

The ceftolozane PK/PD index that correlated with in vivo ceftolozane efficacy is time above MIC as a fraction of the dosing interval that plasma concentrations remain above the minimum inhibitory concentration (%T>MIC). The mean (median) %T>MIC across the 8 P. aeruginosa and Enterobacterales strains based on total drug concentration associated with bacteriostasis and 1-log kill were 25.2 (24.8) and 31.5 (32.2), respectively. As ceftolozane plasma protein binding in mice is <10% and as no notable impact of serum on MIC was observed in *in vitro* studies, no conversion to free fraction was applied to these PK/PD targets. Based on these results, the %fT>MIC of 30% was selected as the ceftolozane PK/PD target for probability of target attainment (PTA) analysis.

Based on data from neutropenic mouse thigh infection models, the PK/PD index of tazobactam that correlated with efficacy is time as a fraction of the dosing interval that free plasma concentrations remain above a threshold concentration of 1 µg/mL (%fT>CT). In this study, 6 bacterial strains (2 *K. pneumoniae* and 4 *E. coli*) were used to infect mice. Infected mice were treated with ceftolozane doses that achieved the ceftolozane PK/PD target of 30% fT>MIC, in conjunction with different tazobactam q2h dosing regimens in order to determine the PK/PD target value of tazobactam.

The CHMP noted that no new *in vitro* studies had been submitted. There are no expected differences in the mechanism of action of C/T based on age as the Gram-negative causative pathogens are similar in adults and children. Joint PK/PD targets in line with the PK/PD targets used to assess PTA in adults with AP/cUTI, cIAI and HAP/VAP, have been used (30% *f*T>MIC for ceftolozane and 20 %fT> 1 µg/mL for tazobactam), which is acceptable.

4.3.4. PK/PD modelling

The population-PK model was used to generate individual model-predicted exposures in paediatric subjects with AP/cUTI and cIAI and to simulate PTA at the targets and MIC breakpoints for the pathogens of interest.

- Selection of Phase 2 dose

The C/T dosage regimens evaluated in the paediatric Phase 2 studies were selected based on the criteria that the projected distributions of ceftolozane and tazobactam plasma exposures (AUC and Ceoi) in paediatric patients would not exceed those in adult AP/cUTI and cIAI patients and that the projected ceftolozane PTA of achieving at least 30% *f*T>MIC = 4 µg/mL would be ≥90%.

- Simulation of exposure and PTA analyses following Phase 2 studies

The final paediatric ceftolozane and tazobactam population-PK models were used in Monte Carlo simulations to assess plasma joint ceftolozane and tazobactam PTA at the dosing regimens evaluated in **P034** and **P035**.

- Children 12 to <18 years, 1.5 g C/T (1 g ceftolozane / 0.5 g tazobactam) q8h by 1-hour IV infusion
- Children from birth to <12 years, 30 mg/kg C/T (20 mg/kg ceftolozane / 10 mg/kg tazobactam) q8h by 1-hour IV infusion

Additional simulations were conducted to assess joint ceftolozane and tazobactam PTA at simplified dosing regimens using a weight cut-off of 50 kg:

- Children ≥50 kg, 1.5 g C/T (1 g ceftolozane/0.5 g tazobactam) q8h by 1-hour IV infusion
- Children <50 kg, 30 mg/kg C/T (20 mg/kg ceftolozane / 10 mg/kg tazobactam) q8h by 1-hour IV infusion

As infection types were identified as significant covariates of ceftolozane PK, separate PTA assessments were conducted for AP/cUTI and cIAI.

In the PTA assessments, 2000 paediatric subjects for each of the 5 age groups (12 to <18 years; 6 to <12 years; 2 to <6 years; 3 months to <2 years; birth to <3 months) were randomly sampled from two virtual paediatric population databases. The first paediatric database included virtual paediatric patients for children ≥3 months. This virtual population database (n = 100,000, with 25,000 per group for groups 1 to 4) was constructed using the variance-covariance relationship among age, body weight, height, and eGFR from paediatric participants in trials in antibacterial and antifungal programs conducted by the MAH. For children 0 to <3 months, a second virtual population database (n = 2400) was constructed using available data for body weight and height distributions by sex and age subgroup from the Centers for Disease Control and Prevention data tables, and the distributions for eGFR based on age derived from Schwartz et al. 2007 and Heilbron et al. 1991. For this group, a lower bound of eGFR (20 mL/min/1.73 m2) was used to be consistent with the physiological limit. These two databases of virtual patients were combined and sampled (n=2000 per group) to create the simulated population for PTA simulations.

The %*f*T>MIC of 30% for ceftolozane and 20% *f*T>C_T of 1µg/mL for tazobactam were selected as the PK/PD targets for the joint PTA analyses. In the paediatric AP/cUTI and cIAI population receiving the proposed simplified dosing regimen, the C/T joint PTA was >94% over the MIC range of 0.015 to 4 µg/mL and >85% at 8 µg/mL across all age groups. While, in the paediatric AP/cUTI and cIAI population receiving the clinically evaluated dosing regimen, the C/T joint PTA was >93% over the MIC range of 0.015 to 4 µg/mL and >85% at 8 µg/mL across all age groups. According to the MAH, the data support that participants infected with *P. aeruginosa* (MIC ≤4 µg/mL) or Enterobacterales (MIC ≤2 µg/mL) can be adequately treated with the proposed C/T dosing regimens.

A tabular summary of the simulated Day 1 joint C/T plasma PTA in paediatric AP/cUTI and cIAI patients at the proposed dose is presented in Table 18 and Table 19, respectively. In Figure 3 and Figure 4, steady-state joint C/T plasma PTA in paediatric patients with AP/cUTI and cIAI across age groups, are shown. The joint PTA curves are overlaid on a histogram illustrating the 2017 – 2019 surveillance data from the US and the EU, and the MIC distribution for *P. aeruginosa* isolates and Enterobacterales isolates from **P034** (Figure 3) and **P035** (Figure 4).

Based on the MIC distributions from the surveillance studies, 95% (US), and 93% (EU) of *P. aeruginosa* isolates have C/T **MIC ≤4 µg/mL** and 97.5% (US), and 87.6% (EU) of Enterobacterales isolates have C/T **MIC ≤2 µg/mL**. Therefore, according to the MAH, the totality of the data suggests that >90% or greater of *P. aeruginosa* clinical isolates and ~90% or greater of Enterobacterales clinical isolates could be adequately treated at the recommended clinical C/T doses.

Table 18: *Percentage of Paediatric cUTI patients Achieving 30% of fT>MIC for Ceftolozane and 20% of fT>CT of 1 µg/mL for Tazobactam at the Proposed C/T Dose Across all Age Groups*

Age Group	MIC (µg/mL)												
	0.015	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Group 1 12 to <18 years	95	95	95	95	95	95	95	95	95	95	63	3.5	0
Group 2 7 to <12 years	95	95	95	95	95	95	95	95	95	95	69	4.7	0
Group 3 2 to <7 years	94	94	94	94	94	94	94	94	94	92	54	2.2	0
Group 4 3 months to <2 years	95	95	95	95	95	95	95	95	95	92	52	2.8	0.05
Group 5 Birth to <3 months	100	100	100	100	100	100	100	100	100	100	96	40	0.9

Table 19: *Percentage of Paediatric cIAI patients Achieving 30% of fT>MIC for Ceftolozane and 20% of fT>CT of 1 µg/mL for Tazobactam at the Proposed C/T Dose Across All Age Groups*

Age Group	MIC (µg/mL)												
	0.015	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Group 1 (12 to <18 years	95	95	95	95	95	95	95	95	95	93	44	1.3	0
Group 2 7 to <12 years	95	95	95	95	95	95	95	95	95	93	51	1.5	0
Group 3 2 to <7 years	94	94	94	94	94	94	94	94	94	88	35	0.3	0
Group 4 3 months to <2 years	95	95	95	95	95	95	95	95	94	87	33	0.95	0.1
Group 5 Birth to <3 months	100	100	100	100	100	100	100	100	100	100	90.9	24.3	0.4

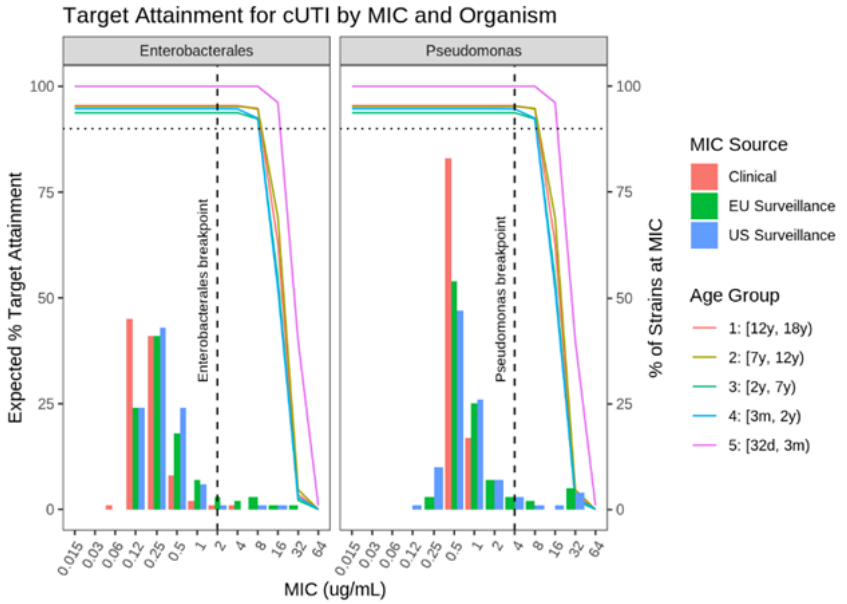


Figure 3: *Percentage of paediatric cUTI Patients Achieving 30% fT>MIC for ceftolozane and 20% fT>C_T in tazobactam in plasma at Steady State with Enterobacterales (Left Panel) and P. aeruginosa (Right Panel) MIC Distributions Amongst Isolates from P034 and Surveillance Data.* The dashed vertical line represents MIC of 2 µg/mL for enterobacterales (left panel) and MIC of 4 µg/mL for P. aeruginosa (right panel); the dashed horizontal line represents 90% PTA. Source: Summary of clinical pharmacology studies page 64.

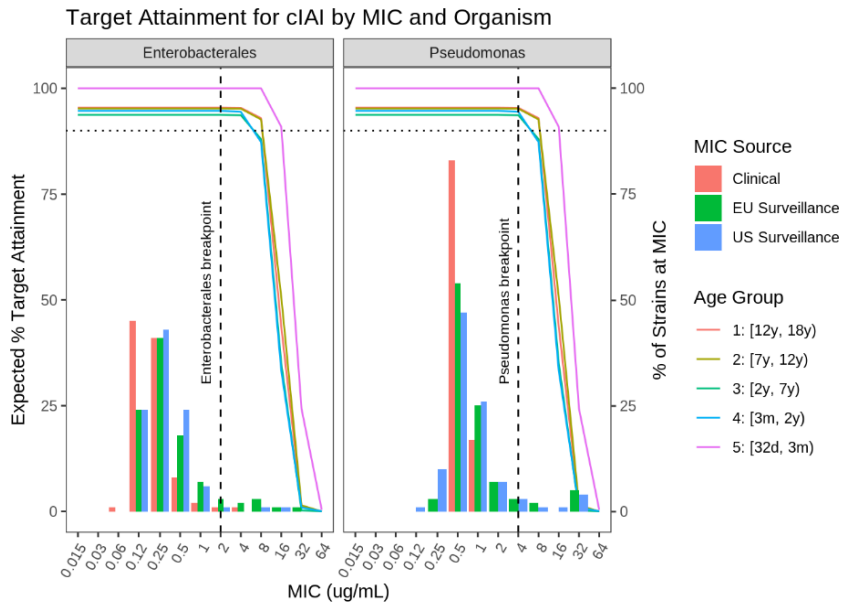


Figure 4: *Percentage of paediatric cIAI Patients Achieving 30% fT>MIC for ceftolozane and 20% fT>C_T in tazobactam in plasma at Steady State With Enterobacterales (Left Panel) and P. aeruginosa (Right Panel) MIC Distributions Amongst Isolates from P035 and Surveillance.* The dashed vertical line represents MIC of 2 µg/mL for enterobacterales (left panel) and MIC of 4 µg/mL for P. aeruginosa (right panel); the dashed horizontal line represents 90% PTA. Source: Summary of clinical pharmacology studies page 65.

- Simulation of exposure and PTA analyses for paediatric patients with renal impairment

The population-PK models of ceftolozane and tazobactam, which were used to inform the dose and dosing strategy for paediatric AP/cUTI and cIAI patients, were used to perform additional simulations for dosing recommendation in paediatric patients with renal impairment category (moderate and severe), on request from the CHMP. Various scenarios of adjustment of dosing regimens for moderate and severe renal impairment were explored using modelling and simulation to select the optimal regimens to meet the criteria outlined in Table 20.

Table 20: *Scenarios of Dose Adjustment for Paediatric cUTI and cIAI Patients with Moderate and Severe Renal Impairment.*

Age Groups	C/T Dose in Normal & Mild Renal Impairment	C/T Dose in Moderate & Severe Renal Impairment			
		25% Reduction from Normal Dose	30% Reduction from Normal Dose	35% Reduction from Normal Dose	40% Reduction from Normal Dose
12 to <18 Years	1000/500 mg	750/375 mg	700/350 mg	650/325 mg	600/300 mg
6 to <12 Years	20/10 mg/kg	15/7.5 mg/kg	14/7 mg/kg	13/6.5 mg/kg	12/6 mg/kg
2 to <6 Years	20/10 mg/kg	15/7.5 mg/kg	14/7 mg/kg	13/6.5 mg/kg	12/6 mg/kg

Further to additional questions by the CHMP, the MAH withdrew the proposals for dosing recommendations in paediatric patients aged 2 to <18 years of age with moderate or severe renal impairment (see section Special populations – Paediatric patients with impaired or immature renal function).

The CHMP considered that the C/T dosage regimens evaluated in the paediatric Phase 2 studies were selected based on the criteria that ceftolozane and tazobactam plasma exposures (AUC and C_{eoi}) in paediatric patients would not exceed those in adult AP/cUTI and cIAI patients, and that the projected C/T joint PTA would be ≥90%. Even though the exposure of ceftolozane and tazobactam trended lower in some age groups compared to that observed in adults, all paediatric subgroups achieved acceptable PTAs of ≥94% over the MIC range of 0.015 to 4 µg/mL at the proposed dosing recommendations using the same joint PK/PD targets as employed in the original MAA for adult cIAI and AP/cUTI indications. The MAH also assessed the joint C/T PTA at the dosing regimens evaluated in **P034** and **P035**, and similar joint PTAs of >93% over the MIC range of 0.015 to 4 µg/mL were observed. Based on the joint PTA analysis, the proposed dosing regimen seems overall appropriate. As stated by the MAH, the proposed dosing regimen will account for children in Group 1 with a body weight <50 kg, which in the dosing regimens evaluated in the clinical studies (**P034** and **P035**) received a fixed dose of 1g/0.5g C/T.

In the adult patients the joint PTA for C/T was >97%, which is slightly higher than what is modelled in the paediatric population. In general, throughout the submitted application, the MAH has described the paediatric data acceptably.

4.3.5. Dose response studies

Exposure-efficacy analyses

Exposure-response (ER) analysis were conducted to assess the potential relationship between individual ceftolozane plasma PK/PD target (%*f*T>MIC, where MIC was the highest MIC for the identified organism) and tazobactam plasma PK/PD target (%*f*T>1 µg/mL), and secondary efficacy endpoints: clinical success

rate and per-participant microbiological success rate at the end of IV (EOIV) end of therapy (EOT) and test of cure (TOC) visit in **P034** and **P035**.

- Dataset

For **P034**, 97 of 100 subjects in the C/T treatment group completed the study. Participants in the Microbiological Modified Intent-to-Treat (mMITT) population (n=71) who received C/T and whose PK were characterized in the Population-PK models were used in the analysis for both clinical and microbiological responses (n=65) at the TOC visit and the EOT visit. The mMITT population was a subset of randomised participants who received any amount of study treatment and had at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture (a baseline study-qualifying urine culture had to contain 1 and not more than 2 gram-negative bacterial isolates at $\geq 10^5$ CFU/mL each). A majority of participants in the mMITT population received oral step-down antibacterial medication (70.4%). For subjects who received only IV study treatment and were not switched to oral step-down therapy, the EOIV (end of IV treatment) assessment served as the EOT assessment, and these subjects did not have a separate EOT assessment. Subjects who were switched to oral step-down therapy had both an EOIV and EOT assessment.

For **P035**, participants in the modified intent to treat (MITT) population (n=70) who received C/T and whose PK were characterized in the Population-PK models were used in the analysis for clinical response (N=55) at the TOC visit and EOT visit). The MITT population (n=70) consisted of all randomised participants who received any amount of study treatment. Participants in the mMITT population (n=63) who received C/T and whose PK were characterized in the Population-PK models were used in the analysis for microbiological response (N=55 at the TOC visit and EOT visit). In the MITT population 37 out of 70 (50%) received oral step-down antibacterial medication.

- Results AP/cUTI

In the exposure-efficacy dataset for paediatric Phase 2 study in AP/cUTI (**P034**), individual values of ceftolozane PK/PD index (%fT>MIC) were 100% in all paediatric participants with clinical cure or observed failure at TOC (Figure 5). In the same dataset, the individual values of tazobactam PK/PD index (%fT>1 µg/mL) in paediatric participants were >20%, in those with clinical cure or observed failure at TOC. Therefore, the MAH stated that there was no apparent trend in the exposure measures for either ceftolozane or tazobactam with clinical response at TOC in paediatric participants with AP/cUTI in **P034**.

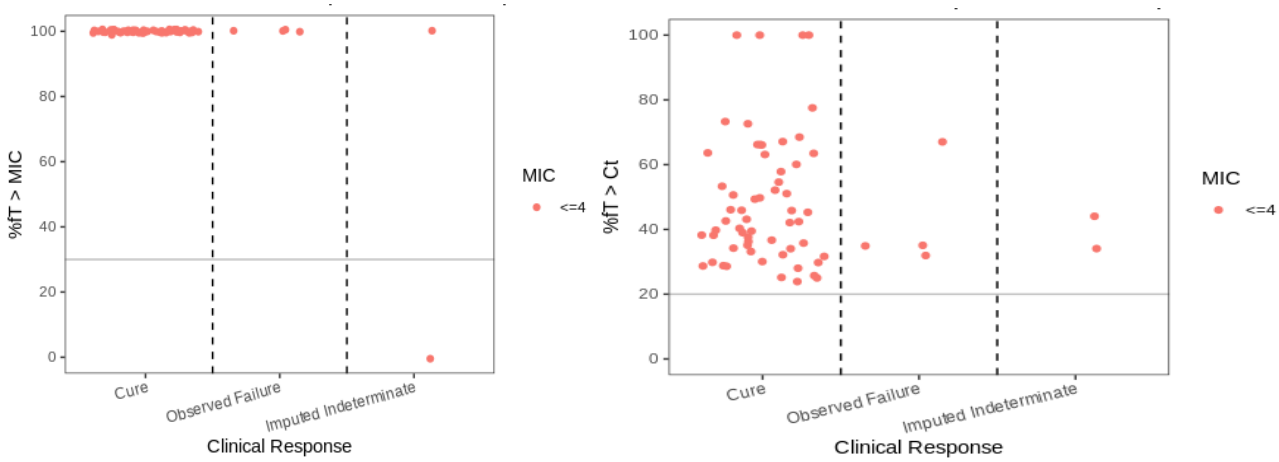


Figure 5: *Distribution of Ceftolozane (%fT>MIC) and Tazobactam (%fT>1 µg/mL) PK/PD Targets with Overall Clinical Response Between Cure, Failure, and Indeterminate at Test of Cure in Paediatric cUTI (P034). MIC refers to the highest MIC of all pathogens isolated from the baseline culture.*

In the exposure-efficacy dataset for the paediatric Phase 2 study in AP/cUTI (**P034**), there was no apparent trend in the exposure measures for either ceftolozane or tazobactam with clinical response at EOIV in paediatric participants with AP/cUTI (Figure 6). Exposure-efficacy analyses using other efficacy endpoints (per-participant microbiology response at EOIV) for paediatric AP/cUTI patients (Figure 7) yielded results consistent with those described above.

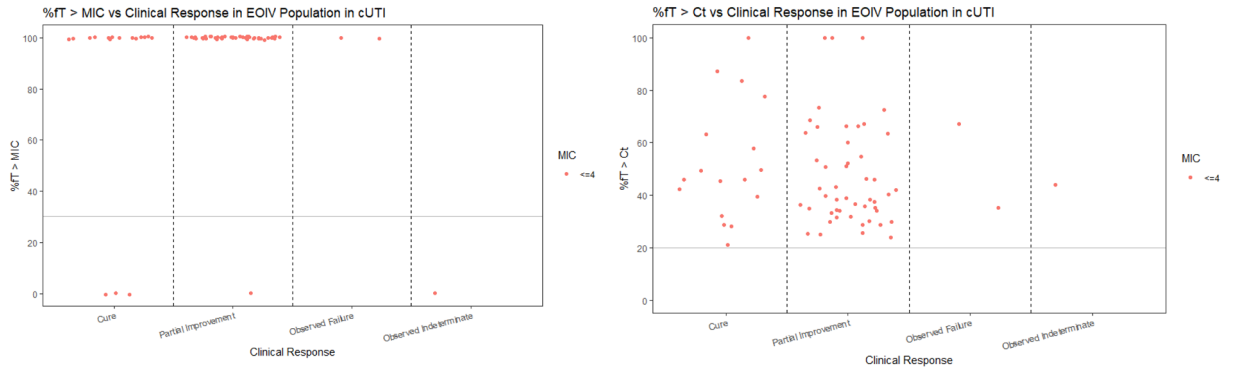


Figure 6: *Distribution of Ceftolozane (%fT>MIC) and Tazobactam (%fT>1 µg/mL) PK/PD Index Values with Overall Clinical Response (Cure, Failure, and Indeterminate) at the End of IV Treatment in Paediatric cUTI (P034). All MICs collected refers to the highest MIC of all pathogens isolated from the baseline culture which is <= 4 µg/mL.*

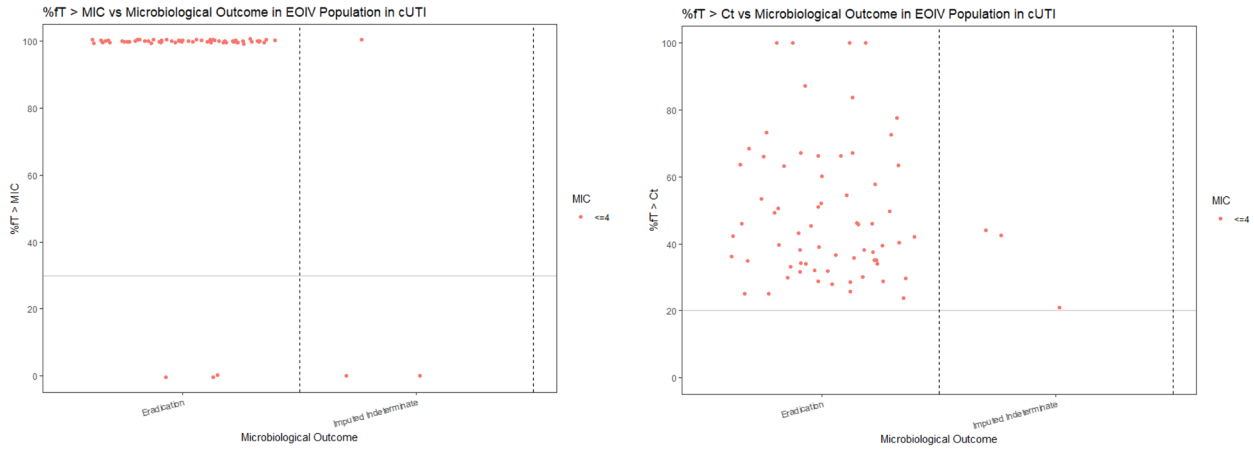


Figure 7: *Distribution of Ceftolozane (%fT>MIC) and Tazobactam (%fT>1 µg/mL) PK/PD Index Values with Overall Microbiological Outcome (Cure, Failure, and Indeterminate) at the End of IV Treatment in Paediatric cUTI (P034). All MICs collected refers to the highest MIC of all pathogens isolated from the baseline culture which is <= 4 µg/mL.*

- Results cIAI

In the exposure-efficacy dataset for paediatric Phase 2 study in cIAI (**P035**), a total of 56 participants in the C/T arm had exposure measures and MIC, 37 of which had 100% fT>MIC, 8 of which had 0% fT>MIC, and 11 of which had fT>MIC ranged from ~14% to ~92%. Of the participants with 100% fT>MIC, 35 achieved clinical cure at TOC (95%); of the participants with 0% fT>MIC, 6 achieved clinical cure at TOC (75%); and of the participants with fT>MIC between 14% and 92%, 9 achieved clinical cure at TOC (82%). Like AP/cUTI, no interpretable trend between either efficacy endpoint or exposure

measures of ceftolozane and tazobactam was identified at TOC in paediatric participants with cIAI in **P035**.

The exploratory graphical analysis indicated that all paediatric cIAI participants with fT>MIC below the ceftolozane PK/PD target (30%), except one, at the highest MIC breakpoint for ceftolozane (MIC > 4 µg/mL) and most of these participants achieved clinical cure at TOC (Figure 8). The individual %fT>1 µg/mL values for tazobactam in the same dataset were >20% for all but one paediatric participant, irrespective of clinical cure or observed failure at TOC.

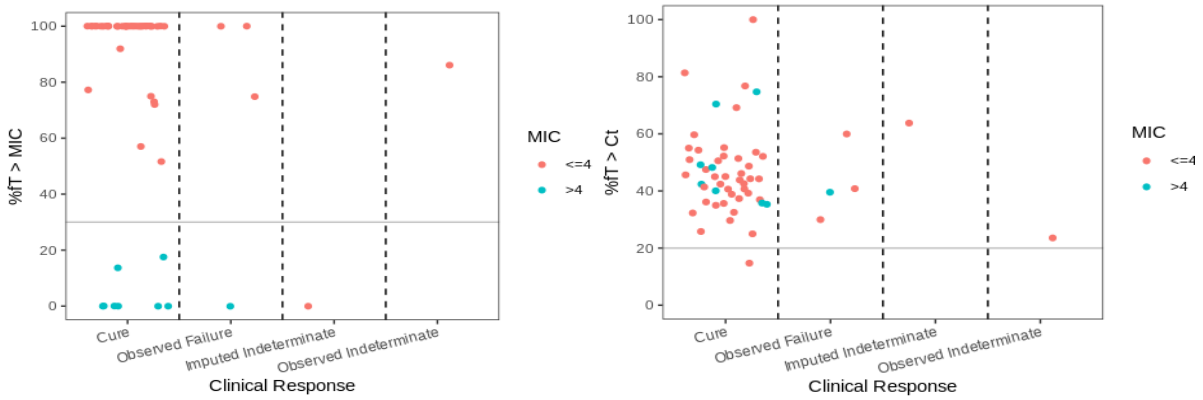


Figure 8: *Distribution of Ceftolozane (%fT>MIC) and Tazobactam (%fT>1 µg/mL) PK/PD Targets by Overall Response Between Cure, Failure, and Indeterminate at Test of Cure in P035. MIC refers to the highest MIC of all pathogens isolated from the baseline culture.*

In the exposure-efficacy dataset for the paediatric Phase 2 study in cIAI (**P035**), there was no apparent trend in the exposure measures for either ceftolozane or tazobactam with clinical response at EOIV in paediatric participants with cIAI (Figure 9). Exposure-efficacy analyses using other efficacy endpoints (per-participant microbiology response at EOIV) for paediatric cIAI patients (Figure 10) yielded results consistent with those described above.

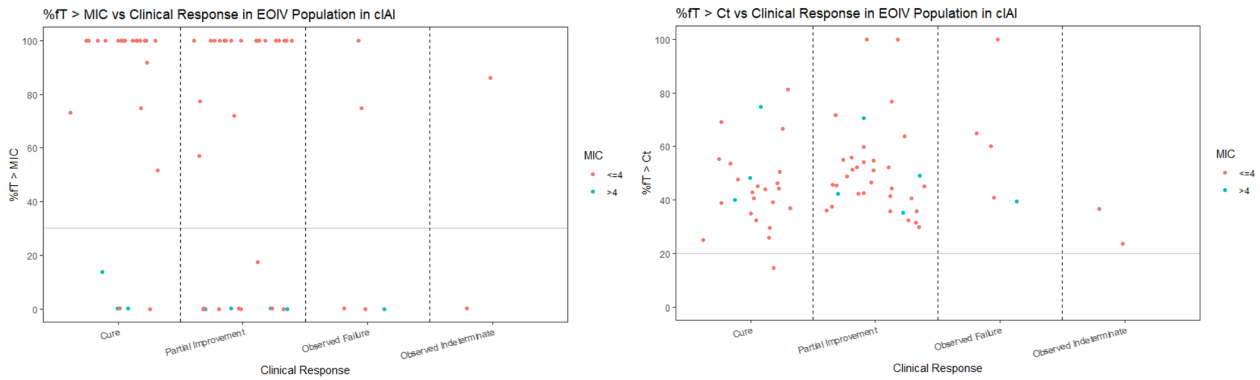


Figure 9: *Distribution of Ceftolozane (%fT>MIC) and Tazobactam (%fT>1 µg/mL) PK/PD Index Values with Overall Clinical Response (Cure, Failure, and Indeterminate) at the End of IV Treatment in Paediatric cIAI (P035).*

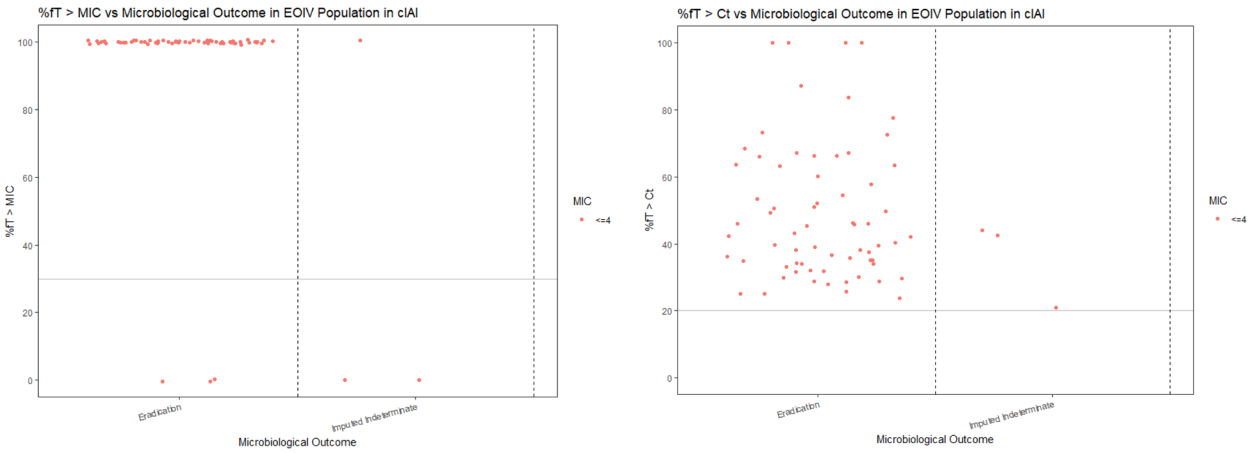


Figure 10: *Distribution of Ceftolozane (%fT>MIC) and Tazobactam (%fT>1 µg/mL) PK/PD Index Values with Overall Microbiological Outcome (Cure, Failure, and Indeterminate) at the End of IV Treatment in Paediatric cIAI (P035). All MICs collected refers to the highest MIC of all pathogens isolated from the baseline culture which is <= 4 µg/mL.*

Exposure-efficacy analyses using other efficacy endpoints for paediatric AP/cUTI and cIAI (clinical response at EOT, per-participant microbiology response at TOC and EOT) yielded results consistent with those described above. Taken together, the MAH states that, the exploratory analyses supported that the concentrations of ceftolozane and tazobactam attained at the paediatric dosing regimens evaluated in **P034** and **P035** are at the flat regions of the exposure-response relationship.

The CHMP noted that exposure-response analyses were conducted to check for possible association between individual ceftolozane plasma PK/PD target and tazobactam plasma PK/PD target and secondary efficacy endpoints. The endpoints used in the exposure response analysis is clinical success rate and per-participant microbiological success rate at the EOT and TOC visit in **P034** and **P035**. Since these endpoints do not solely reflect the response to C/T, but also the response to the oral step-down antibiotic therapy (the majority of participants in the mMITT population (which consisted of 71 patients) received oral step-down antibacterial medication (70.4%)), the MAH was requested to perform the explorative exposure response analysis again, with EOIV as endpoint. The answer showed no apparent trend in the exposure measures for either ceftolozane (%fT>MIC) or tazobactam (%fT>1 µg/mL) with clinical response or per-participant microbiological responses at EOIV in paediatric participants with AP/cUTI or cIAI. The concentrations of ceftolozane and tazobactam attained at the paediatric dosing regimens evaluated in **P034** and **P035** are likely at the flat regions of the exposure-response relationship.

Exposure-safety analyses

The planned exposure-safety analyses were not conducted as no drug-related TEAEs met the incidence rate threshold of 20%, and no events of clinical interest were identified.

4.3.6. Discussion on clinical pharmacology

The MAH applied to extend the adult cUTI, AP and cIAI indications to children and adolescents from birth to <18 years.

In accordance with the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/CHMP/187859/2017), extrapolation of efficacy to the paediatric populations could be made provided similar exposures (and similar safety profile) to those in adults. The guideline outlines that *it may not be necessary to obtain pharmacokinetic data from all age subgroups in which use is to be*

proposed. In some circumstances, modelling and simulation of adult data may be sufficient to support dosing recommendations for certain age subgroups (e.g., adolescent subjects). On other hand, pharmacokinetic data will need to be generated in neonates in almost all cases owing to the rapid developmental changes in absorption, distribution, metabolism and excretion.

The variation application is supported by one phase 1 (P010: P010MK7625A) and two phase 2 studies (P034: P034MK7625A, P035: P035MK7625A) as well as PK and PK/PD modelling.

Pharmacokinetics

- Bioanalytical methods

The analytical methods submitted to support the new phase 1 and 2 clinical studies have been adequately validated in previous procedures in accordance with the EMA bioanalytical guideline (*EMEA/CHMP/EWP/192217/2009 Rev. 1*). The analysis of PK samples from the phase 1 and phase 2 studies are acceptable.

In previous Zerbaxa procedures, a relatively high proportion of tazobactam plasma concentration measures were BLQ. This is also the case in the 3 clinical studies included to support the current application. This hampered the population-PK modelling and the PTA simulations. However, since most of the BLQ samples were collected either pre-dose or at 6-7 hours after end of infusion, and the target exposure of tazobactam is 20% $fT>C_T$ of 1µg/mL, the available dataset was considered sufficient for the PK assessment.

- Modelling and simulation

To support dosing recommendations in the new target population, population-PK models describing C/T PK in adults have been modified and updated with available paediatric PK data from the three clinical studies to predict exposure in children <18 years old using a Bayesian approach. Separate models were developed for ceftolozane and tazobactam, as in adults. The regulatory impact of the models is considered moderate to high as there is clinical data in paediatric patients available for validation activities of the models, but the data is sparse and not fully covering all factors that are known to influence PK exposure (age, weight, type of infection, renal function). The limitations in the observed data impact the ability to validate the model predictions at low weight, low renal function and for the cIAI indication. Further, a high proportion of the tazobactam samples were below the LOQ. In the initial dossier in support of this procedure, the respective model evaluations indicated reasonable fit for the ceftolozane model and model mis-specifications for tazobactam. In response to consequent CHMP questions, the MAH provided pcVPCs for the tazobactam model, as well as graphical presentations of the exposure metrics AUC and Ceoi versus body weight and age on continuous scales for the full paediatric populations with additional separate plot focused on the children 0 – 1 year of age. The newly provided overall pcVPC indicates no major mis-specification in the model, and overall, the additional presentations submitted indicate that the tazobactam population-PK model fit to the paediatric data reasonably well, also at the lower age range. The model is considered however of low reliability, particularly for the lowest age ranges (below 3 months for AP/cUTI and below 2 years for cIAI). Limited clinical data exists from paediatric patients with CrCL <50 mL/min/1.73m^2, and the paediatric population PK-model for ceftolozane did not adequately describe the influence of renal function. Consequently, no dosing recommendations could be provided for paediatric patients with immature or impaired renal function as part of this variation.

- Paediatric patient populations

cIAI and AP/cUTI

In study **P010** the aim of the dose selection was to achieve comparable exposures to those calculated for adult patients with cIAI and AP/cUTI. The selected exposure target for ceftolozane covers the range of AUCs reported in healthy adults, adult AP/cUTI and adult cIAI patients and seems appropriate. The ceftolozane PK parameters were generally comparable across Groups 1-4 in study **P010**, but the ceftolozane and tazobactam CL appeared to be lower in subjects aged birth to <3 months (Groups 5 and 6). After accounting for weight, the ceftolozane CL was comparable across most age groups with a lower weight corrected CL in patients in Group 6 with CrCL <50 mL/min/1.73m2, these patients also received a lower dose of C/T. Hence, the lower CL observed in infants and neonates is likely due to their immature renal function.

Overall, the exposure of ceftolozane in study **P034** and **P035** estimated by the population-PK model are within the defined target exposure. Although some trends are observed in the steady-state ceftolozane and tazobactam plasma PK parameter values estimated by population-PK modelling, the presented data are still within the range of observations in the adult participants with AP/cUTI and cIAI. Of note, there are few patients included in each age group, especially in the lower age groups which brings uncertainties to the estimates. Still, the provided data are considered sufficient in support of extension of indication to the paediatric AP/cUTI patients and cIAI patients ≥2 years. The patient population in study **P034** includes both cUTI and pyelonephritis of sufficient severity requiring hospitalisation and treatment with intravenous (IV) antibiotics. The MAH did not present any specific analysis to investigate potential differences in PK between the AP and cUTI patients. However, there is no expected difference in pharmacokinetics between cUTI and AP based on adult PK data, and it is considered that the paediatric PK data is representative for both cUTI and AP.

Concerning cIAI patients <2 years of age, PK data is only available for one single patient (age group birth to <3 months). According to the *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population* (EMEA/CHMP/EWP/147013/2004), pharmacokinetic information from one indication can be extrapolated to another indication if it can be assumed that the diseases and commonly used concomitant medications are not affecting the pharmacokinetics of the drug. In the adult population-PK models, body weight, renal function (eGFR) and age were identified as significant covariates for ceftolozane and tazobactam, while infection types (cUTI, cIAI and NP) were identified as significant covariates for ceftolozane, but not for tazobactam. Of note, the expected difference in exposure between the two infection types are not large and does not lead to adjustments in the dosing regimen for adults or children.

The single patient <3 months of age with cIAI had estimated exposures of ceftolozane comparable to the patients <3 months of age with AP/cUTI in study **P034**, while the estimated tazobactam exposures was higher. Of importance, this is an estimated measure from one single cIAI patient, the tazobactam exposure distribution in the AP/cUTI patients <3 months of age are wide, and the exposure measures from the patient with cIAI <3 months of age is only slightly higher than the highest estimated values in the AP/cUTI population (69.9 µg*h/mL vs. ~65 µg*h/mL). Further, the estimated measures of AUC and Ceoi for the patient <3 months of age with cIAI are within the range of values observed in adults with cIAI. In addition, as discussed in the section *model qualification*, the credibility of the tazobactam model is low, particularly for the lowest age ranges (<3 months for AP/cUTI and <2 years for cIAI). The model overpredicts the tazobactam exposures, most prominently at the end of the dosing interval. Even so, considering the target of fraction of time above 1mg/mL at 20%, the observed exposure data indicate that patients are above this limit. Due to the limited PK data available, it is difficult to draw any clear conclusions on the comparison between the cIAI and AP/cUTI populations <2 years of age.

However, based on the totality of the data presented, albeit limited, it is supported that the proposed dosing regimens can be extended to the age groups <2 years with cIAI based on extrapolation from the modelling and simulations.

- Reduced renal function

One exclusion criterion in study **P034** and **P035** were moderate or severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the Bedside Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration. No dose recommendations in paediatric patients below 18 years of age with eGFR ≤ 50 mL/min/1.73 m^2 was initially established. Considering that the ceftolozane and tazobactam both are renally excreted, dosing recommendations in renal impairment is generally required.

Considering the low GFR expected in new-born (children born at term is expected to have GFR of approximately 10-20 mL/min/1.73m2 the first day of life, thereafter rising up to approximately 30-40 mL/min/1.73m2 after two weeks, reaching adult levels 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. Hence, this cut-off will most likely exclude a large proportion of the youngest patients born at term and possibly all the youngest preterm patients from treatment with C/T. Further, the estimation of GFR in paediatric patients is challenging, and the proposed posology with a cut-off based on CrCL/eGFR might not be well-suited for clinical practice.

After additional investigation and refinements of the submitted population PK model, it emerged that the model is not considered suitable for predicting dosing recommendations for paediatric patients above/below 2 years of age with immature or impaired renal function. Considering the limitations in the data and the lack of a reliable population PK model, no dosing recommendations could be provided for paediatric patients with reduced/immature renal function at the time of this procedure. The MAH confirmed that the ongoing study MK-7625A-036, is expected to yield data from patients from birth to <3 months of age with an eGFR ≥ 20 mL/min/1.73 m2 and further that additional experience in older children with an eGFR between 50 to 90 mL/min/1.73 m2 may be available to inform any effect of eGFR on ceftolozane and tazobactam. When the data in paediatric patients with reduced renal function will be available it is expected that an application be submitted for a variation to include in sections 4.2 and 5.2 of the SmPC (and other sections as relevant) dosing recommendations to paediatric patients with AP/cUTI or cIAI with immature or impaired renal function, if supported by the data. To support this variation, the MAH is recommended to submit full results of updated/relevant population PK model(s).

In the SmPC "from birth" is now defined as >32 weeks gestational age and ≥7 days postnatal, in both Section 4.2 and 5.1, reflecting the population actually studied.

- Drug-drug interactions

No new DDI studies have been provided in support of the current application. Data from previous procedures indicates a low risk of DDIs during C/T treatment, and it is reasonable that the low DDI potential observed in adults can be extended to the paediatric population. In the two paediatric Phase 2 studies (**P034** and **P035**) submitted for the current application based on the low risk of DDIs related with C/T, no further assessment of concomitant treatment in the two clinical studies (**P034** and **P035**) have been made.

Pharmacodynamics and PK/PD modelling

C/T appears to demonstrate potent *in vitro* activity against Enterobacterales and *P. aeruginosa* isolates collected globally from paediatric patients (2017-2019), regardless of infection site. The overall

distribution of C/T MICs among the *P. aeruginosa* clinical trial isolates from study **P034** and **P035** was similar to that of the surveillance study isolates in both the US and EU. The Enterobacterales modal C/T MIC from the surveillance studies seems to be somewhat higher than what is found in the clinical studies. Since this is an application where efficacy data mainly are extrapolated from adult data to paediatric patients, the surveillance data and MIC distributions is considered more of a descriptive part of the application and has not been further assessed.

No new *in vitro* studies were submitted. There are no expected differences in the mechanism of action of C/T based on age as the Gram-negative causative pathogens are similar in adults and children. Joint PK/PD targets in line with the PK/PD targets used to assess PTA in adults (AP/cUTI, cIAI and NP), have been used (30% *f*T>MIC for ceftolozane and 20 %fT> 1 µg/mL for tazobactam), which is acceptable. Although there are uncertainties whether the tazobactam target of 20% fT>CT 1 µg/mL should have been more conservative, due to concerns whether the tazobactam dose is sufficient to protect ceftolozane from betalactamases produced by Enterobacterales. This was an issue both in the initial procedure (AP/cUTI/cIAI) and in the extension of the adult indication to include NP. The issue has not been further pursued in this procedure but is highlighted due to the importance of the awareness of the uncertainties that underlies the results from the joint PTA analysis (see below) which in turn supports the dosing rationale provided by the MAH.

The C/T dosage regimens evaluated in the paediatric Phase 2 studies were selected based on the criteria that ceftolozane and tazobactam plasma exposures (AUC and Ceoi) in paediatric patients would not exceed those in adult AP/cUTI and cIAI patients, and that the projected C/T joint PTA would be ≥90%. Even though the exposure of ceftolozane and tazobactam was slightly lower in some age groups compared to that observed in adults, all paediatric subgroups achieved acceptable PTAs of ≥94% over the MIC range of 0.015 to 4 µg/mL at the proposed dosing recommendations using the same joint PK/PD targets as for the adult cIAI, AP/cUTI and NP indications. The MAH did also assess the joint C/T PTA at the dosing regimens evaluated in **P034** and **P035**, and similar joint PTAs of >93% over the MIC range of 0.015 to 4 µg/mL were observed. Based on the joint PTA analysis, the proposed dosing regimen seems overall appropriate. Compared to the dosing regimen evaluated in study **P034** and **P035**, the proposed dosing regimen will account for children in Group 1 with a body weight <50 kg, which were given a fixed dose, similar to the adult population, in the clinical studies.

The tazobactam PK/PD target of 20 %fT> 1 µg/mL is not well founded, however, the concern regarding the chosen PK/PD target has not been further pursued in the current application.

- *Exposure-response analysis*

Exposure-response (ER) analysis were conducted to assess the potential relationship between individual ceftolozane plasma PK/PD target and tazobactam plasma PK/PD target, and the secondary efficacy endpoints in study **P034** and **P035**. The endpoints initially used in the exposure response analysis is clinical success rate and per-participant microbiological success rate at the EOT and TOC visit in **P034** and **P035**. Since these endpoints will not solely reflect the response to C/T, but also the response to the oral step-down antibiotic therapy (the majority of participants in the mMITT population received oral step-down antibacterial medication, 70.4%), the MAH was requested to perform the explorative exposure response analysis again with EOIV as endpoint. The re-analysis showed no apparent trend in the exposure measures for either ceftolozane (%fT>MIC) or tazobactam (%fT>1 µg/mL) with clinical response or per-participant microbiological responses at EOIV in paediatric participants with AP/cUTI or cIAI. The concentrations of ceftolozane and tazobactam attained at the paediatric dosing regimens evaluated in **P034** and **P035** are likely at the flat regions of the exposure-response relationship.

4.3.7. Conclusions on clinical pharmacology

Overall, the totality of the data allows for concluding that the proposed dosing recommendations are adequate for both ceftolozane and tazobactam for the majority of the paediatric patients and that the exposures are sufficiently similar to allow extrapolation of safety and efficacy from adults for cIAI, AP and cUTI infections in paediatric patients with eGFR >50 mL/min/1.73m^2. This is reflected in the SmPC approved with this procedure.

Of note, with the current dosing recommendations for Zerbaxa, a proportion of the youngest patients born at term and possibly all the youngest preterm patients will not be covered.

4.4. Clinical efficacy in paediatric AP and cUTI

4.4.1. Main study

P034MK7625A (abbreviated P034) – AP/cUTI

Clinical study to evaluate safety, tolerability and efficacy of ceftolozane and tazobactam, compared with meropenem in paediatric patients from birth to less than 18 years of age with acute pyelonephritis (AP) and complicated urinary tract infections (cUTIs).

Methods

P034 was a Phase 2 randomised (3:1), active comparator-controlled, multicentre and double-blind study conducted in paediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cUTI, including pyelonephritis of sufficient severity requiring hospitalisation and treatment with intravenous (IV) antibiotics. Its study design is shown in the figure below.

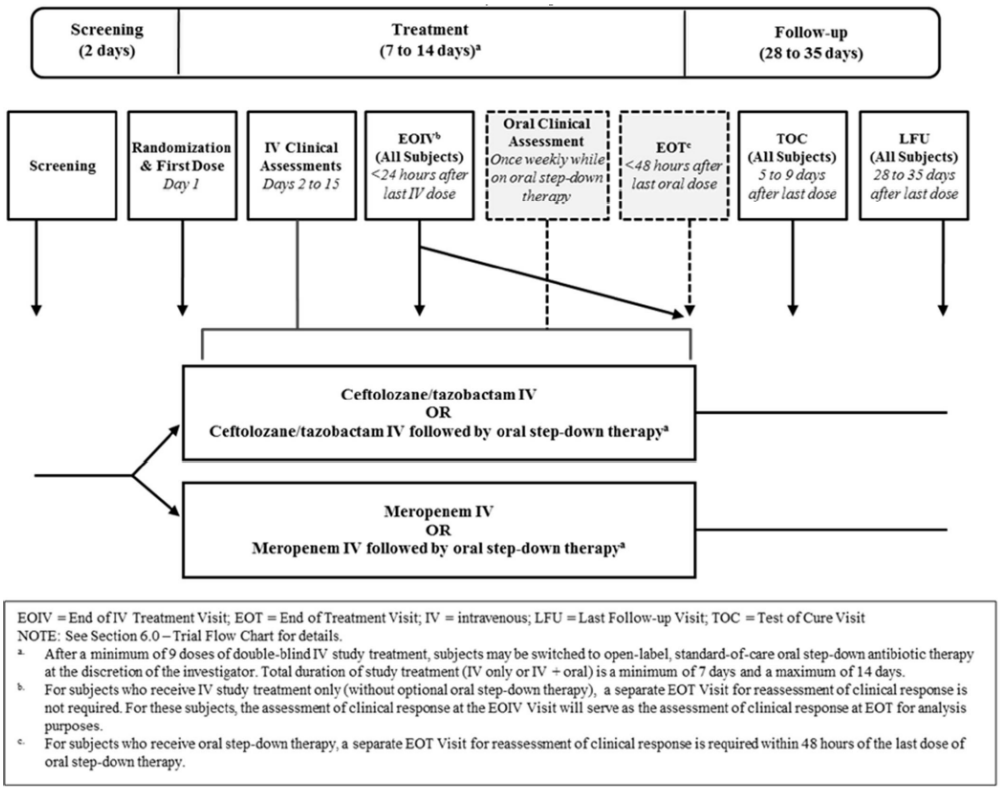


Figure 11: *Study design of Study P034*

Of note, efficacy data beyond the TOC visit were not collected in the study.

Study participants

Main inclusion criteria:

1. Must be male or female from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age.

2. Must require IV antibacterial therapy for the treatment of cUTI.

3. Must have a pre-treatment baseline urine culture specimen obtained within 48 hours before the start of administration of the first dose of study treatment and preferably prior to administration of any potentially therapeutic antibiotics. Specimen was to be obtained by suprapubic aspiration, clean intermittent urethral catheterization, indwelling urethral catheter, or mid-stream clean catch.

NOTE: Subjects could be enrolled in this trial and start IV study treatment before the investigator knew the results of the baseline urine culture; however, subjects without documented $\geq 10^5$ colony-forming units (CFU)/mL of an appropriate gram-negative uropathogen cultured from a baseline urine specimen had to discontinue study treatment immediately following culture result.

4. Must have pyuria, defined as dipstick analysis positive for leukocyte esterase,

OR:

a) If ≥1 year of age: White blood cell (WBC) count >10 cells/µL in unspun urine or ≥10 cells/high power field in spun urine

b) If <1 year of age: WBC count >5 cells/µL in unspun urine or ≥5 cells/high power field in spun urine

5. Must have clinical signs and/or symptoms of cUTI (pyelonephritis or cLUTI) at the screening visit.

a. For pyelonephritis, participants must have had at least 2 of the following new or worsening signs and/or symptoms:

i. If 0 to <2 years of age: fever (as defined by the investigator); failure to thrive; recent weight loss; irritability; poor feeding; lack of normal level of activity; abdominal tenderness on physical examination; vomiting; jaundice.

ii. If 2 to <18 years of age: fever (as defined by the investigator); dysuria; urinary urgency; urinary frequency; new-onset urinary incontinence; suprapubic pain, flank pain, or abdominal pain; suprapubic tenderness or CVA tenderness on physical examination; nausea or vomiting.

OR

b. For cLUTI, participants must have had at least 2 of the new or worsening signs and/or symptoms listed above AND must have had at least 1 of the following complicating factors: obstructive uropathy; congenital, functional, or anatomic abnormality of the urogenital tract; temporary indwelling urinary catheter; bladder instrumentation within <24 hours; recurrent UTI (≥2 events within a 12-month period).

Main exclusion criteria

1. Had received potentially therapeutic antibacterial therapy (e.g., with gram-negative activity), including bladder infusions with topical urinary antiseptics or antibacterial agents, for a duration of more than 24 hours during the 48 hours preceding the first dose of study treatment.

NOTE: Provided all other eligibility criteria were met including obtaining a baseline study-qualifying urine culture, the following subjects may be enrolled (however, subjects without documented $\geq 10^5$ CFU/mL of an appropriate gram-negative uropathogen had to discontinue study treatment immediately following culture results):

a. Participants who had an active cUTI who received at least 48 hours of a prior antibiotic regimen, if in the opinion of the investigator there was evidence they were failing the prior antibiotic regimen.

b. Participants who were receiving antibiotic prophylaxis for cUTI who presented with signs and symptoms consistent with an active new cUTI due to an appropriate gram-negative uropathogen.

2. Had any of the following conditions, current devices, or procedures:

a. Intractable UTI or pyelonephritis infection at baseline that the investigator anticipated would require more than 14 days of study treatment

b. Confirmed fungal urinary tract infection at time of randomization with $\geq 10^3$ fungal CFU/mL

c. Permanent indwelling bladder catheter or instrumentation including nephrostomy

d. Current urinary catheter that was not scheduled to be removed before the end of all study treatment (intermittent straight catheterization during the study treatment period was acceptable)

e. Complete, permanent obstruction of the urinary tract

f. Suspected or confirmed perinephric or intrarenal abscess

g. Documented ileal loop reflux

h. Suspected or confirmed prostatitis, urethritis, or epididymitis

i. Trauma to pelvis/urinary tract

3. Had moderate or severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the Bedside Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration.

4. Had 1 or more of the laboratory abnormalities as noted in the protocol in a specimen obtained at baseline.

a. ANC <1000/mm^3

b. AST or ALT ≥3 × ULN

c. Total bilirubin ≥2 × ULN (if 7 to ≤28 days of age and breastfeeding, total bilirubin >10 mg/dL OR ≥2 × ULN)

5. Had an immunocompromising condition or receipt of immunosuppressive therapy.

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

Treatments

Paediatric participants from 12 to <18 years of age with cUTI received the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam); children <12 years of age, including neonates, received a weight-based dosing regimen of 30 mg/kg C/T (20 mg/kg ceftolozane and 10 mg/kg tazobactam) that did not exceed the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam).

The dose of meropenem was 20 mg/kg (maximum 1 g/dose) for all age groups. However, due to that some literature supports a higher meropenem dosage (up to 30 mg/kg every 8 hours) for participants 14 days to <3 months of age, meropenem dosing up to 30 mg/kg every 8 hours could be used for participants 14 days to <3 months of age at the investigator's discretion.

Both ceftolozane/tazobactam and meropenem were to be dosed every 8 hours (±1 hour) after the previous infusion.

Each dose of ceftolozane/tazobactam was administered as a 60-minute infusion. To ensure blinding, each dose of meropenem was also administered as a 60-minute (±10 minutes) infusion (versus the 30-minute infusion as approved in Member States) to match the duration of infusion of ceftolozane/tazobactam.

After receiving at least 9 doses of double-blind IV study treatment, participants could be switched to open-label, standard-of-care, oral step-down therapy at the investigator's discretion. The total duration of study treatment (IV only or IV + oral) was a minimum of 7 days and a maximum of 14 days.

The CHMP noted that the MAH chose meropenem (which is approved in Europe in the treatment of cUTI in adults and children from 3 months and above) as comparator. Meropenem is a broad-spectrum antibiotic and should preferably be reserved for use in severe, multidrug-resistant and complicated infections. However, the Committee acknowledged that there is increasing resistance towards narrow-spectrum antibiotics worldwide, and thus the use of meropenem might be justified in some cases also for cUTI.

The MAH's view that the use of the same comparator in the two trials P034 and P035 would allow for a larger sized safety database by pooling the data from these two trials was also understood, especially considering that safety was the primary endpoint for these studies.

The chosen doses for meropenem from 3 months to < 18 years is in accordance with what is previously approved. The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, the off-label dose used in the study (20 mg/kg with the possibility to increase to 30mg/kg at the investigator's discretion) seems to be in line with data from current available publications (Fasugba et al, 2015; Cohen-Wolkowiez et al, 2012).

In the Initial MAA for Zerbaxa, the active comparator in the Phase 3 trials of ceftolozane/tazobactam in adults with cUTI (CXA-cUTI-10-04 [MK-7625A-005] and CXA-cUTI-10-05 [MK-7625A-006]), was a fluoroquinolone (levofloxacin). However, the MAH pointed out that fluoroquinolones may not be appropriate as comparators in the paediatric population due to concerns about increased musculoskeletal AEs in paediatric patients who receive fluoroquinolones compared with other classes of antibiotics (Bradley and Jackson, 2011). In addition, rising rates of fluoroquinolone resistance among common uropathogens have rendered this class of antibacterial agents a questionable choice for initial empiric therapy in certain parts of the world (Wagenlehner et al, 2015; Hanna-Wakim et al, 2015; Fasugba et al, 2015). This was agreed by the Committee.

The EAU/ European Society for Paediatric Urology (ESPU) guidelines for UTI in children recommend that parenteral antibiotic therapy should be given until the child is afebrile, before switching to and continuing on oral antibiotics for additional 7-14 days (Stein et al. 2015). In the majority of patients with UTI, normalisation of body temperature can be expected within 24-48 hours after start of therapy. Hence, both the timing of the optional switch from parenteral to oral antibiotics from the fourth day after treatment initiation, and the recommended total duration of IV and oral treatment of 7-14 days, are considered acceptable. Recommended antibiotic or antibiotic class options for step-down therapy by the MAH were: β-lactam/BLI combinations, cephalosporins, quinolones, nitrofurantoin, trimethoprim, or trimethoprim/sulfamethoxazole. The oral treatment options for switching are all frequently used oral antibacterial agents known to be effective for treatment of paediatric UTIs.

The doses chosen for ceftolozane/tazobactam were based on population PK models, exposure data and PTA criteria.

Objectives

Primary objective

To evaluate the safety and tolerability of C/T compared with that of MERO.

Secondary objectives

1. To evaluate the efficacy of C/T compared with that of MERO with respect to clinical response at the EOT and TOC Visits
2. To evaluate the efficacy of C/T compared with that of MERO with respect to per-participant microbiological response at the EOT and TOC Visits

Outcomes/endpoints

Primary endpoint (safety)

To evaluate the safety and tolerability of ceftolozane/tazobactam in paediatric subjects (based on the APaT population).

Secondary endpoints (efficacy)

1. Clinical success rate at the EOT and TOC Visits, defined as the proportion of participants in the analysis population who have a clinical response of cure.
2. Per-participant microbiological eradication rate at the EOT and TOC Visits, defined as the proportion of participants in the analysis population who have an overall outcome of microbiological eradication.

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

Clinical outcome categories

Outcome	Definition
Cure [a]	Complete resolution or marked improvement in signs and symptoms of the cUTI or return to preinfection signs and symptoms, such that no further antibiotic therapy (IV or oral) is required for the treatment of the cUTI.
Partial improvement (only at the EOIV Visit [b] for participants who switch to oral step-down therapy)	Partial resolution of signs and symptoms of the cUTI such that no further IV antibiotic therapy is required for the treatment of the cUTI; however, additional oral step-down therapy is required.
Failure	Any of the following is considered a clinical outcome of failure: • Persistence or reappearance of 1 or more sign or symptom of infection that requires alternative nonstudy treatment for the current cUTI • New signs or symptoms of infection that require alternative nonstudy treatment for the treatment of a cUTI due to an appropriate gram-negative uropathogen • Requirement of antibiotic therapy beyond the protocol-defined treatment duration of 14 days • Death related to cUTI
Indeterminate	Trial data are not available for evaluation of efficacy for any reason, including death during the trial period unrelated to the cUTI or extenuating circumstances, which preclude classification as cure, partial improvement, or failure (eg, participant is lost to follow-up).

cUTI = complicated urinary tract infection; EOIV = End of IV Treatment; EOT = End of Treatment; IV = intravenous; TOC = Test of Cure
a Clinical success rate was defined at the EOT and TOC visits as the proportion of participants in the analysis population who had a clinical response of "cure."
b The clinical success rate at the EOIV visit was defined as the proportion of participants in the analysis population who had a clinical response of "cure" or "partial improvement." The definition for clinical success at the EOIV visit included "partial improvement" to accommodate those participants with partial improvement who were switched to oral step-down therapy at this time point. For participants who received IV study treatment only (without optional oral step-down therapy), a separate assessment was not performed at the EOT Visit; the EOIV visit served as the EOT Visit.

Microbiological outcome categories

Outcome	Definition
Eradication	A postbaseline urine culture shows all uropathogens found at baseline at $\geq 10^5$ CFU/mL are reduced to $<10^4$ CFU/mL.
Persistence	A postbaseline urine culture shows the uropathogen(s) found at baseline at $\geq 10^5$ CFU/mL persist(s) at $\geq 10^4$ CFU/mL.
Indeterminate	No appropriate urine culture result available.

CFU = colony-forming units
The per-pathogen microbiological outcome will be determined for each uropathogen isolated by the Sponsor from a baseline study-qualifying culture. In order for the participant to have a per-participant microbiological response of eradication, each baseline pathogen must have had a microbiological response of eradication. Eradication will be considered a favorable microbiological response.

Sample size

This was an estimation trial; no formal statistical testing was to be performed for the efficacy or safety endpoints. Due to enrolment challenges the protocol was amended which led to a lower total enrolment than originally planned (i.e., 240 participants). The amendment was accepted by the PDCO. A total of 228 participants were enrolled across both studies, i.e., 134 participants in P034 and 94 participants in P035.

Randomisation

Treatment randomisation was to be stratified across the following 5 age groups:

- Group 1: Ages 12 to <18 years
- Group 2: Ages 6 to <12 years
- Group 3: Ages 2 to <6 years
- Group 4: Ages 3 months to <2 years
- Group 5: Ages birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <3 months

Blinding (masking)

A double-blinding technique with in-house blinding was to be used.

Statistical methods

There were no prespecified statistical hypotheses for this trial. Secondary efficacy endpoints were included to provide point estimates of the efficacy of each treatment regimen; the study was not powered for formal hypothesis testing of between treatment group comparisons.

Descriptive summaries were provided for each of the primary and secondary variables. In general, summaries were presented by cohort, treatment group and overall, for treatment group across all cohorts. The Safety analysis set was used for summaries and listings. Clinical response outcomes were summarised by cohort, treatment group and overall, for each treatment in the mMITT, CE and ME analysis sets (defined below).

Analysis sets

Safety analysis population: the APaT (=All Participants as Treated) population consisted of all randomised participants who received any amount of study treatment. This population was used for the analysis of safety data.

Efficacy analyses were based on the microbiological modified intent-to-treat (mMITT), clinically evaluable (CE) and microbiologically evaluable (ME) populations.

Definitions of efficacy analysis populations in P034 in AP/cUTI

- mMITT: the mMITT population served as the primary population for the analyses of clinical response and microbiological eradication rate. This population was a subset of randomised participants who received any amount of study treatment and had at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture (a baseline study-qualifying urine culture had to contain 1 and not more than 2 gram-negative bacterial isolates at $\geq 10^5$ CFU/mL each).
- CE: the CE population served as the secondary population for the analysis of clinical response data in this study. This population was a subset of the mMITT population who adhered to study procedures, did not have a significant protocol deviation impacting efficacy assessment, and received a minimum amount of study therapy. Participants with an indeterminate clinical outcome were excluded from the CE population.
- ME: the ME population served as the secondary population for the analysis of microbiological data in this study. This population was a subset of the CE population who had an interpretable urine culture at the visit of interest within the visit window.

Results

Participant flow

A total of 143 participants were screened and 134 were randomised (101 in the C/T group and 33 in the MERO group). All non-randomised participants were screen failures.

Table 21: *Disposition of participants - All randomised participants – Study P034*

	Group 1 12 to <18 y C/T		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	15		5		24		8		22		7	
Study Disposition												
Completed	15	(100.0)	5	(100.0)	23	(95.8)	8	(100.0)	22	(100.0)	7	(100.0)
Discontinued	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Other	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	Group 4 3 mo to <2 y C/T		Group 4 3 mo to <2 y MERO		Group 5 Birth to < 3 mo C/T		Group 5 Birth to < 3 mo MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	24		7		16		6		101		33	
Study Disposition												
Completed	22	(91.7)	7	(100.0)	15	(93.8)	6	(100.0)	97	(96.0)	33	(100.0)
Discontinued	2	(8.3)	0	(0.0)	1	(6.3)	0	(0.0)	4	(4.0)	0	(0.0)
Withdrawal By Parent/Guardian	2	(8.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.0)	0	(0.0)
Other	0	(0.0)	0	(0.0)	1	(6.3)	0	(0.0)	1	(1.0)	0	(0.0)

C/T = ceftolozane/tazobactam, MERO = meropenem, y = Years, mo = Months
Each participant is counted once based on the latest corresponding disposition record.

Source: [P034MK7625A: adam-adsl]

Numbers analysed

Table 22: *Summary of analysis populations - all randomised participants – Study P034*

Population	C/T		Mero		Total	
	n	(%)	n	(%)	n	(%)
All Randomized Participants	101		33		134	
Treated Population	100	99.0	33	100.0	133	99.3
Microbiological Modified Intent-to-Treat Population	71	70.3	24	72.7	95	70.9
Clinically Evaluable at EOIV Population	67	66.3	21	63.6	88	65.7
Clinically Evaluable at EOT Population	66	65.3	21	63.6	87	64.9
Clinically Evaluable at TOC Population	48	47.5	17	51.5	65	48.5
Microbiologically Evaluable at EOIV Population	60	59.4	21	63.6	81	60.4
Microbiologically Evaluable at EOT Population	58	57.4	20	60.6	78	58.2
Microbiologically Evaluable at TOC Population	44	43.6	17	51.5	61	45.5
C/T=ceftolozane/tazobactam, MERO=meropenem, EOIV=End of IV Treatment Visit, EOT=End of Treatment Visit, TOC=Test of Cure Visit n=Number of participants in specific category N=Number of participants in the randomized population Percentages are calculated as 100 x (n/N).						

Source: [P034MK7625A: analysis-adsl]

The most common reason for exclusion from all populations (mMITT and therefore consequently also in CE and ME) was "did not have at least 1 qualifying baseline uropathogen". This included no culture taken, a negative culture or no growth at baseline, or sub-threshold growth of a qualifying pathogen.

In total 28.4% of the patients were excluded for this reason from the mMITT population.

It is noted that in the CE population at TOC, 17.8% in the C/T group vs. 12.1% in the MERO group were excluded due to "confounding antibacterial post-treatment".

A majority of the treated participants in both treatment groups completed IV study medication (69/100, 69.0% in the C/T group vs. 24/33, 72.7% in the MERO group). The most common reason for discontinuation of IV study medication was lack of qualifying event (i.e., lack of a study-qualifying baseline urine culture) in both groups (27/100, 27.0% in the C/T group and 8/33, 24.2% in the MERO group).

In both treatment groups, of those participants who completed IV study medication, most switched to oral step-down therapy and all of these patients completed the study.

Recruitment

First patient visit: 26 April 2018, last patient visit: 03 December 2020, database lock date: 22 January 2021. The study was conducted at 28 study sites in the following 8 countries (number of patients randomised): Greece (36 patients), Hungary (22 patients), Mexico (9 patients), Poland (17 patients), Russia (8 patients), Turkey (14 patients), Ukraine (22 patients) and the US (6 patients).

Conduct of the study

Protocol amendments

Amendment	Date of Issue	Overall Rationale
Amendment 1 (Ukraine specific amendment) (MK-7625A-034-01)	30-APR-2018	Country-specific required amendment to exclude enrollment of participants <3 months old (Group 5) in Ukraine.
Amendment 2 (MK-7625A-034-02)	26-APR-2019	Enrollment targets for Groups 3-5 were applied across the present trial in pediatric participants with cUTI (MK-7625A-034) and the companion trial in pediatric participants with cIAI (MK-7625A-035).
Amendment 3 (MK-7625A-034-03)	14-SEP-2020	Due to enrollment challenges in the remaining age groups in both this trial in pediatric participants with cUTI (MK-7625A-034) and also in the companion trial in pediatric participants with cIAI (MK-7625A-035), individual study age group minimum requirements for Groups 3-5 were removed in both studies, and the overall combined enrollment minimum targets for Groups 3 and 5 were reduced to facilitate more timely availability of these important pediatric data to health care providers and patients. These changes do not impact the key goals or scientific validity of either study.

Please refer to study P035 below for details.

Protocol deviations

Important protocol deviations were reported for 29 (29.0%) participants in the C/T treatment group and 7 (21.2%) in the MERO treatment group.

No important protocol deviations were classified as serious GCP compliance issues.

It is noted that for 10% of the patients in the C/T group vs. none in the MERO group, no urine culture was obtained where required by protocol.

Baseline data

Table 23: *Participant characteristics - all randomised participants – Study P034*

	Group 1 12 to <18 y C/T		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T		Group 3 2 to <6 y MERO		Group 4 3 mo to <2 y C/T	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	15		5		24		8		22		7		24	
Sex														
Male	5	(33.3)	1	(20.0)	1	(4.2)	2	(25.0)	6	(27.3)	1	(14.3)	11	(45.8)
Female	10	(66.7)	4	(80.0)	23	(95.8)	6	(75.0)	16	(72.7)	6	(85.7)	13	(54.2)
Age (Years)														
12 - < 18 (Years)	15	(100.0)	5	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
6 - < 12 (Years)	0	(0.0)	0	(0.0)	24	(100.0)	8	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
2 - < 6 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	22	(100.0)	7	(100.0)	0	(0.0)
3 (Months) - < 2 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	24	(100.0)
Birth - < 3 (Months)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Participants with data	15		5		24		8		22		7		24	
Mean	15.342		16.140		8.219		8.729		3.928		3.521		0.966	
SD	1.5869		1.8839		1.6930		1.8823		0.8964		1.3643		0.4108	
Median	15.400		16.362		7.659		9.007		3.884		3.080		0.989	
Range	12.164 to 17.408		13.227 to 17.800		6.063 to 11.948		6.038 to 11.660		2.318 to 5.808		2.052 to 5.606		0.260 to 1.696	

	Group 4 3 mo to <2 y MERO		Group 5 Birth to < 3 mo C/T		Group 5 Birth to < 3 mo MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	7		16		6		101		33	
Sex										
Male	5	(71.4)	13	(81.3)	4	(66.7)	36	(35.6)	13	(39.4)
Female	2	(28.6)	3	(18.8)	2	(33.3)	65	(64.4)	20	(60.6)
Age (Years)										
12 - < 18 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	15	(14.9)	5	(15.2)
6 - < 12 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	24	(23.8)	8	(24.2)
2 - < 6 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	22	(21.8)	7	(21.2)
3 (Months) - < 2 (Years)	7	(100.0)	0	(0.0)	0	(0.0)	24	(23.8)	7	(21.2)
Birth - < 3 (Months)	0	(0.0)	16	(100.0)	6	(100.0)	16	(15.8)	6	(18.2)
Participants with data	7		16		6		101		33	
Mean	0.795		0.121		0.137		5.336		5.502	
SD	0.5971		0.0475		0.0662		5.2538		5.7466	
Median	0.499		0.112		0.140		3.808		3.080	
Range	0.285 to 1.929		0.063 to 0.214		0.027 to 0.236		0.063 to 17.408		0.027 to 17.800	

	Group 1 12 to <18 y C/T		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T		Group 3 2 to <6 y MERO		Group 4 3 mo to <2 y C/T	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Race														
Asian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
White	15	(100.0)	5	(100.0)	24	(100.0)	8	(100.0)	22	(100.0)	7	(100.0)	23	(95.8)
Ethnicity														
Hispanic Or Latino	0	(0.0)	0	(0.0)	2	(8.3)	2	(25.0)	4	(18.2)	1	(14.3)	1	(4.2)
Not Hispanic Or Latino	15	(100.0)	5	(100.0)	21	(87.5)	6	(75.0)	18	(81.8)	6	(85.7)	16	(66.7)
Not Reported	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Unknown	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)	6	(25.0)
Region														
North America	0	(0.0)	0	(0.0)	3	(12.5)	2	(25.0)	4	(18.2)	1	(14.3)	1	(4.2)
Europe	15	(100.0)	5	(100.0)	21	(87.5)	6	(75.0)	18	(81.8)	6	(85.7)	23	(95.8)
Baseline Diagnosis														
Pyelonephritis	14	(93.3)	2	(40.0)	16	(66.7)	6	(75.0)	17	(77.3)	4	(57.1)	19	(79.2)
cLUTI	1	(6.7)	3	(60.0)	8	(33.3)	2	(25.0)	5	(22.7)	3	(42.9)	5	(20.8)
Bacteremia at Baseline														

	Group 4 3 mo to <2 y MERO		Group 5 Birth to < 3 mo C/T		Group 5 Birth to < 3 mo MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Race										
Asian	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)
White	7	(100.0)	16	(100.0)	6	(100.0)	100	(99.0)	33	(100.0)
Ethnicity										
Hispanic Or Latino	1	(14.3)	2	(12.5)	1	(16.7)	9	(8.9)	5	(15.2)
Not Hispanic Or Latino	6	(85.7)	11	(68.8)	4	(66.7)	81	(80.2)	27	(81.8)
Not Reported	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)
Unknown	0	(0.0)	3	(18.8)	1	(16.7)	10	(9.9)	1	(3.0)
Region										
North America	1	(14.3)	2	(12.5)	1	(16.7)	10	(9.9)	5	(15.2)
Europe	6	(85.7)	14	(87.5)	5	(83.3)	91	(90.1)	28	(84.8)
Baseline Diagnosis										
Pyelonephritis	6	(85.7)	15	(93.8)	6	(100.0)	81	(80.2)	24	(72.7)
cLUTI	1	(14.3)	1	(6.3)	0	(0.0)	20	(19.8)	9	(27.3)
Bacteremia at Baseline										

	Group 1 12 to <18 y C/T		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T		Group 3 2 to <6 y MERO		Group 4 3 mo to <2 y C/T	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Yes	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.1)	0	(0.0)	0	(0.0)
No	14	(93.3)	5	(100.0)	24	(100.0)	8	(100.0)	20	(90.9)	7	(100.0)	24	(100.0)
Urine sample collected via urinary catheter														
Yes	1	(6.7)	0	(0.0)	3	(12.5)	0	(0.0)	4	(18.2)	0	(0.0)	20	(83.3)
No	14	(93.3)	5	(100.0)	21	(87.5)	8	(100.0)	18	(81.8)	7	(100.0)	4	(16.7)
Height (cm)														
Participants with data	15		5		24		8		22		7		24	
Mean	163.7		161.8		130.4		130.8		101.7		99.4		72.3	
SD	8.32		2.68		14.31		9.99		7.44		9.91		6.72	
Median	162.0		160.0		126.5		130.8		103.8		98.0		72.5	
Range	147.0 to 178.0		160.0 to 166.0		100.0 to 157.0		115.0 to 144.0		89.0 to 113.5		83.0 to 116.0		56.6 to 88.0	
Weight (kg)														
Participants with data	15		5		24		8		22		7		24	
Mean	50.63		55.60		30.91		29.60		15.78		16.43		8.45	
SD	8.539		6.427		12.335		6.271		2.269		3.608		1.655	
Median	52.00		54.00		27.90		28.40		16.00		16.70		8.45	
Range	33.00 to 63.00		50.00 to 65.00		12.00 to 75.30		21.60 to 39.00		12.90 to 20.00		11.00 to 23.00		5.20 to 11.00	

	Group 4 3 mo to <2 y MERO		Group 5 Birth to < 3 mo C/T		Group 5 Birth to < 3 mo MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Yes	1	(14.3)	2	(12.5)	2	(33.3)	5	(5.0)	3	(9.1)
No	6	(85.7)	14	(87.5)	4	(66.7)	96	(95.0)	30	(90.9)
Urine sample collected via urinary catheter										
Yes	5	(71.4)	11	(68.8)	5	(83.3)	39	(38.6)	10	(30.3)
No	2	(28.6)	5	(31.3)	1	(16.7)	62	(61.4)	23	(69.7)
Height (cm)										
Participants with data	7		16		6		101		33	
Mean	70.0		57.1		56.8		103.7		102.5	
SD	4.56		4.21		1.72		37.12		37.67	
Median	68.5		57.5		57.0		102.0		98.0	
Range	65.0 to 78.0		51.0 to 66.0		55.0 to 59.0		51.0 to 178.0		55.0 to 166.0	
Weight (kg)										
Participants with data	7		16		6		101		33	
Mean	7.97		4.72		4.77		21.06		21.64	
SD	1.425		0.933		0.715		16.987		17.689	
Median	7.50		4.71		4.75		15.50		16.70	
Range	6.39 to 9.77		2.60 to 6.18		3.81 to 5.70		2.60 to 75.30		3.81 to 65.00	

	Group 1 12 to <18 y C/T		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T		Group 3 2 to <6 y MERO		Group 4 3 mo to <2 y C/T	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Baseline Creatinine Clearance (ml/min/1.73 m2)[a]														
CrCl >= 80	11	(73.3)	4	(80.0)	20	(83.3)	7	(87.5)	16	(72.7)	4	(57.1)	19	(79.2)
CrCl>=50 - <80	4	(26.7)	1	(20.0)	4	(16.7)	1	(12.5)	6	(27.3)	3	(42.9)	5	(20.8)
CrCl>=30 - <50	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Participants with data	15		5		24		8		22		7		24	
Mean	91.108		84.594		102.629		110.423		107.267		104.713		111.397	
SD	14.8124		17.0903		24.2610		28.2161		36.8772		31.4298		52.9010	
Median	93.881		84.718		105.792		107.421		103.151		106.548		106.993	
Range	67.158 to 124.131		60.073 to 108.328		51.212 to 155.482		63.746 to 159.885		66.080 to 230.411		74.187 to 158.846		50.478 to 321.222	
Failure of Prior Antibacterial Therapy														
Yes	1	(6.7)	0	(0.0)	2	(8.3)	1	(12.5)	3	(13.6)	0	(0.0)	1	(4.2)
No	14	(93.3)	5	(100.0)	22	(91.7)	7	(87.5)	19	(86.4)	7	(100.0)	23	(95.8)

	Group 4 3 mo to <2 y MERO		Group 5 Birth to < 3 mo C/T		Group 5 Birth to < 3 mo MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Baseline Creatinine Clearance (ml/min/1.73 m2)[a]										
CrCl >= 80	6	(85.7)	5	(31.3)	1	(16.7)	71	(70.3)	22	(66.7)
CrCl>=50 - <80	1	(14.3)	11	(68.8)	4	(66.7)	30	(29.7)	10	(30.3)
CrCl>=30 - <50	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	1	(3.0)
Participants with data	7		16		6		101		33	
Mean	106.637		76.721		71.673		99.908		97.450	
SD	28.0302		27.5471		36.6816		36.7719		31.2398	
Median	120.596		64.688		59.903		100.200		94.400	
Range	60.590 to 135.164		51.195 to 128.030		36.509 to 140.906		50.478 to 321.222		36.509 to 159.885	
Failure of Prior Antibacterial Therapy										
Yes	0	(0.0)	0	(0.0)	0	(0.0)	7	(6.9)	1	(3.0)
No	7	(100.0)	16	(100.0)	6	(100.0)	94	(93.1)	32	(97.0)

C/T=ceftolozane/tazobactam, cLUTI=complicated lower uniary tract infection, MERO= meropenem, mo = Months, y = Years
Age was derived in years with 3 decimals, from data collected in years and months when subjects were randomized. For subjects 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 = 0.019 years.)
[a] Creatinine clearance rates were calculated by the revised Schwartz equation at baseline.

Source: [P034MK7625A: adam-adsl]

The CHMP considered that demographic and baseline characteristics were relatively well balanced between the treatment groups.

Overall, most of the patients was predominantly white, European, females with a median age of 3.8 years in the C/T group and 3.08 years in the MERO group and with normal renal function.

Of note, the majority of patients were diagnosed with pyelonephritis at baseline; 80.2% in the C/T group vs. 72.7% in the MERO group. Overall, a higher proportion of the patients in the C/T group had cUTI complicating factors compared to the patients in the MERO group.

Baseline microbiology

In total, 98.6% in the C/T group and 95.8% in the MERO group had one study qualifying baseline pathogen identified from urine cultures, thereby encompassing the mMITT population.

The most common baseline qualifying gram-negative uropathogens were *Escherichia coli* (C/T: 74.6%; MERO: 87.5%), *Klebsiella pneumonia* (8.5%; 4.2%), and *Pseudomonas aeruginosa* (7.0%; 8.3%).

Nearly all participants' infections at baseline were monomicrobial (C/T: 98.6%: MERO: 95.8%).

Overall, most baseline isolates tested were reported to be susceptible to C/T and MERO. For C/T there was one isolate of *Serratia marcescens* with intermediate susceptibility while for MERO 2 isolates; an *E coli* and a *K pneumoniae* were resistant.

Concomitant antibiotic medications

In the mMITT population, between the first dose of IV study medication and the EOT visit, no participants in either treatment group received any doses of concomitant non-study antibiotic therapy (excluding a protocol-allowed single dose of prophylactic antibiotics).

Between the first dose of IV study medication and the TOC visit, 25.4% (18/71) of participants in the C/T treatment group and 16.7% (4/24) in the MERO group, received at least one dose of concomitant antibiotic therapy; this included participants who received protocol-allowed antibiotic prophylaxis after the EOT visit, based on site-level standard of care for participants at increased risk of recurrent cUTI.

According to the MAH, only one patient each in the C/T group and the MERO group was excluded from the CE population due to "concomitant antibacterial violation". Only 1 patient (in the C/T group) was excluded from the CE population due to "prior antibacterial violation". However, 18/71 patients from the C/T group and 4/24 from the MERO group were excluded (CE population at TOC) due to "confounding antibacterial post-treatment".

The CHMP noted that participants who received non-study antibiotics that were stopped on the same date as the first dose of IV study medication or started on the same date as the EOT or TOC visit date (for which a start or stop time for the non-study antibiotic was not recorded), were not included as having received concomitant antibiotics. With this approach, it cannot be excluded that the non-study antibiotics might have had an effect on the study treatment for these patients. However, considering that the efficacy should be extrapolated from adults, this issue was not further pursued in the context of efficacy.

Extent of exposure

The median (range) number of IV treatment doses was comparable between participants in the C/T (13.5 [1.0 – 41.0]) and MERO (14 [3.0-29.0]) treatment groups.

The median (range) duration of IV treatment was comparable between participants in the C/T (4.5 [0.3 to 13.7] days) and MERO (4.6 [1.0 to 9.7] days) treatment groups. The majority of participants in the C/T (55.0%) received IV treatment for >3 to ≤7 days while in the MERO the majority received IV treatment for ≥ 1 to ≤ 3 days (39.4%) - *data not shown*. It is stated by the MAH though that only 2 participants received <9 doses of IV treatment due to 1 discontinuation due to an AE and 1 discontinuation due to withdrawal by parent/guardian.

The median (range) duration of overall treatment (i.e., IV only or IV + oral) was generally comparable between participants in the C/T (9.0 [0.3 to 14.2] days) and MERO (9.3 [1.0 to 14.6] days) treatment groups.

For those participants who switched to oral step-down treatment (C/T: 51/101 [50.5%]; MERO: 20/33 [60.6%]), the median (range) duration of oral treatment was comparable between participants in the C/T (6.3 [1.0 to 9.6] days) and MERO (6.2 [4.0 to 9.8] days) treatment groups. The most common oral step-down treatments (>10% in either treatment group) were cefixime, amoxicillin/clavulanate potassium, and cefuroxime.

Outcomes and estimation

Compliance with the overall treatment regimen (both IV and oral step-down) in the mMITT population was high in both treatment groups, with all participants being >90% compliant. Median overall treatment compliance was 100.0% in both the C/T and MERO groups.

Clinical success rates were high and comparable between both treatment groups at both the EOT visit and the TOC visit in the mMITT population, see table below.

Table 24: *Clinical response by visit - mMITT population – Study P034*

Visit Clinical Response	C/T			MERO			% Difference (C/T minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
Number of Participants	71			24			
End of Treatment (EOT) Visit							
Success	67	(94.4)	(86.39, 97.79)	24	(100.0)	(86.20, 100.00)	-5.6 (-14.09, 8.88)
Failure	4	(5.6)		0	(0.0)		
Observed Failure	2	(2.8)		0	(0.0)		
Observed Indeterminate	2	(2.8)		0	(0.0)		
Test of Cure (TOC) Visit							
Success	63	(88.7)	(79.31, 94.18)	23	(95.8)	(79.76, 99.26)	-7.3 (-17.99, 10.05)
Failure	8	(11.3)		1	(4.2)		
Observed Failure	4	(5.6)		1	(4.2)		
Observed Indeterminate	1	(1.4)		0	(0.0)		
Imputed Indeterminate	3	(4.2)		0	(0.0)		

C/T=ceftolozane/tazobactam, MERO=meropenem

[a] The 95% CIs of each treatment are unstratified Wilson CIs.

[b] The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights. If there is a zero count in any class of the stratum, the groups with the lower count will be pooled with its near age group stratum in the model.

The participants with a missing clinical response (eg. Indeterminate) are considered treatment failures.

Imputed indeterminate clinical response includes participants who had a clinical cure, partial improvement or indeterminate at the previous visit(s) and had missing clinical response at the specific visit.

Source: [P034MK7625A: adam-adsl; adeff]

The CHMP noted that in the mMITT population at TOC, 63/71 patients (88.7%) in the C/T group and 23/24 patients (95.8%) in the MERO group had a favourable clinical response. It was also noted that although the clinical success rates in the mMITT population at the TOC visit was generally high, it was lower in C/T group compared to MERO group. Clinical success rates at the EOT visit were generally consistent with those reported at the TOC visit. In the mMITT population at the EOIV visit, 67/71 patients (94.4%) in the C/T group and 24/24 patients (100%) in the MERO group had a favourable clinical response. Of note, the majority of the patients at the EOIV visit had only a partial improvement (50/71, 70.4% in the C/T arm vs. 20/24, 83.3% in the MERO group). Thus, these patients did not need further IV treatment with either C/T or MERO, but additional oral step-down therapy was still required. The definition for clinical success at the EOIV visit included "partial improvement" to accommodate those participants with partial improvement who were switched to oral step-down therapy at this time point.

The clinical response rates in the individual age-cohorts were in general consistent with that observed in the overall study population.

The Committee additionally noted that the lowest clinical response rates were reported in the age group 6 -< 12 years (this was also the case at EOT – *data not shown*).

The clinical success rate at EOIV, EOT and TOC in the CE population was also high and comparable between treatment groups (at TOC: C/T: 44/48 patients, 91.7% vs. 16/17 patients, 94.1% in the MERO group) – *data not shown*.

Of note, the efficacy results at the TOC visit will not solely reflect the effect of C/T or MERO, but also the effect from the oral step-down antibiotic therapy. In the P034 study, it was 51/100 patients in the C/T group and 20/33 patients in the MERO group (safety analysis population) who received oral step-down antibiotic treatment. However, it has to be kept in mind that for this application, it is the PK and safety data, which are critical for the final opinion. As previously mentioned, the use of oral step-down antibiotic treatment is considered acceptable, however, regarding the safety evaluation, it might hamper the assessment of possible drug-related AEs (please refer to the safety part of this Assessment Report). Concerning the PK analyses, these will not be affected as blood was collected from all subjects while they still received IV study treatment. However, in order to better reflect the results achieved after treatment with only ceftolozane/tazobactam, the results for the exploratory efficacy endpoint clinical success at the EOIV visit, have also been included. It has to be emphasized though that, as mentioned above, the main proportion of the patients in each arm only had partial improvement and were not assessed as cured solely by the IV antibiotic treatment.

Study P034 was descriptive in nature and not powered for inferential testing as the intention was to provide descriptive statistics only. Based on the 3:1 randomisation, meaningful interpretation of direct comparisons is not possible. Consequently, no further evaluation or pursue of issues regarding the efficacy results will be made. The basis for approval of this variation lies on the PK and safety data, not efficacy.

Table 25: *Per-participant microbiological outcome by visit - mMITT population – Study P034*

Visit Microbiological Outcome Outcome Categories	C/T n	(%)	95% CI[a]	MERO n	(%)	95% CI[a]	% Difference (C/T minus MERO) 95% CI[b]
Number of Participants	71			24			
End of Treatment (EOT) Visit							
Eradication	66	(93.0)	(84.55, 96.95)	23	(95.8)	(79.76, 99.26)	-3.4 (-12.67, 13.41)
Persistence	5	(7.0)		1	(4.2)		
Observed Persistence	1	(1.4)		0	(0.0)		
Observed Indeterminate	0	(0.0)		1	(4.2)		
Imputed Indeterminate	4	(5.6)		0	(0.0)		
Test of Cure (TOC) Visit							
Eradication	60	(84.5)	(74.35, 91.12)	21	(87.5)	(69.00, 95.66)	-3.0 (-17.13, 17.40)
Persistence	11	(15.5)		3	(12.5)		
Observed Persistence	4	(5.6)		3	(12.5)		
Imputed Indeterminate	7	(9.9)		0	(0.0)		

C/T=ceftolozane/tazobactam, MERO=meropenem

[a] The 95% CIs of each treatment are unstratified Wilson CIs.

[b] The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights. If there is a zero count in any class of the stratum, the groups with the lower count will be pooled with its near age group stratum in the model.

Participants with a missing or indeterminate microbiological outcome are considered persistence.

Imputed indeterminate microbiological outcome includes participants who had missing microbiological outcome at the specific visit.

Source: [P034MK7625A: adam-adsl; adeff]

The CHMP noted that per-participant microbiological eradication rates at the EOT visit were generally consistent with those reported at the TOC visit.

In the mMITT population at EOIV, 68/71 patients (95.8%) in the C/T group vs. 24/24 patients (100%) in the MERO group had microbiological success (i.e., eradication).

The clinical response rates in the individual age-cohorts were in general consistent with that observed in the overall study population (*data not shown*).

The per-participant microbiological eradication rates at both at EOT and TOC in the ME population were generally consistent with those reported in the mMITT populations (at TOC: 40/44 patients, 90.9% in the C/T group vs. 15/17 patients, 88.2% in the MERO group).

Emergent infections

No participants in either treatment group had a superinfection. Three (4.2%) participants (all in the C/T group) had at least 1 new infection. One (1.4%) participant had a new infection of *Klebsiella pneumoniae*, and 2 (2.8%) participants had a new infection of *Pseudomonas aeruginosa*.

4.5. Clinical efficacy in paediatric cIAI

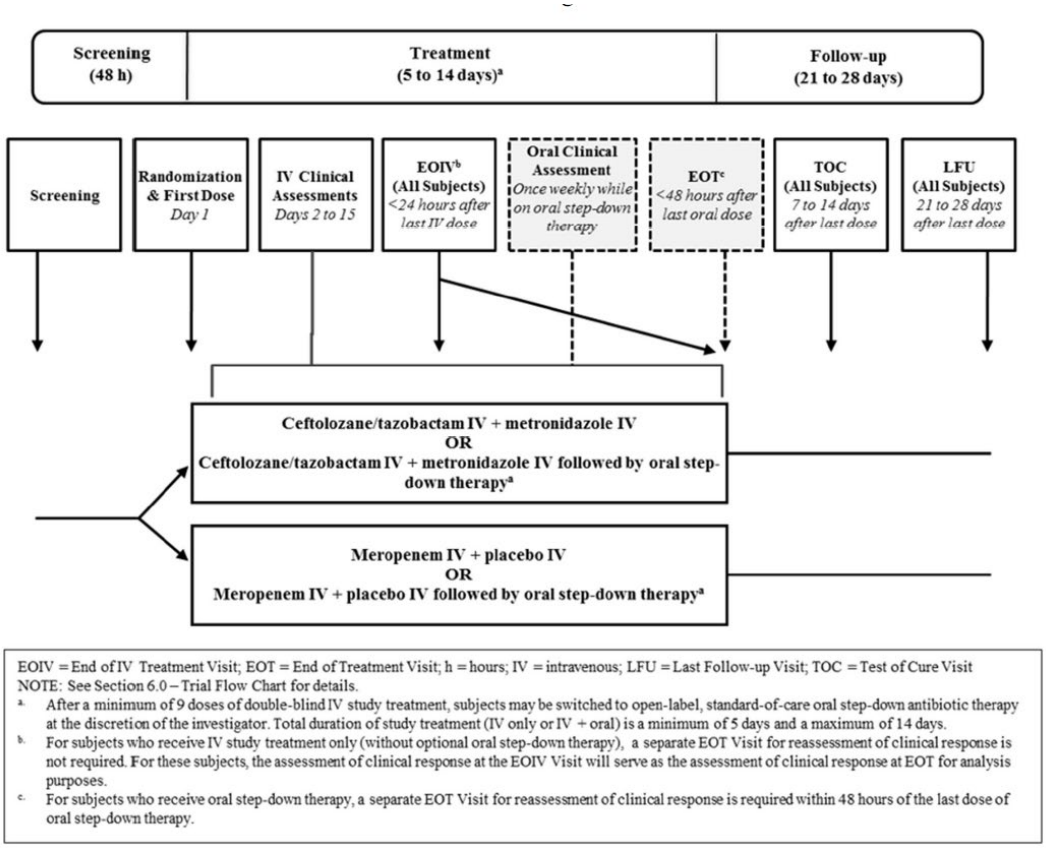
4.5.1. Main study

P035MK7625A (abbreviated P035) – cIAI

Clinical study to evaluate safety, tolerability and efficacy of ceftolozane and tazobactam when given in combination with metronidazole, compared with meropenem in paediatric patients from birth to less than 18 years of age with complicated intra-abdominal infections (cIAIs).

Methods

Study P035 was a Phase 2, randomised (3:1), active comparator-controlled, multicentre and double-blind study conducted in paediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cIAI of sufficient severity requiring hospitalisation and treatment with intravenous (IV) antibiotics. The study design of study P035 is shown in the figure below.



EOIV = End of IV Treatment Visit; EOT = End of Treatment Visit; h = hours; IV = intravenous; LFU = Last Follow-up Visit; TOC = Test of Cure Visit
NOTE: See Section 6.0 – Trial Flow Chart for details.

a. After a minimum of 9 doses of double-blind IV study treatment, subjects may be switched to open-label, standard-of-care oral step-down antibiotic therapy at the discretion of the investigator. Total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.
b. For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate EOT Visit for reassessment of clinical response is not required. For these subjects, the assessment of clinical response at the EOIV Visit will serve as the assessment of clinical response at EOT for analysis purposes.
c. For subjects who receive oral step-down therapy, a separate EOT Visit for reassessment of clinical response is required within 48 hours of the last dose of oral step-down therapy.

Figure 12: *Study design of Study P035*

Of note, efficacy data beyond the TOC visit were not collected in the study.

Study participants

Main inclusion criteria

1. Must be male or female from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age.

2. Had to require IV antibacterial therapy for the treatment of presumed or documented cIAI as demonstrated by either:

Operative diagnosis (laparotomy, laparoscopy or percutaneous drainage) of cIAI, defined as evidence of infection within the abdominal cavity extending beyond the hollow viscus of origin into the peritoneal space as demonstrated by either abscess formation or peritonitis.

OR

Preoperative diagnosis of cIAI, defined as meeting both of the criteria below:

a) Clinical evidence of cIAI as indicated by one or more systemic signs or symptoms that accompany cIAI, such as fever, leukocytosis, hypotension, abdominal pain, nausea/vomiting, anorexia, abdominal mass on clinical examination, or altered mental status.

b) Radiographic evidence consistent with intra-abdominal abcess or peritonitis.

3. Had to have an operative procedure for the current diagnosis and management of cIAI planned or completed within 24 hours of the first dose of an antibacterial drug. (Participants with a diagnosis of NEC

were exempt from this inclusion criterion and were not required to have surgery planned or completed in order to be eligible for enrolment.)

Main exclusion criteria

1. Had received potentially therapeutic antibacterial therapy (e.g., with gram-negative activity) for a duration of more than 24 hours during the 48 hours preceding the first dose of study treatment, unless the participant was considered to be failing antibiotic therapy for cIAI.

NOTE: A participant who was considered to be failing a previous antibiotic regimen was required to meet all of the following criteria:

a. Had received the systemic antibacterial treatment for at least 48 hours

b. Had clinical and operative or radiographic findings clearly indicating ongoing infection

c. Had planned operative intervention no more than 24 hours after the first dose of study treatment

d. Had not received any further non-study antibiotics post-operatively

2. Had any of the following conditions, current devices, or procedures as noted in the protocol:

a. Intractable cIAI that the Investigator anticipated would require more than 14 days of study treatment

b. Abdominal wall abscess

c. Small bowel obstruction

d. Ischemic bowel disease without perforation

e. Traumatic bowel perforation with surgery within 12 hours of perforation

f. Perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation (these were considered situations of peritoneal soiling before the infection had become established)

g. Suspected uncomplicated intra-abdominal infection (e.g., cholecystitis without rupture or extension beyond the gallbladder wall)

h. Acute suppurative cholangitis

i. Infected necrotizing pancreatitis

j. Pancreatic abscess

3. Had moderate or severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the Bedside Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration.

4. Had one or more of the laboratory abnormalities as noted in the protocol in a specimen obtained at baseline:

a. ANC <1000/mm^3

b. AST or ALT ≥3× ULN

c. Total bilirubin ≥2× ULN (if 7 to ≤28 days of age and breastfeeding, total bilirubin >10 mg/dL OR ≥2× ULN)

5. Was receiving or expected to receive immunosuppressive agents, probenecid, valproic acid, disulfiram, ergot derivatives, or non-study systemic (IV or oral) antibacterial treatments

> NOTE: Subjects who required empiric enterococcal coverage for the index cIAI may receive concomitant therapy with an enterococcal antibiotic with activity limited to gram-positive coverage (e.g., vancomycin, daptomycin, teicoplanin, linezolid). One dose of prophylactic antibiotic with gram-negative activity is allowed.
>
> Subjects who required empiric antifungal coverage for the index cIAI may receive concomitant antifungal coverage with an azole, echinocandin, or polyene antifungal as chosen by the investigator based on local standard of care.

6. Had an immunocompromising condition or receipt of immunosuppressive therapy.

The CHMP considered that, according to the inclusion and exclusion criteria, it can be concluded that patients with complicated intra-abdominal infections are enrolled as the required infections will lead to infectious processes proceeding beyond the organ that is the source of the infection. Simple appendicitis is not explicitly mentioned in the exclusion criteria. However, it would be covered by the general term "Suspected uncomplicated intra-abdominal infection". Of note, originally the protocol (dated March 2017) had a requirement that the maximum percentage of patients enrolled with complicated appendicitis should be 60%. Subsequently, the MAH wanted to remove this requirement, but the PDCO recommended retaining a limit of 90% (April 2019). However, in the last modification of the studies, the MAH again expressed the wish to delete this requirement entirely (Amendment 3, September 2020). Despite the MAH's efforts to enrich the study population for other cIAI diagnoses, it turned out to be difficult to recruit non-appendicitis subjects. On this occasion the removal was accepted by the PDCO (see also below, under "Conduct of the study").

Overall, the included types of intra-abdominal infections could be categorised as infections that are neither so limited that just surgery would be curative, nor so complicated that several additional confounding factors would affect curation.

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

Treatments

Please refer to "Treatments" for Study P034 above.

The difference from Study P034 was that subjects in the ceftolozane/tazobactam arm received adjunctive therapy with IV metronidazole. The addition of metronidazole in combination with ceftolozane/tazobactam ensured coverage of intra-abdominal infections caused by anaerobic bacteria.

The dose of metronidazole was 10 mg/kg (maximum 1.5 g/day for all age groups apart from the age group birth to < 3 months. Data on the PK and ideal dosing of metronidazole in paediatric patients are limited, especially for paediatric patients less than 1 month of age. As a result, dosing recommendations are highly variable without an accepted standard. Suggested dosing recommendations for subjects <1 month old outlined in the protocol were based on one of the more commonly used dosing schedules (Cohen-Wolkowiez et al, 2012). However, to allow for potential variations in metronidazole dosing between different sites participating in this trial, the protocol allowed for the use of site - specific standard-of-care dosing in subjects <1 month of age.

The total duration of study treatment (IV only or IV + oral) was a minimum of 5 days and a maximum of 14 days.

The CHMP considered that metronidazole was added for anaerobic coverage, in line with clinical recommendations. The chosen doses for the youngest children were, overall, in line with what is commonly recommended.

The doses chosen for ceftolozane/tazobactam were based on population PK models, exposure data and PTA criteria, please refer to the clinical pharmacology section for more details.

The proposed treatment duration of 5-14 days and the option to switch to oral therapy is generally in line with current IDSA guideline 2010 and World Society of Emergency Surgery (WSES) guidelines 2017 for management of intra-abdominal infections. These guidelines state that patients with cIAI require 4 to 7-day courses of antibiotic therapy, either as oral or parenteral treatment. Switch from parenteral therapy to oral therapy is recommended after at least three days as long as they are clinically improving, according to pre-defined objective criteria. In the current study, clinical improvement at EOIV was defined, and had to be fulfilled before allowing a switch to oral therapy. Thus, the strategy of switching from IV to oral treatment to complete a short course of therapy is considered acceptable.

Options for step-down therapy recommended by the MAH were: β-lactam/BLI combination; second- or third-generation cephalosporin in combination with MTZ; quinolone (if ciprofloxacin or levofloxacin then used in combination with MTZ) which was acceptable to the CHMP.

Objectives

Primary objectives and secondary objectives

Please refer to study P034 (AP/cUTI) above.

Outcomes/endpoints

Primary endpoint

Please refer to study P034 (AP/cUTI) above.

Secondary endpoints

1. Clinical success rate at the EOT and TOC Visits, defined as the proportion of subjects in the analysis population who have a clinical response of cure.
2. Per-participant microbiological success rate at the EOT and TOC Visits, defined as the proportion of participants in the analysis population who have microbiological eradication or presumed eradication of all baseline pathogens.

Clinical outcome categories

Outcome	Definition
Cure [a]	Complete resolution or marked improvement in signs and symptoms of the cIAI or return to preinfection signs and symptoms such that no further antibiotic therapy (IV or oral) or surgical or drainage procedure is required for treatment of the cIAI.
Partial improvement (only at the EOIV Visit [b] for participants who switch to oral step-down therapy)	Partial resolution of signs and symptoms of the cIAI such that no further IV antibiotic therapy is required for the treatment of the cIAI; however, additional oral step-down therapy is required.
Failure	Any of the following is considered a clinical outcome of failure: • Requirement of antibiotic therapy beyond the protocol-defined treatment duration of 14 days. • Persisting or recurrent infection within the abdomen requiring additional intervention, including nonstudy antibiotics or repeat surgical intervention. NOTE: Repeat percutaneous aspiration of an abscess within 72 hours of the original aspiration, without worsening clinical signs and symptoms, is not considered a failure. However, the need to repeat any procedure after 72 hours of study treatment to cure the infection should be considered a failure. Exploratory or diagnostic procedures with no evidence of an ongoing infection are not considered a failure. • Post-surgical wound infection with signs of local infection, such as purulent exudate, erythema, or warmth that requires additional antimicrobial therapy and/or nonroutine wound care. • Death related to IAI
Indeterminate	Trial data are not available for evaluation of efficacy for any reason, including death during the trial period unrelated to the cIAI or extenuating circumstances which preclude classification as cure, partial improvement, or failure (eg, participants is lost to follow-up).

cIAI = complicated intra-abdominal infection; EOIV = End of IV Treatment; EOT = End of Treatment; IAI=intra-abdominal infection; IV = intravenous; TOC = Test of Cure
a Clinical success rate was defined at the EOT and TOC visits as the proportion of participants in the analysis population who had a clinical response of "cure."
B The clinical success rate at the EOIV visit was defined as the proportion of participants in the analysis population who had a clinical response of "cure" or "partial improvement." The definition for clinical success at the EOIV visit included "partial improvement" to accommodate those participants with partial improvement who were switched to oral step-down therapy at this time point. For participants who received IV study treatment only (without optional oral step-down therapy), a separate assessment was not performed at the EOT visit; the EOIV visit served as the EOT visit.

Microbiological outcome categories

Outcome [a]	Definition
Eradication [b]	Absence of the baseline pathogen(s) in a postbaseline specimen appropriately obtained from the original site of infection.
Presumed eradication [b]	Absence of material to culture in a participant who was assessed as having partial improvement, or clinical cure.
Persistence	Presence of the baseline pathogen(s) in an appropriately obtained postbaseline specimen from the site of infection or surgical wound. NOTE: Cultures from indwelling drains were not considered appropriate.
Presumed persistence	Absence of material to culture in a participant who was assessed as a clinical failure.
Persistence acquiring resistance	Presence of baseline pathogen(s) in an appropriately obtained postbaseline specimen where the baseline pathogen(s) was susceptible to study treatment pretreatment and is resistant to study treatment post-treatment.
Indeterminate	• Baseline culture either not obtained or has no growth. • Postbaseline culture was not obtained and clinical assessment was not possible. • Any other circumstance that makes it impossible to define the microbiological response (eg, participant lost to follow-up).

a The per-pathogen microbiological outcome was determined for each baseline infecting pathogen isolated by the Sponsor.
B Eradication or presumed eradication was considered favorable microbiological responses. In order for the participant to have a favorable overall microbiological response (i.e., eradication or presumed eradication), it was required that each baseline pathogen have a favorable microbiological outcome.

Sample size, randomisation and blinding (masking)

Please refer to the description of study P034 (AP/cUTI) further above.

Statistical methods

Please refer to the description of study P034 (AP/cUTI) further above for details.

Analysis sets

Safety analysis population – also called the All Participants as Treated (APaT) population: consisted of all randomised participants who received any amount of study treatment.

Efficacy analyses were based on the modified intent-to treat (MITT), microbiological modified intent-to - treat (mMITT), clinically evaluable (CE) and microbiologically evaluable (ME) populations.

Definitions of efficacy analysis populations in P035 in cIAI

- MITT: the MITT population consisted of all randomised participants who received any amount of study treatment. Participants were categorised based on the IV study treatment that participants were randomised to, irrespective of what treatment they actually received.
- mMITT: the mMITT population was the subset of participants in the MITT population who had at least 1 pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment.
- CE: the CE population served as the secondary population for the analysis of clinical response data in this study. It was a subset of participants in the MITT population who adhered to trial procedures, did not have any significant protocol deviations impacting efficacy assessment and received a minimum number of study therapy, and had an evaluable clinical outcome at the visit of interest (EOT, TOC, and EOIV; an interpretable culture was not required at the visit of interest. All participants' eligibility status was reviewed and determined in a blinded manner prior to final

database lock. Participants with an indeterminate clinical outcome were excluded from the CE population.

- ME: the ME population served as the secondary population for the analysis of microbiological data in this study. It was the subset of participants in the CE population who had at least 1 causative pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment, at the visit of interest (EOT, TOC and EOIV).

Results

Participant flow

A total of 98 participants were screened and 94 were randomised (n=71 in the C/T+MTZ group and n=23 in the MERO group). The majority of non-randomised participants were screen failures.

Table 26: *Disposition of participants – All randomised participants – Study P035*

	Group 1 12 to <18 y C/T+MTZ		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T+MTZ		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T+MTZ		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	17		6		30		10		22		7	
Study Disposition												
Completed	15	(88.2)	5	(83.3)	29	(96.7)	8	(80.0)	21	(95.5)	7	(100.0)
Discontinued	2	(11.8)	1	(16.7)	1	(3.3)	2	(20.0)	1	(4.5)	0	(0.0)
Lost To Follow-Up	1	(5.9)	0	(0.0)	1	(3.3)	1	(10.0)	0	(0.0)	0	(0.0)
Site Randomized The Subject In Error And Was Discontinued As Per Sponsor's Advice	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Subject Did Not Meet Criteria After Randomization And Not Dosed.	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)
Subject Discontinued By Site After Consultation With Sponsor Due To Dispensing Error	1	(5.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)

	Group 4 3 mo to <2 y C/T+MTZ		Group 5 Birth to < 3 mo C/T+MTZ		Total C/T+MTZ		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1		1		71		23	
Study Disposition								
Completed	1	(100.0)	1	(100.0)	67	(94.4)	20	(87.0)
Discontinued	0	(0.0)	0	(0.0)	4	(5.6)	3	(13.0)
Lost To Follow-Up	0	(0.0)	0	(0.0)	2	(2.8)	1	(4.3)
Site Randomized The Subject In Error And Was Discontinued As Per Sponsor's Advice	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
Subject Did Not Meet Criteria After Randomization And Not Dosed.	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
Subject Discontinued By Site After Consultation With Sponsor Due To Dispensing Error	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)

C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole, mo = Months, y = Years
Each subject is counted once based on the latest corresponding disposition record.

Source: [P035MK7625A: adam-adsl]

The CHMP acknowledged that the majority of patients were enrolled in the older age cohorts. Of note, there was no patients in the age group 4 (3 months -< 2 years) and 5 (birth to < 3 months) in the MERO group and only 1 in each of these age groups in the C/T+MTZ group. The prevalence of cIAI is low in children under 6 years of age. Furthermore, in line with CHMP Addendum guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements, efficacy results presented in the initial marketing authorisation application for adults in the cIAI indication can be extrapolated to the paediatric population provided similar exposure. In addition, the efficacy results observed in the youngest children with AP/cUTI could be extrapolated to the same age cohorts for children with cIAI as these two infectious diseases are expected to have similar pathophysiology.

Numbers analysed

Table 27: *Summary of analysis populations – All Randomised Participants – Study P035*

Population	C/T+MTZ		MERO		Total	
	n	(%)	n	(%)	n	(%)
All Randomized Participants	71		23		94	
Modified Intent-to-Treat Population	70	98.6	21	91.3	91	96.8
Microbiological Modified Intent-to-Treat Population	63	88.7	19	82.6	82	87.2
Clinically Evaluable at EOIV Population	61	85.9	20	87.0	81	86.2
Clinically Evaluable at EOT Population	59	83.1	19	82.6	78	83.0
Clinically Evaluable at TOC Population	58	81.7	19	82.6	77	81.9
Microbiologically Evaluable at EOIV Population	56	78.9	18	78.3	74	78.7
Microbiologically Evaluable at EOT Population	54	76.1	17	73.9	71	75.5
Microbiologically Evaluable at TOC Population	53	74.6	17	73.9	70	74.5

C/T=ceftolozane/tazobactam , EOIV=End of IV Treatment Visit, EOT=End of Treatment Visit, MERO= Meropenem, MTZ=Metronidazole, TOC=Test of Cure Visit
n=Number of participants in specific category
N=Number of participants in the randomized population
Percentages are calculated as 100 x (n/N).

Source: [P035MK7625A: adam-adsl]

The most common reason for exclusion from the CE population for the C/T+MTZ group was "no clinical efficacy assessment or only indeterminate clinical assessments" (4 patients, 5.6% at the EOIV, 6 patients, 8.5% at the EOT and TOC visits) and "prior antibacterial violation" (5 patients, 7% for EOIV, EOT and TOC visits). Exclusions due to "concomitant antibacterial violation" comprised only 1 participant in all of the visits EOIV, EOT and TOC in the C/T+MTZ group. In the MERO group no patients were excluded due to "prior (or concomitant) antibacterial violation" and in regards to other reasons for exclusion it mainly affected only one patient.

Most of the treated participants in both treatment groups completed IV study medication (65/70, 92.9% in the C/T+MTZ group vs. 20/21, 95.2% in the MERO group). The most common reason for discontinuation of IV study medication was adverse events (n=2) in the C/T+MTZ group. These AEs were pneumonia in one patient, and pneumonia and abdominal sepsis in the second patient. None of the Aes leading to discontinuation were considered by the investigator to be drug-related, please refer to the Safety part of this Assessment Report for more information. No participant in the MERO group discontinued IV study medication (i.e., 1 participant in the MERO treatment group was incorrectly recorded as having discontinued due to "other" reason; this subject completed IV study therapy and was included in efficacy assessments).

In both treatment groups, of those participants who completed IV study medication, most switched to oral step-down therapy. All who switched to oral step-down therapy, apart from 1 participant in the C/T+MTZ group who discontinued due to lack of efficacy, completed the study.

Of note, no patients in the age group 3 months to < 2 years completed treatment (the one patient in the C/T+MTZ group who received treatment discontinued due to physician decision), and there was only one patient completing the treatment in the age group birth to < 3 months (in the C/T+MTZ group).

Recruitment

First participant first visit was 03 April 2018, last participant last visit was 16 March 2020, and database lock date was 22 January 2021.

Twenty-seven (27) centers in 11 countries randomised and enrolled participants into the study (number of patients randomised): Brazil (1), Hungary (11), Lithuania (8), Malaysia (3), Mexico (16), Russia (7), South Africa (6), Spain (10), Turkey (2), Ukraine (12) and the US (18).

Conduct of the study

Protocol amendments

The original protocol, dated 21-MAR-2017, was amended 3 times. Main changes in the planned conduct of the study implemented by protocol amendment(s) are shown below.

Amendment	Date of Issue	Overall Rationale
Amendment 1 (Ukraine-specific amendment) (MK-7625A-035-01)	30-APR-2018	Country-specific amendment to exclude enrollment of subjects <3 months old (Group 5) in Ukraine.
Amendment 2 (MK-7625A-035-02)	26-APR-2019	Enrollment targets for Groups 3–5 were applied across the present trial in pediatric subjects with cIAI (MK-7625A-035) and the companion trial in pediatric subjects with cUTI (MK-7625A-034).
Amendment 3 (MK-7625A-035-03)	14-SEP-2020	Due to enrollment challenges in the remaining age groups in both this trial in pediatric subjects with cIAI (MK-7625A-035) and also in the companion trial in pediatric subjects with cUTI (MK7625A-034), individual study age group minimum requirements for Groups 3–5 were removed in both studies, and the overall combined enrollment minimum targets for Groups 3 and 5 were reduced to facilitate more timely availability of these important pediatric data to health care providers and patients. These changes do not impact the key goals or scientific validity of either study.

The CHMP noted that all the amendments were implemented after the first subject first visit.

Amendment 1: In Ukraine, meropenem is not approved for use in children < 3 months of age and metronidazole is not approved for use in children < 2 years of age, therefore in this country enrolment was limited to subjects > 2 years old.

Amendment 2: enrolment targets for age groups 3-5 were applied across studies P034 (AP/cUTI) and P035 (cIAI) and thus patients from both studies would be pooled for the safety analysis. The PDCO agreed with the proposal of a pooled safety analysis in order to overcome the limitation imposed by the scarce number of young children with cIAI. However, it was pointed out that sufficient patients with cIAI should be included as cIAI can be of a more severe nature than AP/cUTI.

Furthermore, Amendment 2 also comprised an increase of the maximum percentage of patients enrolled with complicated appendicitis from 60% to 90%. This change was also approved by the PDCO.

Amendment 3: the sample size of the two studies P034 and P035 were reduced due to recruitment difficulties in connection with the COVID-19 pandemic. The MAH stated that the data gathered in the 222 subjects (originally planned sample size was 240, with 120 patients in each study) enrolled to date represented a robust database with which to analyse the primary endpoint of safety. It was also pointed out that pursuing further enrolment to the planned 240 subjects would substantially delay the finalising of the studies without any appreciable improvement in the ability of the study to achieve the goals of assessing the safety, PK and efficacy.

In addition, the MAH wanted to delete the requirement in study P035 that at least 10% of patients evaluable for primary analysis must have a diagnosis other than acute complicated appendicitis.

The PDCO acknowledged the MAH's arguments regarding recruitment issues due to COVID-19. Furthermore, the Committee concluded that the proposed reduced overall number of patients likely was acceptable and sufficient to draw conclusions on safety in the paediatric population. Moreover, in light of the already reduced patient numbers the PDCO also tended to agree with the requested deletion of the requirement that at least 10% of patients in study P035 must have a diagnosis other than acute complicated appendicitis. It was acknowledged that recruiting these patients were difficult and the MAH had made reasonable efforts to boost recruitment.

Protocol deviations

Important protocol deviations were reported for 22 (31.4%) participants in the C/T+MTZ group, and 7 (33.3%) participants in the MERO group.

No important protocol deviations were classified as a serious GCP compliance issue.

Baseline data

Table 28: *Participant characteristics – all randomised participants – Study P035*

	Group 1 12 to <18 y C/T+MTZ		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T+MTZ		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T+MTZ		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	17		6		30		10		22		7	
Sex												
Male	13	(76.5)	4	(66.7)	20	(66.7)	2	(20.0)	13	(59.1)	2	(28.6)
Female	4	(23.5)	2	(33.3)	10	(33.3)	8	(80.0)	9	(40.9)	5	(71.4)
Age (Years)												
12 - < 18 (Years)	17	(100.0)	6	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
6 - < 12 (Years)	0	(0.0)	0	(0.0)	30	(100.0)	10	(100.0)	0	(0.0)	0	(0.0)
2 - < 6 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	22	(100.0)	7	(100.0)
3 (Months) - < 2 (Years)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Birth - < 3 (Months)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Participants with data	17		6		30		10		22		7	
Mean	14.501		13.139		9.183		8.991		4.241		4.250	
SD	1.7773		0.3502		1.8070		1.7901		1.1657		0.5637	
Median	14.400		13.058		9.147		9.021		4.147		4.247	
Range	12.175 to 17.559		12.671 to 13.559		6.252 to 11.912		6.608 to 11.808		2.562 to 5.959		3.403 to 5.134	

	Group 4 3 mo to <2 y C/T+MTZ		Group 5 Birth to < 3 mo C/T+MTZ		Total C/T+MTZ		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1		1		71		23	
Sex								
Male	1	(100.0)	1	(100.0)	48	(67.6)	8	(34.8)
Female	0	(0.0)	0	(0.0)	23	(32.4)	15	(65.2)
Age (Years)								
12 - < 18 (Years)	0	(0.0)	0	(0.0)	17	(23.9)	6	(26.1)
6 - < 12 (Years)	0	(0.0)	0	(0.0)	30	(42.3)	10	(43.5)
2 - < 6 (Years)	0	(0.0)	0	(0.0)	22	(31.0)	7	(30.4)
3 (Months) - < 2 (Years)	1	(100.0)	0	(0.0)	1	(1.4)	0	(0.0)
Birth - < 3 (Months)	0	(0.0)	1	(100.0)	1	(1.4)	0	(0.0)
Participants with data	1		1		71		23	
Mean	0.729		0.085		8.678		8.630	
SD					4.3555		3.6241	
Median	0.729		0.085		8.233		8.512	
Range	0.729 to 0.729		0.085 to 0.085		0.085 to 17.559		3.403 to 13.559	

	Group 1 12 to <18 y C/T+MTZ		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T+MTZ		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T+MTZ		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Race												
Asian	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	2	(9.1)	1	(14.3)
Black Or African American	2	(11.8)	1	(16.7)	4	(13.3)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)
White	15	(88.2)	5	(83.3)	25	(83.3)	9	(90.0)	20	(90.9)	6	(85.7)
Ethnicity												
Hispanic Or Latino	3	(17.6)	2	(33.3)	8	(26.7)	4	(40.0)	6	(27.3)	1	(14.3)
Not Hispanic Or Latino	14	(82.4)	4	(66.7)	22	(73.3)	6	(60.0)	13	(59.1)	6	(85.7)
Not Reported	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.1)	0	(0.0)
Region												
North America	4	(23.5)	2	(33.3)	14	(46.7)	5	(50.0)	7	(31.8)	1	(14.3)
Europe	11	(64.7)	3	(50.0)	13	(43.3)	5	(50.0)	13	(59.1)	5	(71.4)
South America	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
Africa	2	(11.8)	1	(16.7)	3	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)
Asia/Pacific	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	1	(14.3)

	Group 4 3 mo to <2 y C/T+MTZ		Group 5 Birth to < 3 mo C/T+MTZ		Total C/T+MTZ		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)
Race								
Asian	1	(100.0)	0	(0.0)	3	(4.2)	2	(8.7)
Black Or African American	0	(0.0)	0	(0.0)	6	(8.5)	1	(4.3)
Multiple	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)
White	0	(0.0)	1	(100.0)	61	(85.9)	20	(87.0)
Ethnicity								
Hispanic Or Latino	0	(0.0)	1	(100.0)	18	(25.4)	7	(30.4)
Not Hispanic Or Latino	1	(100.0)	0	(0.0)	50	(70.4)	16	(69.6)
Not Reported	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)
Unknown	0	(0.0)	0	(0.0)	2	(2.8)	0	(0.0)
Region								
North America	0	(0.0)	1	(100.0)	26	(36.6)	8	(34.8)
Europe	0	(0.0)	0	(0.0)	37	(52.1)	13	(56.5)
South America	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)
Africa	0	(0.0)	0	(0.0)	5	(7.0)	1	(4.3)
Asia/Pacific	1	(100.0)	0	(0.0)	2	(2.8)	1	(4.3)

	Group 1 12 to <18 y C/T+MTZ		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T+MTZ		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T+MTZ		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Baseline Diagnosis												
Complicated Appendicitis	15	(88.2)	6	(100.0)	29	(96.7)	9	(90.0)	21	(95.5)	7	(100.0)
Other Complicated Intra-Abdominal Infection	2	(11.8)	0	(0.0)	1	(3.3)	0	(0.0)	1	(4.5)	0	(0.0)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)
Bacteremia at Baseline												
Yes	1	(5.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
No	16	(94.1)	6	(100.0)	30	(100.0)	10	(100.0)	21	(95.5)	7	(100.0)
Height (cm)												
Participants with data	17		6		30		9		22		7	
Mean	162.9		156.8		134.1		133.5		104.3		105.4	
SD	12.36		4.58		10.48		18.04		7.69		9.95	
Median	161.0		159.5		132.5		135.9		104.5		108.7	
Range	144.0 to 180.0		150.0 to 160.0		115.0 to 149.5		90.0 to 149.0		90.0 to 121.0		87.0 to 118.0	
Weight (kg)												

	Group 4 3 mo to <2 y C/T+MTZ		Group 5 Birth to < 3 mo C/T+MTZ		Total C/T+MTZ		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)
Baseline Diagnosis								
Complicated Appendicitis	0	(0.0)	0	(0.0)	65	(91.5)	22	(95.7)
Other Complicated Intra-Abdominal Infection	1	(100.0)	1	(100.0)	6	(8.5)	0	(0.0)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
Bacteremia at Baseline								
Yes	0	(0.0)	0	(0.0)	2	(2.8)	0	(0.0)
No	1	(100.0)	1	(100.0)	69	(97.2)	23	(100.0)
Height (cm)								
Participants with data	1		1		71		22	
Mean	70.0		54.0		129.7		130.9	
SD					26.65		23.86	
Median	70.0		54.0		130.4		134.0	
Range	70.0 to 70.0		54.0 to 54.0		54.0 to 180.0		87.0 to 160.0	
Weight (kg)								

	Group 1 12 to <18 y C/T+MTZ		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T+MTZ		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T+MTZ		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants with data	17		6		30		9		22		7	
Mean	58.27		51.66		31.65		32.29		17.00		16.77	
SD	17.447		10.199		8.360		6.414		3.803		2.768	
Median	55.00		51.00		30.00		31.00		17.00		18.20	
Range	32.00 to 90.00		41.00 to 63.30		18.50 to 54.00		24.50 to 42.80		11.80 to 25.00		11.00 to 19.00	
Baseline Creatinine Clearance (ml/min/1.73 m2)[a]												
CrCl >= 80	14	(82.4)	6	(100.0)	29	(96.7)	9	(90.0)	19	(86.4)	7	(100.0)
CrCl>=50 - <80	2	(11.8)	0	(0.0)	1	(3.3)	0	(0.0)	3	(13.6)	0	(0.0)
CrCl>=30 - <50	1	(5.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)
Participants with data	17		6		30		9		22		7	
Mean	102.674		107.086		130.512		116.019		138.851		159.903	
SD	39.7282		14.1867		38.1939		19.7197		74.6993		65.0035	
Median	95.905		105.405		125.472		110.273		125.665		176.319	
Range	34.724 to 205.533		88.500 to 130.783		76.061 to 220.576		93.545 to 153.942		56.616 to 421.260		83.155 to 269.255	
Failure of Prior Antibacterial Therapy												
Yes	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)
No	17	(100.0)	6	(100.0)	29	(96.7)	9	(90.0)	22	(100.0)	7	(100.0)

	Group 4 3 mo to <2 y C/T+MTZ		Group 5 Birth to < 3 mo C/T+MTZ		Total C/T+MTZ		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with data	1		1		71		22	
Mean	7.00		3.13		32.74		32.63	
SD					19.015		15.164	
Median	7.00		3.13		28.30		30.75	
Range	7.00 to 7.00		3.13 to 3.13		3.13 to 90.00		11.00 to 63.30	
Baseline Creatinine Clearance (ml/min/1.73 m2)[a]								
CrCl >= 80	0	(0.0)	0	(0.0)	62	(87.3)	22	(95.7)
CrCl>=50 - <80	1	(100.0)	1	(100.0)	8	(11.3)	0	(0.0)
CrCl>=30 - <50	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
Participants with data	1		1		71		22	
Mean	58.348		55.755		124.361		127.546	
SD					54.4520		43.9190	
Median	58.348		55.755		111.809		111.304	
Range	58.348 to 58.348		55.755 to 55.755		34.724 to 421.260		83.155 to 269.255	
Failure of Prior Antibacterial Therapy								
Yes	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)
No	1	(100.0)	1	(100.0)	70	(98.6)	22	(95.7)

	Group 1 12 to <18 y C/T+MTZ		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T+MTZ		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T+MTZ		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)
Prior Antibiotic Use												
Yes	16	(94.1)	6	(100.0)	28	(93.3)	9	(90.0)	22	(100.0)	7	(100.0)
No	1	(5.9)	0	(0.0)	2	(6.7)	1	(10.0)	0	(0.0)	0	(0.0)
Number of Baseline Pathogens												
Polymicrobial	7	(41.2)	4	(66.7)	15	(50.0)	6	(60.0)	16	(72.7)	5	(71.4)
Monomicrobial	10	(58.8)	1	(16.7)	11	(36.7)	2	(20.0)	4	(18.2)	2	(28.6)
Missing	0	(0.0)	1	(16.7)	4	(13.3)	2	(20.0)	2	(9.1)	0	(0.0)

	Group 4 3 mo to <2 y C/T+MTZ		Group 5 Birth to < 3 mo C/T+MTZ		Total C/T+MTZ		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
Prior Antibiotic Use								
Yes	1	(100.0)	1	(100.0)	68	(95.8)	22	(95.7)
No	0	(0.0)	0	(0.0)	3	(4.2)	1	(4.3)
Number of Baseline Pathogens								
Polymicrobial	0	(0.0)	0	(0.0)	38	(53.5)	15	(65.2)
Monomicrobial	1	(100.0)	1	(100.0)	27	(38.0)	5	(21.7)
Missing	0	(0.0)	0	(0.0)	6	(8.5)	3	(13.0)

C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole, mo = Months, y = Years
The one multiple race is for Black Or African American, White.
Age was derived in years with 3 decimals, from data collected in years and months when subjects were randomized. For subjects 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 = 0.019 years.)
[a] Creatinine clearance rates were calculated by the revised Schwartz equation at baseline.

Source: [P035MK7625A: adam-adsl]

The CHMP noted that, for some of the demographic and baseline characteristics, there were imbalances between the two treatment groups. The proportion of males was for instance much higher in the C/T+ MTZ group (67.6%) than in the MERO group (34.8%).

Overall, the majority of the patients was predominantly white, European, males with a median age of 8.2 years in the C/T+MTZ group and 8.5 years in the MERO group and had normal renal function. Only 1 patient in each of the two age groups 3 months - < 2 years and birth - < 3 months was included in the study, and both was in the C/T+MTZ group.

Almost all patients in both treatment arms had a baseline diagnosis of complicated appendicitis (in total 65 patients [91.5%] in the C/T+MTZ arm vs. 22 patients [95.7%] in the MERO arm). However, as previously mentioned, this was accepted by the PDCO (please refer to the section above "Conduct of the study"). In total there were 6 participants (all in the C/T+MTZ group) enrolled with a diagnosis of other

cIAI (3 with intra-abdominal abscess, 2 with diffuse peritonitis, and 1 with perforated jejunum/ileum and diffuse peritonitis).

Only 2 patients in total (both in the C/T+MTZ group) had bacteraemia at baseline.

Baseline microbiology

The most common gram-negative pathogens (C/T+MTZ; MERO) were *Escherichia coli* (47 [67.1%]; 13 [61.9%]), *Pseudomonas aeruginosa* (19 [27.1%]; 6 [28.6%]), and *Bacteroides fragilis* (13 [18.6%]; 4 [19.0%]). Both study treatments were active against all isolates of these 3 organisms.

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

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

Concomitant antibiotic medications

Between the first dose of IV study medication and the EOT visit, 1 participant in the C/T+MTZ group (none in the MERO group) received concomitant non-study antibiotic therapy (excluding a protocol-allowed single dose of prophylactic antibiotics); this participant received both cefotaxime sodium and MTZ.

Between the first dose of IV study medication and the TOC visit, 2 participants in the C/T+MTZ group and 1 participant in the MERO group received at least 1 dose of concomitant antibiotic therapy; this included participants who received protocol-allowed antibiotic prophylaxis after the EOT visit.

In the view of the MAH, only one patient in the C/T+MTZ group (and none in the MERO group) was excluded from the CE population due to "concomitant antibacterial violation". Regarding "prior antibacterial violation", it was 5 patients in the C/T+MTZ group (vs. none in the MERO group) that were excluded. One patient from each of the two study arms was excluded due to "confounding antibacterial post-treatment" (at TOC).

The CHMP noted that participants who received non-study antibiotics that were stopped on the same date as the first dose of IV study medication or started on the same date as the EOT or TOC visit date (for which a start or stop time for the non-study antibiotic was not recorded), were not included as having received concomitant antibiotics. With this approach, it cannot be excluded that the non-study antibiotics might have had an effect on the study treatment for these patients. However, considering that the efficacy should be extrapolated from adults, this issue was not further pursued in the context of efficacy.

Extent of exposure

The median (range) number of IV treatment doses was comparable between participants in the C/T+MTZ (19 [0.5-42.0]) and MERO (18 [7.0-26.0]) treatment groups.

The median (range) duration of IV treatment was comparable between participants in the C/T+MTZ (6.3 [0.3 to 14.0] days) and MERO (6.0 [2.3 to 8.8] days) treatment groups, with the majority of participants in both the C/T+MTZ (55.7%) and MERO (71.4%) groups receiving IV treatment for >3 to ≤7 days (for the latter: *data not shown*).

The median (range) duration of overall treatment (i.e., IV only or IV + oral) was generally comparable between participants in the C/T+MTZ (10.0 [0.3 to 18.3] days) and MERO (8.0 [4.3 to 14.8] days) treatment groups.

For those participants who switched to oral step-down treatment (C/T+MTZ: 35/70 [50%]; MERO: 12/21 [57%]), the median (range) duration of oral treatment was comparable between participants in the C/T+MTZ (6.3 [0.5 to 10.0] days) and MERO (5.2 [1.3 to 10.1] days) treatment groups. The most common oral step-down treatments (>10% in either treatment group) were metronidazole, amoxicillin/clavulanate, and ciprofloxacin.

Outcomes and estimation

Compliance with the overall treatment regimen (both IV and oral step-down) in the MITT population was high in both treatment groups with only 1 participant in the study being ≤80% compliant with the overall treatment.

Table 29: *Clinical response by visit – MITT population – Study P035*

Visit Clinical Response	C/T+MTZ			MERO			% Difference (C/T+MTZ minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
Number of Participants	70			21			
End of Treatment (EOT) Visit							
Success	56	(80.0)	(69.18, 87.70)	20	(95.2)	(77.33, 99.15)	-14.3 (-26.67, 4.93)
Failure	14	(20.0)		1	(4.8)		
Observed Failure	8	(11.4)		0	(0.0)		
Observed Indeterminate	3	(4.3)		0	(0.0)		
Imputed Indeterminate	3	(4.3)		1	(4.8)		
Test of Cure (TOC) Visit							
Success	56	(80.0)	(69.18, 87.70)	21	(100.0)	(84.54, 100.00)	-19.1 (-30.18, -2.89)
Failure	14	(20.0)		0	(0.0)		
Observed Failure	8	(11.4)		0	(0.0)		
Observed Indeterminate	3	(4.3)		0	(0.0)		
Imputed Indeterminate	3	(4.3)		0	(0.0)		

C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole

[a] The 95% CIs of each treatment are unstratified Wilson CIs.

[b] The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights. If there is a zero count in any class of the stratum, the groups with the lower count will be pooled with its near age group stratum in the model.

The participants with a missing clinical response (eg. Indeterminate) are considered treatment failures.

Imputed indeterminate clinical response includes participants who had a clinical cure, partial improvement or indeterminate at the previous visit(s) and had missing clinical response at the specific visit.

Source: [P035MK7625A: adam-adsl; adeft]

The CHMP noted that in the MITT population at TOC, 56/70 patients (80.0%) in the C/T+MTZ group and 21/21 patients (100.0%) in the MERO group had a favourable clinical response. Clinical success rates at the EOT visit were consistent with those reported at the TOC visit. It is noted that the clinical response rates were lower in the C/T+MTZ group compared to the MERO group. The MAH attributed that to the fact that the difference in clinical success may have been driven in part by a particularly high cure rate in the MERO group rather than by a lower than-expected efficacy in the C/T+MTZ group. The clinical response rates in the C/T+MTZ group were comparable to those in the MITT population for the pivotal Phase 3 study in adults (submitted in connection with the application for marketing authorisation for Zerbaxa), which demonstrated the non-inferiority of C/T+MTZ to MERO in adult participants with cIAI (C/T+MTZ: 83.0%; MERO: 87.3%). In addition, the MAH pointed out that in the C/T+MTZ group of the MITT population, 6 of the 14 clinical failures were indeterminate responses (e.g., participant was lost to follow-up or a clinical assessment was unable to be made for other reasons); in this intention-to-treat population, these participants were considered failures. The MAH's points were acknowledged by the Committee.

As for the AP/cUTI-study (P034) the efficacy results at the TOC visit will not solely reflect the effect of C/T+MTZ or MERO, but also the effect from the oral step-down antibiotic therapy. In the P035 (cIAI)

study, it was 35/70 patients in the C/T+MTZ group and 12/21 patients in the MERO group (safety analysis population) who received oral step-down antibiotic treatment. However, it is noted that data from the MITT population at the EOIV visit showed high clinical responses in both treatment groups (61/70 patients [87.1%] in the C/T+MTZ group vs. 21/21 patients [100.0%] in the MERO group had a favourable clinical response). Of note though, the main part of the patients in both arms had partial improvement (35/70 patients, 50% in the C/T+MTZ arm vs. 12/21 patients, 57.1% in the MERO arm) meaning that these patients were not cured but required further oral step-down therapy.

Furthermore, as this study was descriptive in nature, it was not powered for inferential testing and was intended to provide descriptive statistics only. Based on the 3:1 randomisation, meaningful interpretation of direct comparisons is not possible. Consequently, no further issues regarding the efficacy results were pursued. The basis for approval of this variation relies on the PK and safety data, not efficacy.

Clinical success rates by age group (in groups with >1 participant) were generally consistent with the overall clinical success rates by treatment group, i.e., between treatment groups, within each age group, and across age groups.

Table 30: *Clinical response at TOC visit – CE population – Study P035*

Clinical Response	C/T+MTZ			MERO			% Difference (C/T+MTZ minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
Number of Participants	58			19			
Success	52	(89.7)	(79.21, 95.17)	19	(100.0)	(83.18, 100.00)	-10.7 (-21.48, 6.84)
Failure	6	(10.3)		0	(0.0)		
Observed Failure	6	(10.3)		0	(0.0)		

C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole

[a] The 95% CIs of each treatment are unstratified Wilson CIs.

[b] The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights. If there is a zero count in any class of the stratum, the groups with the lower count will be pooled with its near age group stratum in the model.

Success is defined as cure or partial improvement. The participants with a missing clinical response (eg. Indeterminate) are considered treatment failures.

Imputed indeterminate clinical response includes participants who had a clinical cure, partial improvement or indeterminate at the previous visit(s) and had missing clinical response at the specific visit.

Source: [P035MK7625A: adam-adsl; adeff]

In the CE population at TOC, 52/58 patients (89.7%) in the C/T+MTZ group and 19/19 patients (100.0%) in the MERO group had a favourable clinical response.

The clinical success rates at the EOT and EOIV visits in the CE population were consistent with those reported at the TOC visit (*data not shown*).

The same pattern as observed for the MITT population was seen, the clinical success rates were high, but lower in the C/T + MTZ group compared to in the MERO group.

The clinical response rates in the individual cohorts were in general consistent with that observed in the overall study population (*data not shown*).

In the mMITT population at TOC, the microbiological success rates were also lower in the C/T+MTZ group compared to the MERO group as, 53/63 patients (84.1%) in the C/T+MTZ group vs. 19/19 patients (100.0%) in the MERO group, had microbiological success. The microbiological success rates at the EOT visit were consistent with those reported at the TOC visit. At the EOIV visit the microbiological success rates were 57/63, 90.5% in the C/T+MTZ arm vs. 19/19, 100% in the MERO arm.

The microbiological response rates in the individual cohorts were in general consistent with that observed in the overall study population (*data not shown*).

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

The microbiological response rates in the ME population were in general consistent with that observed in the mMITT population *(data not shown*).

Emergent infections

In the C/T+MTZ group, 1 participant had a superinfection (*P. aeruginosa*), and 1 participant had a new infection (*Klebsiella pneumoniae*). No participants in the MERO group had a superinfection or new infection.

Ancillary analyses

N/A

Summary of main studies

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

Table 31: *Summary of efficacy for study MK-7625A-034 (P034)*

Title: A Phase 2, Randomised, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Versus Meropenem in Paediatric Subjects with Complicated Urinary Tract Infection, Including Pyelonephritis	
Study identifier	Protocol Number: P034 (MK-7625A-034) IND: 104,490 EudraCT: 2016-004153-32
Design	This was a Phase 2 randomised, active comparator-controlled, multicenter, double-blind study evaluating the safety and efficacy of ceftolozane/tazobactam (C/T) versus meropenem (MERO) in paediatric participants from birth to <18 years of age with complicated urinary tract infection (cUTI), including pyelonephritis. Eligible participants in P034 were randomised in a 3:1 ratio to receive intravenous (IV) C/T or MERO, respectively, with stratification by age group: Group 1 (Ages 12 to <18 years): Ceftolozane 1 g and tazobactam 0.5 g IV every 8 hours OR MERO 20 m g/kg (maximum of 1 g/dose) IV every 8 hours Group 2 (Ages 6 to <12 years): Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours Group 3 (Ages 2 to <6 years): Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours Group 4 (Ages 3 months to <2 years): Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam

	0.5 g/dose) IV every 8 hours OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours Group 5 (Ages birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months): Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours After receiving at least 9 doses of double-blind IV study treatment, participants in either treatment arm may have switched to open-label, standard-of-care oral step-down antibiotic therapy at the investigator's discretion. Oral step-down therapy was considered study treatment. Recommendations for oral step-down therapy were BL/BLI combination, cephalosporin, quinolone, nitrofurantoin and trimethoprim or trimethoprim/sulfamethoxazole.		
Design	The total duration of study treatment (IV only or IV + oral) was a minimum of 7 days and a maximum of 14 days.		
	Duration of main phase:	After a screening phase of up to 48 hours, each participant received study treatment (IV only or IV + oral) for a minimum of 7 to a maximum of 14 days. After the end of treatment (EOT), each participant entered a follow-up phase consisting of a Test of Cure (TOC) Visit 5 to 9 days after the last dose of study treatment and a Last Follow-up (LFU) Visit 28 to 35 days after the last dose of study treatment. Of note: efficacy data beyond the TOC visit were not collected in these paediatric studies.	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	Not applicable	
Hypothesis	There were no formal hypotheses in P034.		
Treatments groups	Age Groups	Randomised/ Treated/ Completed IV Study Medication	
	Group 1 (12 to <18 years)	C/T: 15/ 15/ 10 MERO: 5/ 5/ 2	
	Group 2 (6 to <12 years)	C/T: 24/ 24/ 12 MERO: 8/ 8/ 4	
	Group 3 (2 to <6 years)	C/T: 22/ 22/ 15 MERO: 7/ 7/ 6	
	Group 4 (3 months to <2 years)	C/T: 24/ 24/ 19 MERO: 7/ 7/ 6	
	Group 5 (Birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months)	C/T: 16 / 15/ 13 MERO: 6/ 6/ 6	
Endpoints and definitions	Primary endpoint	Safety	Adverse events (Aes), vital signs, and laboratory safety tests in the all-subjects-as-treated (AsaT) population

	Secondary endpoint	Efficacy	Clinical success rate at the EOT and TOC Visits
	Secondary endpoint	Efficacy	Per-participant microbiological eradication rate at the EOT and TOC Visits
Database lock	22-JAN-2021		
Results and Analysis			
Analysis description	A 2-sided 95% CI based on the Miettinen and Nurminen method (1985) (M&N) and stratified by age group was provided to evaluate the treatment differences for (1) clinical success at the EOT and TOC Visits and (2) per-participant microbiological eradication at the EOT and TOC Visits. There was no efficacy hypothesis testing in this estimation study.		
Analysis population and time point description	Efficacy analyses of data in this study were based on 3 efficacy analysis populations defined as: • Microbiological modified intent-to-treat (mMITT): subset of randomized participants who received any amount of study treatment and had at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture. Participants were categorized based on the IV study treatment to which they were randomized, irrespective of what they actually received. • Clinically evaluable (CE): subset of the mMITT population who adhered to study procedures, did not have any significant protocol deviations impacting efficacy assessment, and received a minimum amount of study therapy. An interpretable urine culture was not required at the visit of interest and all participants had an evaluable clinical outcome at the visit of interest. All participants' eligibility status were reviewed and determined in a blinded manner before final database lock. • Microbiologically evaluable (ME): subset of the CE population who had an interpretable urine culture at the visit of interest within the visit window.		
Notes	Not applicable.		

Descriptive statistics and estimate variability

Population: mMITT							
	C/T			MERO			% Difference (C/T minus MERO) 95% CI[b]
Clinical Response	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	71			24			
Success	63	(88.7)	(79.31, 94.18)	23	(95.8)	(79.76, 99.26)	-7.3 (-17.99, 10.05)
Failure	8	(11.3)		1	(4.2)		
EOT Visit (N)	71			24			
Success	67	(94.4)	(86.39, 97.79)	24	(100.0)	(86.20, 100.00)	-5.6 (-14.09, 8.88)
Failure	4	(5.6)		0	(0.0)		

Population: mMITT							
	C/T			MERO			% Difference (C/T minus MERO) 95% CI[b]
Microbiological Outcome	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	71			24			

Eradication	60	(84.5)	(74.35, 91.12)	21	(87.5)	(69.00, 95.66)	-3.0 (-17.13, 17.40)
Persistence	11	(15.5)		3	(12.5)		
EOT Visit (N)	71			24			
Eradication	66	(93.0)	(84.55, 96.95)	23	(95.8)	(79.76, 99.26)	-3.4 (-12.67, 13.41)
Persistence	5	(7.0)		1	(4.2)		

Population: CE

	C/T			MERO			% Difference (C/T minus MERO) 95% CI[b]
Clinical Response	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	48			17			
Success	44	(91.7)	(80.45, 96.71)	16	(94.1)	(73.02, 98.95)	-1.2 (-14.67, 21.41)
Failure	4	(8.3)		1	(5.9)		
EOT Visit (N)	66			21			
Success	64	(97.0)	(89.61, 99.17)	21	(100.0)	(84.54, 100.00)	-2.5 (-10.57, 13.86)
Failure	2	(3.0)		0	(0.0)		

Population: ME

	C/T			MERO			% Difference (C/T minus MERO) 95% CI[b]
Microbiological Outcome	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	44			17			
Eradication	40	(90.9)	(78.84, 96.41)	15	(88.2)	(65.66, 96.71)	2.5 (-13.39, 27.13)
Persistence	4	(9.1)		2	(11.8)		
EOT Visit (N)	58			20			
Eradication	58	(100.0)	(93.79, 100.00)	20	(100.0)	(83.89, 100.00)	0.0 (-7.13, 17.08)

CE=clinically evaluable; CI=confidence interval; C/T=ceftolozane/tazobactam; EOT=end of treatment; ME=microbiologically evaluable; MERO=meropenem; mMITT=microbiological modified intent-to-treat; n=number of subjects; TOC=test of cure.

[a] The 95% Cis of each treatment are unstratified Wilson Cis.

[b] The % difference is based on the M&N method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights. If there is a zero count in any class of the stratum, the groups with the lower count will be pooled with its near age group stratum in the model.

Table 32: *Summary of efficacy for study MK-7625A-035 (P035)*

Title: A Phase 2, Randomised, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Plus Metronidazole Versus Meropenem in Paediatric Subjects with Complicated Intra-Abdominal Infection	
Study identifier	Protocol Number: P035 (MK-7625A-035) IND: 104,490 EudraCT: 2016-004820-41

Design	This was a Phase 2 randomised, active comparator-controlled, multicenter, double-blind study evaluating the safety and efficacy of C/T plus metronidazole (MTZ) versus MERO plus placebo in paediatric participants from birth to <18 years of age with complicated intra-abdominal infection (cIAI). Eligible participants were randomized in a 3:1 ratio to receive IV C/T plus MTZ or comparator (MERO+placebo) treatment arm administered as a 60-minute (±10 minutes) infusion as follows: <u>Group 1 (Ages 12 to <18 years):</u> Ceftolozane 1 g and tazobactam 0.5 g IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours <u>Group 2 (Ages 6 to <12 years):</u> Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours <u>Group 3 (Ages 2 to <6 years):</u> Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours <u>Group 4 (Ages 3 months to <2 years)</u>: Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours <u>Group 5 (Ages birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months):</u> Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole IV every 8 to 12 hours (for details, please refer to the description of Study P035 under the Efficacy part of the Assessment Report). OR MERO 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours. After receiving at least 9 doses of double-blind IV study treatment, participants in either treatment arm may have switched to open-label, standard-of-care oral step-down antibiotic therapy at the investigator's discretion. Oral step-down therapy was considered study treatment. Recommendations for oral step-down therapy were BL/BLI combinations, 2. Or 3. Generation cephalosporin in combination with metronidazole or quinolone (ciprofloxacin or levofloxacin should be used in combination with metronidazole).

	The total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.		
	Duration of main phase:		After a screening phase of up to 48 hours, each participant received study treatment (IV only or IV + oral) for a minimum of 5 days to a maximum of 14 days. After the EOT, each participant entered a follow-up phase consisting of a TOC Visit 7 to 14 days after the last dose of study treatment and a LFU Visit 21 to 28 days after the last dose of study treatment. Of note: efficacy data beyond the TOC visit were not collected in these paediatric studies.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	There were no formal hypotheses in P035.		
Treatments groups	Age Groups		Randomised/ Treated/ Completed IV Study Medication
	Group 1 (12 to <18 years)		C/T+MTZ: 17/ 16/ 16 MERO: 6/ 5 / 4
	Group 2 (6 to <12 years)		C/T+MTZ: 30/ 30/ 29 MERO: 10/ 9/ 9
	Group 3 (2 to <6 years)		C/T MTZ: 22/ 22/ 19 MERO: 7/ 7/ 7
	Group 4 (3 months to <2 years)		C/T+MTZ: 1/ 1/ 0 MERO: 0/ 0/ 0
	Group 5 (Birth to <3 months)		C/T+MTZ: 1/ 1/ 1 MERO: 0/ 0/ 0
Endpoints and definitions	Primary endpoint	Safety	Aes, vital signs, and laboratory safety tests in the AsaT population
	Secondary endpoint	Efficacy	Clinical success rate at the EOT and TOC Visits, defined as the proportion of participants in the analysis population who had a clinical response of cure.

	Secondary endpoint	Efficacy	Per-participant microbiological success rate at the EOT and TOC Visits, defined as the proportion of participants in the analysis population who had microbiological eradication or presumed eradication of all baseline pathogens.
Database lock	22-JAN-2021		
Results and Analysis			
Analysis description	A 2-sided 95% CI based on the M&N method and stratified by age group was provided to evaluate (1) the treatment differences for clinical success at the EOT and TOC Visits and (2) per-participant microbiological eradication at the EOT and TOC Visits.		
Analysis population and time point description	Efficacy analyses of data in this study were based on 4 analysis populations defined as: • Modified intent-to-treat (MITT): all randomized participants who received any amount of study treatment. Participants were categorized based on the IV study treatment to which participants were randomized, irrespective of what treatment they received. • mMITT: subset of participants in the MITT population who had at least 1 pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment. • CE: subset of participants in the MITT population who adhered to study procedures, did not have any significant protocol deviations impacting efficacy assessment, and received a minimum amount of study therapy, and had a clinical outcome at the visit of interest; an interpretable culture was not required at the visit of interest. All participants' eligibility status were reviewed and determined in a blinded manner before final database lock. • ME: subset of participants in the CE population who had at least 1 causative pathogen identified from the baseline intra-abdominal culture.		

Descriptive statistics and estimate variability

Population: MITT

Clinical Response	C/T+MTZ			MERO			% Difference (C/T+MTZ minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	70			21			
Success	56	(80.0)	(69.18, 87.70)	21	(100.0)	(84.54, 100.00)	-19.1 (-30.18, -2.89)
Failure	14	(20.0)		0	(0.0)		
EOT Visit (N)	70			21			
Success	56	(80.0)	(69.18, 87.70)	20	(95.2)	(77.33, 99.15)	-14.3 (-26.67, 4.93)
Failure	14	(20.0)		1	(4.8)		

Population: CE

Clinical Response	C/T+MTZ			MERO			% Difference (C/T+MTZ minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	58			19			
Success	52	(89.7)	(79.21, 95.17)	19	(100.0)	(83.18, 100.00)	-10.7 (-21.48, 6.84)
Failure	6	(10.3)		0	(0.0)		
EOT Visit (N)	59			19			
Success	53	(89.8)	(79.54, 95.26)	19	(100.0)	(83.18, 100.00)	-10.6 (-21.22, 6.95)

Failure	6	(10.2)		0	(0.0)		

Population: ME

Microbiological Outcome	C/T+MTZ			MERO			% Difference (C/T+MTZ minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	53			17			
Microbiological Success	49	(92.5)	(82.14, 97.03)	17	(100.0)	(81.57, 100.00)	-8.3 (-19.31, 10.99)
Microbiological Failure	4	(7.5)		0	(0.0)		

Population: mMITT

Microbiological Outcome	C/T+MTZ			MERO			% Difference (C/T+MTZ minus MERO) 95% CI[b]
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	
TOC Visit (N)	63			19			
Microbiological Success	53	(84.1)	(73.19, 91.14)	19	(100.0)	(83.18, 100.00)	-16.3 (-27.59, 1.39)
Microbiological Failure	10	(15.9)		0	(0.0)		

CE=clinically evaluable; CI=confidence interval; C/T=ceftolozane/tazobactam; EOT=end of treatment; ME=microbiologically evaluable; MERO=meropenem; MITT=modified intent-to-treat; mMITT=microbiological modified intent-to-treat; n=number of subjects; TOC=test of cure.

[a] The 95% Cis of each treatment are unstratified Wilson Cis.

[b] The % difference is based on the M&N method stratified by age group with CMH weights. If there is a zero count in any class of the stratum, the groups with the lower count will be pooled with its near age group stratum in the model.

4.5.2. Discussion on clinical efficacy

This application is intended to broaden the approved indications of Zerbaxa (ceftolozane/tazobactam) for adults: acute pyelonephritis (AP), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI), to include paediatric population from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age.

According to draft "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/187859/2017)", no appropriately powered efficacy study is requested in the paediatric population. Efficacy can be extrapolated from data in adults provided that similar exposure of ceftolozane/tazobactam is achieved and a sufficiently amount of safety data is collected in the paediatric age groups. It is therefore the safety and PK data that are critical to the final outcome of this assessment.

Consequently, the efficacy data described below in this submission are only descriptive and this is considered acceptable.

Design and conduct of clinical studies

The MAH conducted two phase 2 studies that aimed to include children from birth to less than 18 years of age with cIAI (study P035) and AP/cUTI (study P034). The studies were double-blind, randomised, multicentre and active-controlled studies, in which efficacy was defined as a secondary objective, and hence were not powered to determine efficacy.

Participants were randomised 3:1 and stratified by 5 age groups (12 to < 18 years, 6 to < 12 years, 2 to < 6 years, 3 months to < 2 years and birth to < 3 months) to receive double-blind IV ceftolozane/tazobactam (C/T) ± metronidazole (MTZ) or meropenem (MERO) for at least 9 doses (~3 days), after which participants in either group could be switched to open-label, standard-of-care oral step-down antibiotic therapy at the investigator's discretion.

The proposed treatment duration (5-14 days for cIAI and 7-14 days for AP/cUTI) and the option to switch to oral therapy, is generally in line with current guidance (IDSA guideline 2010 and World Society of Emergency Surgery guidelines 2017 for management of intra-abdominal infections and The EAU/ European Society for Paediatric Urology guidelines for UTI in children).

Dose. Paediatric participants from 12 to <18 years of age with cIAI and AP/cUTI received the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam); children <12 years of age, including neonates, received a weight-based dosing regimen of 30 mg/kg C/T (20 mg/kg ceftolozane and 10 mg/kg tazobactam) that did not exceed the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam).

Comparator. Meropenem was chosen as comparator in both studies. While meropenem is approved in Europe for treating paediatric patients (i.e., ≥ 3 months of age) in both indications, it is a broad-spectrum antibiotic and should thus preferably be reserved for use in severe, multidrug-resistant and complicated infections. Notwithstanding this, it is acknowledged that there is increasing resistance towards narrow-spectrum antibiotics worldwide, and hence the use of meropenem might be justified in some cases also for cUTI (cIAI can be of a more severe nature than cUTI). The MAH's viewpoint that the use of the same comparator in the two trials P034 and P035 would allow for a larger sized safety database by pooling the data from these two trials was acceptable to the CHMP, especially considering that safety was the primary endpoint for these studies.

For paediatric patients under 3 months of age, safety and efficacy data of meropenem are limited, and the optimal dose regimen for this age group has not been identified. However, the off-label dose used in the studies (20 mg/kg with the possibility to increase to 30mg/kg at the investigator's discretion) seems to be in line with data from current available publications (Fasugba et al, 2015; Cohen-Wolkowiez et al, 2012).

For cIAI metronidazole was added to the treatment with C/T for anaerobic coverage, and this is in line with clinical recommendations. Data on the PK and ideal dosing of metronidazole in paediatric patients are limited, especially for paediatric patients less than 1 month of age, however, the chosen doses for the youngest children seem, overall, in line with what is commonly recommended.

Sample size/statistical methods. There were no prespecified statistical hypotheses for this trial. Secondary efficacy endpoints were included to provide point estimates of the efficacy of each treatment regimen; the study was not powered for formal hypothesis testing of between treatment group comparisons.

A combined sample size of 240 participants was originally planned to be enrolled across the two studies. However, due to enrolment challenges in reaching age group, disease state, and/or country-level enrolment targets, and increased recruitment issues due to the COVID-19 pandemic, the Sponsor amended the protocols to lower the target sample size with a total of 228 participants enrolled across both studies, i.e., a total of 134 participants in P034 and a total of 94 participants in P035. This change was accepted by the PDCO. Considering that the ratio was 3:1 to C/T vs. meropenem, this meant that 101 vs. 33 patients were randomised, respectively, in the P034 trial and 71 vs. 23 patients, respectively, in the P035 trial.

Protocol amendments. In addition to the reduction of the pooled sample size (see above under "Sample size/statistical methods"), the most important amendment was the change in Study P035 from an initial limit stating that maximum 60% of the enrolled patients should be diagnosed with acute complicated appendicitis to an increased limit of maximum of 90%, i.e., the MAH wanted to delete the requirement of any limit, but at the time, PDCO demanded that, in line with other PIPs covering the same indication, a limit of no more than 90% of the patients should have other diagnoses than complicated appendicitis should enforced. However, later the MAH again put forward a wish to delete the whole requirement. This time it was accepted by the PDCO, and the Committee acknowledged that recruiting these patients was difficult and that the MAH had made reasonable efforts to boost recruitment. The prevalence of cIAI was generally low in children under 6 years of age.

Efficacy data and additional analyses

- Complicated urinary tract infections including acute pyelonephritis (Study P034)

Of 143 enrolled patients, 134 were randomised in a 3:1 ratio to receive C/T or MERO and 133 patients received treatment. The demographic and baseline characteristics were mainly balanced between the two groups. European subjects were adequately represented; predominantly Whites were included, around 64% females with median age ca. 3.8 years in the C/T group. Most patients were diagnosed with pyelonephritis in both groups (80.2% in the C/T group vs. 72.7% in the MERO group). The most common cUTI complicating factors were recurrent UTI (40.6% in the C/T group and 30.3% in the MERO group) and congenital abnormality of the urogenital tract (31.7% in the C/T group vs. 24.2% in the MERO group).

The paediatric age groups which received C/T were as follows: 12 to <18 years (n= 15), 6 to < 12 years (n= 24), 2 to < 6 years (n= 22), 3 months to < 2 years (n= 24) and birth to < 3 months (n=15).

The most common baseline qualifying gram-negative uropathogens were *Escherichia coli* (C/T: 74.6%; MERO: 87.5%), *Klebsiella pneumonia* (8.5%; 4.2%), and *Pseudomonas aeruginosa* (7.0%; 8.3%). According to the MAH, no patients in either study group received concomitant non-study antibiotic therapy between the first dose of IV study medication and the EOT visit. However, between the first dose of IV study medication and the TOC visit, 25.4% (18/71) of participants in the C/T treatment group and 16.7% (4/24) in the MERO group, received at least one dose of concomitant antibiotic therapy. This included participants who received protocol-allowed antibiotic prophylaxis after the EOT visit, based on site-level standard of care for participants at increased risk of recurrent cUTI.

Most randomised participants in the C/T (97/101, 96.0%) treatment group and all in the MERO (33/33, 100.0%) treatment group completed the study. Four (4.0%) patients in the C/T group discontinued the study vs. none in the MERO group.

The main analysis set for the efficacy analyses was the microbiological modified intent-to-treat population (mMITT), which consisted of all randomised participants who received any amount of study treatment and had at least 1 acceptable causative uropathogen identified from a study-qualifying baseline urine culture. The most common reason for exclusion from the mMITT population was "did not have at least 1 qualifying baseline uropathogen". In total 28.4% of the patients was excluded for this reason.

The microbiological eradication rates were 84.5% (60/71) in the C/T treatment arm and 87.5% (21/24) in the MERO arm in the mMITT population at TOC.

Clinical cure rates were 88.7% (63/71) in the C/T treatment arm and 95.8% (23/24) in the MERO arm in the mMITT population at TOC.

In the microbiologically evaluable (ME) population, the microbiological eradication rates were 90.9% (40/44) in the C/T treatment arm and 88.2% (15/17) in the MERO arm at TOC.

- Complicated intra-abdominal infection (Study P035)

Of 98 enrolled patients, 94 were randomised in a 3:1 ratio to receive C/T + MTZ or MERO and 91 received treatment. The demographic and baseline characteristics were mainly balanced between the two groups. European subjects were adequately represented; predominantly Whites were included, ca. 68% males with median age 8.2 years in the C/T+MTZ group. In total, it was only 6 patients (all in the C/T+MTZ group) enrolled with diagnoses of other cIAI than complicated appendicitis.

The number of patients in the various paediatric age groups who received C/T+MTZ were as follows: 12 to <18 years (n= 16), 6 to < 12 years (n=30), 2 to < 6 years (n= 22), 3 months to < 2 years (n=1) and birth to < 3 months (n=1). Of note, only 1 patient was included in each of the two youngest age cohorts, and of these two, only one (in the age group birth – to < 3 months) completed the study. However, the efficacy results presented in the initial MA application for the adult cIAI indication can be extrapolated to the paediatric population provided similar exposure of ceftolozane/tazobactam. In addition, efficacy observed in the youngest AP/cUTI children could be extrapolated to the same age cohorts for the cIAI patients as these two infectious diseases are expected to have similar pathophysiology.

A high proportion of the randomised patients completed the trial (94% in the C/T+MTZ arm vs. 87% in the MERO arm). According to the MAH, very few patients in both study arms received concomitant non-study antibiotic therapy between the first dose of IV study medication and the EOT visit and the TOC visit (maximum 2 patients).

The main analysis set for the efficacy analyses was the modified intent-to-treat population (MITT), which consisted of all randomised participants who received any amount of study treatment. Clinical cure rates were 80.0% (56/70 patients) in the C/T+MTZ treatment arm and 100.0% (21/21 patients) in the MERO arm in the MITT population at TOC.

In the clinically evaluable (CE) population, the cure rates were 89.7% (52/58) in the C/T+MTZ arm and 100.0% (19/19) in the MERO arm at TOC.

In the microbiological modified intent-to-treat (mMITT) population at TOC, 53/63 patients (84.1%) in the C/T+MTZ group vs. 19/19 patients (100.0%) in the MERO group, had microbiological success (i.e., as usual for cIAI most microbiological outcomes were presumed eradicated based on clinical response).

It is noted that the rates were lower in the C/T+MTZ group compared to the MERO group. The MAH refers to that the difference in clinical success may have been driven in part by a particularly high cure rate in the MERO group rather than by a lower than expected efficacy in the C/T+MTZ group. The clinical response rates in the C/T+MTZ group were comparable to those in the MITT population for the pivotal Phase 3 study in adults (submitted in connection with the application for marketing authorisation for Zerbaxa), which demonstrated the non-inferiority of C/T+MTZ to MERO in adult participants with cIAI (C/T+MTZ: 83.0%; MERO: 87.3%). In addition, the MAH points out that in the C/T+MTZ group of the MITT population, 6 of the 14 clinical failures were indeterminate responses; in this intention-to-treat population, these participants were considered failures. The MAH's points are acknowledged. Furthermore, as this study was descriptive in nature, it was not powered for inferential testing and was intended to provide descriptive statistics only. Based on the 3:1 randomisation, meaningful interpretation of direct comparisons is not possible. Consequently, no further issues regarding these efficacy results will be discussed.

Of note for both studies: the efficacy results at the TOC visit will not solely reflect the effect of C/T or MERO, but also the effect from the oral step-down antibiotic therapy. In the P034 study, it was 51/100 patients in the C/T group and 20/33 patients in the MERO group who received oral step-down antibiotic

treatment while in the P035 study it was 35/70 patients in the C/T+MTZ group and 12/21 patients in the MERO group (safety analysis population). Notwithstanding this, it is noticed that the results of the exploratory efficacy endpoint clinical success at the EOIV (end of IV treatment) visit showed high response rates in both treatment groups in both studies. It should be taken into account though that a large proportion of the patients in both arms in both studies was only partially improved. This implies that they were not in need of further IV antibiotic treatment for their infection, but additional treatment in the form of oral step-down therapy was still required. It is acknowledged that there are some uncertainties with regards to the use of oral step-down antibiotic therapy in these studies (e.g., variations in type of oral agent chosen by the investigator, duration of treatment). However, this issue was not further pursued considering that the efficacy data are not critical for this application. Furthermore, the choice of oral agents will also be dependent on the susceptibility of specific antibiotics, as well as the availability of the agents, in different countries and regions.

4.5.3. Conclusions on clinical efficacy

Overall, available efficacy data from paediatric patients are limited, and for children < 3 months of age with cIAI, there was only 1 patient who completed the treatment (belonging to the age group birth to < 3 months in the C/T+MTZ group).

Although the available data do not seem to deviate in any major way from the adult efficacy data, they are not intended for providing any sound evidence in support of efficacy and/or adequacy of the proposed dose regimen. The efficacy of ceftolozane/tazobactam is expected to be similar in children, given that available PK data indicate similar exposures in children and adults. Thus, the basis for approval of this variation lies on the PK and safety data, not efficacy.

4.6. Clinical safety

Safety data presented in this application for the paediatric indication extension

This safety assessment summarizes the safety findings from 2 completed Phase 2 studies (P034 and P035) and 1 completed Phase 1 study (P010, mentioned above), which is submitted in support for the extension of indication application for the use of ceftolozane/tazobactam (C/T; also known as MK-7625A) in complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI) indications in paediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age. These three studies randomized 271 paediatric participants <18 years of age across 73 clinical study sites in 20 countries, of which 207 paediatric participants received at least 1 dose of C/T in the 3 paediatric studies.

Study MK-7625A-010 (**P010** or CXA-PEDS-13-08, described above); 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) was submitted as an Article 46 application. Overall, 43 patients were enrolled, of which 37 were treated with C/T. CHMP review was completed in January 2018.

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

- **Study MK-7625A-034 (P034)**: A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Versus Meropenem in Paediatric Subjects with Complicated Urinary Tract Infection, Including Pyelonephritis

- **Study MK 7625A-035 (P035)**: A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Plus Metronidazole Versus Meropenem in Paediatric Subjects with Complicated Intra-Abdominal Infection

The primary endpoint for both studies was to evaluate the safety and tolerability of C/T plus MTZ compared with that of MERO.

Paediatric participants from 12 to <18 years of age with cIAI and AP/cUTI received the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam); children <12 years of age, including neonates, received a weight-based dosing regimen of 30 mg/kg C/T (20 mg/kg ceftolozane and 10 mg/kg tazobactam) that did not exceed the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam).

According to Draft guideline EMA/187859/2017 "Addendum to guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements", no appropriately powered efficacy studies are requested in the paediatric population as efficacy can be extrapolated from adults provided that similar exposure is achieved in the paediatric population. Furthermore, sufficient safety data have to be generated with the intended dose regimen in the paediatric population. In both the paediatric phase 2 studies submitted to support the indication extensions, safety and tolerability are primary endpoint, while pharmacokinetic and efficacy variables are secondary. In addition, one phase 1 study was submitted.

This CHMP safety assessment is based on 2 completed Phase 2 paediatric studies (P034 and P035) in the indications AP/cUTI and cIAI, and 1 completed Phase 1 study (P010). These clinical studies represent data from 207 paediatric participants who received at least 1 dose of C/T in the 3 paediatric studies, including 170 participants in the multi-dose Phase 2 studies (100 and 70 in the studies P034 and P035, respectively), and 37 participants in the single-dose study P010. It is indeed a limited safety database, but acceptable in this setting in the paediatric population. This safety evaluation presents a summary of the safety data and emphasises the pooled safety data from the two phase 2 studies which concerns the target population, regarding age, therapeutic indication and duration of treatment. Details from the individual studies are presented when applicable.

4.6.1. Patient exposure

Overall Safety Evaluation Plan

An overview is provided of the safety profile of ceftolozane/tazobactam (C/T, also known as MK-7625A) for the treatment of paediatric participants, from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age, with cUTI (including pyelonephritis), or cIAI.

Safety data from 3 clinical studies are provided; 2 completed Phase 2 studies (MK-7625A-034 and MK-7625A-035, hereafter referred to as P034 and P035), and a completed Phase 1 PK study (MK-7625A-010, hereafter referred to as P010). Safety data from P034 and P035 were integrated as both studies used a blinded study design, enrolled an acutely ill paediatric population, and used meropenem (MERO) as the comparator. Data from P010 were not integrated with P034 and P035, and are presented separately, as the open-label, single dose study design could have led to bias making interpretation of the pooled data challenging.

Clinical Safety Study Summaries

The evaluation of safety and tolerability of C/T compared with meropenem (MERO) in paediatric participants was the primary objective for the studies P034 and P035. Key design features are presented in the table below.

In P034 and P035, paediatric participants 12 to <18 years of age with AP/cUTI and cIAI received the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam); participants <12 years of age, including neonates, received a weight-based dosing regimen of 30 mg/kg C/T (20 mg/kg ceftolozane and 10 mg/kg tazobactam) that did not exceed the adult fixed dose of 1.5 g C/T.

For both studies, paediatric participants were divided according to 5 age groups:

Age Groups:

- Group 1: 12 to <18 years
- Group 2: 6 to <12 years
- Group 3: 2 to <6 years
- Group 4: 3 months to <2 years
- Group 5: birth to <3 months

Eligible participants were randomly assigned in a 3:1 ratio to receive intravenous (IV) C/T (±MTZ) or MERO (± placebo), respectively, with stratification by age group, see tables below:

Table 33: *Participant Characteristics All Participants as Treated Population*

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	100		33		70		21		170		54	
Sex												
Male	35	(35.0)	13	(39.4)	47	(67.1)	6	(28.6)	82	(48.2)	19	(35.2)
Female	65	(65.0)	20	(60.6)	23	(32.9)	15	(71.4)	88	(51.8)	35	(64.8)
Age (Years)												
12 - < 18 (Years)	15	(15.0)	5	(15.2)	16	(22.9)	5	(23.8)	31	(18.2)	10	(18.5)
6 - < 12 (Years)	24	(24.0)	8	(24.2)	30	(42.9)	9	(42.9)	54	(31.8)	17	(31.5)
2 - < 6 (Years)	22	(22.0)	7	(21.2)	22	(31.4)	7	(33.3)	44	(25.9)	14	(25.9)
3 (Months) - < 2 (Years)	24	(24.0)	7	(21.2)	1	(1.4)	0	(0.0)	25	(14.7)	7	(13.0)
Birth - < 3 (Months)	15	(15.0)	6	(18.2)	1	(1.4)	0	(0.0)	16	(9.4)	6	(11.1)
Participants with data	100		33		70		21		170		54	
Mean	5.388		5.502		8.624		8.511		6.720		6.672	
SD	5.2542		5.7466		4.3631		3.6519		5.1474		5.2119	
Median	3.884		3.080		8.206		8.512		6.011		5.822	
Range	0.063 to 17.408		0.027 to 17.800		0.085 to 17.559		3.403 to 13.559		0.063 to 17.559		0.027 to 17.800	

Table 34: *Summary of Phase 2 Clinical Safety Studies in Paediatric Participants with Ceftolozane/Tazobactam (C/T)*

<table>
<tr><th>Study Number (Status) [CTD Location] Number of Study Sites (Countries)</th><th>Design (Indication)</th><th>Number of Participants by Treatment Group</th><th>Study Population (N)</th></tr>
<tr><td>MK-7625A-034 (completed) [Ref. 5.3.5.1: P034MK7625A] 52 sites (10 countries)</td><td>Phase 2, randomized, active comparator-controlled, multicenter, double-blind study

Treatment duration: 7-14 days

Indication: treatment of cUTI, including pyelonephritis</td><td>Randomization ratio C/T:MERO=3:1

<u>Overall</u>
C/T: 101 randomized/ 100 treated/ 69 completed
MERO: 33 randomized/ 33 treated/ 24 completed
<u>Age Groups</u>:
Group 1: 12 to <18 years [a] [b]
Group 2: 6 to <12 years [c] [b]
Group 3: 2 to <6 years [c] [b]
Group 4: 3 mos to <2 years [c] [b]
Group 5: birth to <3 mos [c] [b]
<table><tr><th>Age group</th><th>C/T group: participants randomized/treated/completed</th><th>MERO group: participants randomized/treated/completed</th></tr><tr><td>1</td><td>15 / 15 / 10</td><td>5 / 5 / 2</td></tr><tr><td>2</td><td>24 / 24 / 12</td><td>8 / 8 / 4</td></tr><tr><td>3</td><td>22 / 22 / 15</td><td>7 / 7 / 6</td></tr><tr><td>4</td><td>24 / 24 / 19</td><td>7 / 7 / 6</td></tr><tr><td>5</td><td>16 / 15 / 13</td><td>6 / 6 / 6</td></tr></table></td><td><u>Gender and median age by treatment group in the APaT population:</u>

<u>Overall C/T</u>
Gender : 35.0% M / 65.0% F
Median age (range): 3.884 years (0.063 [23 days] to 17.408)

<u>Overall MERO</u>
Gender : 39.4% M / 60.6% F
Median age (range): 3.080 years (0.027 [10 days] to 17.800)</td></tr>
<tr><td>MK-7625A-035 (completed) [Ref. 5.3.5.1: P035MK7625A]</td><td>Phase 2, randomized, active comparator-controlled,</td><td>Randomization ratio C/T + MTZ:MERO=3:1
<u>Overall</u>
C/T + MTZ: 71 randomized/ 70 treated/ 65 completed</td><td><u>Gender and median age by treatment group in the APaT population:</u></td></tr>
</table>

<table>
<tr><th>Study Number (Status) [CTD Location] Number of Study Sites (Countries)</th><th>Design (Indication)</th><th>Number of Participants by Treatment Group</th><th>Study Population (N)</th></tr>
<tr><td>50 sites (12 countries)</td><td>multicenter, double-blind study

Treatment duration: 5-14 days

Indication: treatment of cIAI</td><td>MERO: 23 randomized/ 21 treated/ 20 completed

<u>Age Groups</u>:
Group 1: 12 to <18 years [d] [f]
Group 2: 6 to <12 years [e] [f]
Group 3: 2 to <6 years [e] [f]
Group 4: 3 mos to <2 years [e] [f]
Group 5: birth to 3 mos [e] [f] [g]
<table><tr><th>Age group</th><th>C/T+MTZ group: participants randomized/treated/completed</th><th>MERO group: participants randomized/treated/completed</th></tr><tr><td>1</td><td>17 / 16 / 16</td><td>6 / 5 / 4</td></tr><tr><td>2</td><td>30 / 30 / 29</td><td>10 / 9 / 9</td></tr><tr><td>3</td><td>22 / 22 / 19</td><td>7 / 7 / 7</td></tr><tr><td>4</td><td>1 / 1 / 0</td><td>0 / 0 / 0</td></tr><tr><td>5</td><td>1 / 1 / 1</td><td>0 / 0 / 0</td></tr></table></td><td><u>Overall C/T + MTZ</u>:
Gender : 67.1% M / 32.9% F
Median age (range): 8.206 years (0.085 [31 days] to 17.559)

<u>Overall MERO</u>
Gender: 28.6% M / 71.4% F
Median age (range): 8.512 years (3.403 to 13.559)</td></tr>
<tr><td colspan="4">APaT=all participants as treated; C/T=ceftolozane/tazobactam; CTD=common technical document; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EOT=end of treatment; F=female; IV= intravenous; M=male; max=maximum; MERO=meropenem; mos=months; MTZ=metronidazole.
[a] C/T (1.0/0.5 g) IV every 8 hours, 7-14 days.
[b] MERO 20 mg/kg (max 1 g/dose) IV every 8 hours, 7-14 days.
[c] C/T (20/10 mg/kg) (max 1/0.5 g/dose) IV every 8 hours, 7-14 days.
[d] C/T (1.0/0.5 g) IV q 8 hours + MTZ 10 mg/kg IV every 8 hours, 5-14 days.
[e] C/T (20/10 mg/kg) IV q 8 hours + MTZ 10 mg/kg IV every 8 hours, 5-14 days.
[f] MERO 20 mg/kg (max of 1 g/dose) IV every 8 hours + placebo for MTZ IV every 8 hours, 5-14 days. (MTZ modification for Group 5 only).
[g] MTZ dose modified: Participants >28 days of age: MTZ 10 mg/kg dose every 8 hours (max dose 1.5 g/day). For participants ≤28 days of age, the suggested dosing regimen follows; however, other site-specific standard of care MTZ dosing was permitted at the investigator's discretion. Participants ≤28 days of age and ≤2 kg: MTZ 15 mg/kg loading dose, then 7.5 mg/kg dose every 12 hours. Participants ≤28 days of age and >2 kg: MTZ 15 mg/kg loading dose, 10 mg/kg dose every 8 hours.</td></tr>
</table>

Study P010 was a Phase 1 open-label study to characterize the PK of a single IV dose of C/T in paediatric participants receiving standard of care antibiotic therapy for proven or suspected gram-negative infection or for peri-operative prophylaxis. Six age groups were assessed:

- Group 1: ≥12 to <18 years (n=6)
- Group 2: ≥7 to <12 years (n=6)
- Group 3: ≥2 to <7 years (n=6)
- Group 4: ≥3 months to <2 years (n=6)
- Group 5: Birth (>32 weeks gestation, 7 days postnatal) to <3 months (n=7)
- Group 6: Birth (≤32 weeks gestation, 7 days postnatal) to <3 months (n=6)

This latter study is previously reviewed (procedure no. EMEA/H/C/003772/P46/002).

Overall Extent of Exposure

Disposition of Participants

Phase 2 Studies (P034, P035, and Integrated Data)

Overall, the disposition of participants was generally comparable between study treatment groups.

Nearly all randomized participants received at least 1 dose of study treatment and the majority of treated participants completed the study. Four participants were randomized but not treated (2 from each treatment group). The most common reason for discontinuation of IV study medication was lack of qualifying event (i.e. lack of a study-qualifying baseline urine culture; C/T: 15.9%; MERO: 14.8%), all in the P034 study. In total 3 patients discontinued due to AEs, all on C/T (2 patients in P035, one in P034), please refer to section 4.6.7. Discontinuation due to adverse events for details. All but 1 participant (in the C/T+MTZ group of P035) who switched to oral step-down therapy completed the study.

Phase 1 Study (P010)

Thirty-seven (37) of the 43 enrolled participants (86.0%) received study treatment and completed the study.

Duration of Exposure

Safety data includes data from 207 paediatric participants who received at least 1 dose of C/T in 3 studies. Of these, 170 were in the multidose Phase 2 studies (P034 and P035) and 37 were in the single dose Phase 1 study (P010).

Phase 2 Studies (P034, P035, and Integrated Data)

Overall, in the ApaT population, the median duration of exposure was generally comparable between treatment groups (C/T was 5.4 days [range: 0.3 to 14.0 days], and MERO was 5.0 days [range: 1.0 to 9.7]), see table below. Study treatment duration for IV therapy, was shorter in P034 compared with P035, because a larger proportion of participants discontinued from study treatment due to no qualifying pathogen.

In total, over half of the participants in both treatment groups (C/T: 86/170; MERO: 32/54) received oral step-down antibacterial medication with a median duration of 6.3 days (range: 0.5 to 10.0 days) in the C/T group and 5.8 days (range: 1.3 to 10.1 days) in the MERO group.

The most common oral step-down antibiotic treatments (>10% in either treatment group, among all ApaT participants) were cefixime (C/T: 14.0%; MERO: 24.2%) in P034, and metronidazole (C/T: 22.9%; MERO: 23.8%), amoxicillin/clavulanate potassium (C/T: 21.4%; MERO: 9.5%), and ciprofloxacin (C/T: 12.9%; MERO: 19.0%) in P035.

Table 35: *3 Study Treatment Exposure All Participants as Treated Population*

	P034 C/T n (%)	P034 MERO n (%)	P035 C/T+MTZ n (%)	P035 MERO n (%)	Total C/T n (%)	Total MERO n (%)
Participants in population	100	33	70	21	170	54
Number of Days on IV Therapy[a]						
Mean	5.2	4.8	6.4	5.8	5.7	5.2
Standard Deviation	2.73	2.47	2.83	1.77	2.83	2.27
Median	4.5	4.6	6.3	6.0	5.4	5.0
Range	0.3 to 13.7	1.0 to 9.7	0.3 to 14.0	2.3 to 8.8	0.3 to 14.0	1.0 to 9.7
Number of Days on IV Therapy[a] Category						
<1	3 (3.0)	0 (0.0)	1 (1.4)	0 (0.0)	4 (2.4)	0 (0.0)
>=1 - <3	13 (13.0)	9 (27.3)	3 (4.3)	1 (4.8)	16 (9.4)	10 (18.5)
>=3 - <5	37 (37.0)	10 (30.3)	19 (27.1)	6 (28.6)	56 (32.9)	16 (29.6)
>=5 - <7	25 (25.0)	6 (18.2)	20 (28.6)	9 (42.9)	45 (26.5)	15 (27.8)
>=7 - <10	17 (17.0)	8 (24.2)	16 (22.9)	5 (23.8)	33 (19.4)	13 (24.1)
>=10 - < 14	5 (5.0)	0 (0.0)	10 (14.3)	0 (0.0)	15 (8.8)	0 (0.0)
>=14 - < 15	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.6)	0 (0.0)
>=15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Days of Oral Step-Down Treatment Received						
N1	51	20	35	12	86	32
Mean	5.8	6.0	5.8	5.6	5.8	5.9
Standard Deviation	1.72	1.50	2.46	2.55	2.04	1.94
Median	6.3	6.2	6.3	5.2	6.3	5.8

	P034 C/T n (%)	P034 MERO n (%)	P035 C/T+MTZ n (%)	P035 MERO n (%)	Total C/T n (%)	Total MERO n (%)
Range	1.0 to 9.6	4.0 to 9.8	0.5 to 10.0	1.3 to 10.1	0.5 to 10.0	1.3 to 10.1
Days of Overall Treatment Received						
Mean	8.2	8.4	9.3	9.0	8.6	8.6
Standard Deviation	4.02	4.26	3.56	3.17	3.87	3.85
Median	9.0	9.3	10.0	8.0	9.2	9.2
Range	0.3 to 14.2	1.0 to 14.6	0.3 to 18.3	4.3 to 14.8	0.3 to 18.3	1.0 to 14.8
Days of Overall Treatment Received Category						
<1	3 (3.0)	0 (0.0)	1 (1.4)	0 (0.0)	4 (2.4)	0 (0.0)
>=1 - <3	9 (9.0)	8 (24.2)	2 (2.9)	0 (0.0)	11 (6.5)	8 (14.8)
>=3 - <5	17 (17.0)	1 (3.0)	4 (5.7)	1 (4.8)	21 (12.4)	2 (3.7)
>=5 - <7	8 (8.0)	1 (3.0)	12 (17.1)	7 (33.3)	20 (11.8)	8 (14.8)
>=7 - <10	26 (26.0)	10 (30.3)	15 (21.4)	6 (28.6)	41 (24.1)	16 (29.6)
>=10 - < 14	36 (36.0)	12 (36.4)	30 (42.9)	5 (23.8)	66 (38.8)	17 (31.5)
>=14 - < 15	1 (1.0)	1 (3.0)	5 (7.1)	2 (9.5)	6 (3.5)	3 (5.6)
>=15	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.6)	0 (0.0)

C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole.
[a] IV treatment duration is calculated as (start datetime of last study drug administration + 8 hours – start datetime of first study drug administration) / 86400, rounded to one decimal place.
N1= Number of participants who received oral step-down treatment.

Phase 1 Study (P010)

Thirty-seven (37) participants received a single IV dose of study treatment.

The CHMP noted that the safety analysis population for each of the 3 studies was the ApaT population consisting of all randomized participants who received any amount of study treatment anda includes data from 207 paediatric participants who received at least 1 dose of C/T. Of these, 170 were in the multidose Phase 2 studies (100 in P034 and 70 in P035) and 37 were in the single dose Phase 1 study P010.

Overall, in the Phase 2 Studies (P034, P035), the disposition of participants was generally comparable between study treatment groups. It should be noted that there were less children in the youngest age group, and only one (1) patient in each of group 4 and 5 (birth to <2 years of age) in the cIAI study

(P035). However, this might be due to the condition of cIAI being less common at very young age and therefore difficult to recruit patients, and is hence, considered acceptable.

With regard to duration of IV therapy, overall in the ApaT population, the median duration of exposure was generally comparable between treatment groups (C/T was 5.4 days [range: 0.3 to 14.0 days], and MERO was 5.0 days [range: 1.0 to 9.7]). Study treatment duration for IV therapy was, however, shorter in the AP/cUTI study (P034) compared with cIAI (P035), because a larger proportion of participants discontinued from study treatment due to no qualifying pathogen in the P034 study.

It should also be noted that the majority of patients in both treatment groups (C/T: 86/170; MERO: 32/54) received concomitant antibiotics; so-called oral step-down antibacterial medication, with a median duration of 6.3 days in the C/T group and 5.8 days in the MERO group. This approach was considered acceptable, albeit making the assessment of possible relationship to drug more difficult.

Demographic and Other Characteristics of Study Population

Phase 2 Studies (P034, P035, and Integrated Data)

Demographic and baseline characteristics were generally comparable between treatment groups and consistent with those for paediatric participants with the study participants' baseline diagnoses.

The median age of participants was 6.01 years (range: 0.06 [23 days] to 17.56) in the C/T group and 5.82 years (range: 0.03 [10 days] to 17.8) in the MERO group. Notably, median ages were higher in the P035 study than in the P034 study; cIAI is less common in younger children in comparison to AP/cUTI, thus P035 enrolled fewer Group 4 and 5 (birth to <2 years of age) participants.

• The majority of participants were female, white, not Hispanic or Latino, and from Europe.

• The majority of participants had a baseline diagnosis of pyelonephritis in P034; and complicated appendicitis in P035.

• Few participants from either study had bacteremia at baseline.

• Few participants from either study were identified by the investigator as having failed prior antibacterial therapy, though the majority of participants had used prior antibiotics.

Overall, the majority of participants from both treatment groups received prior and concomitant non-antibiotic medications, and prior non-study antibiotics.

Overall, between the first dose of IV study medication and the EOT visit, 1 participant in each treatment group received a dose of concomitant non-study antibiotic therapy (excluding a protocol-allowed single dose of prophylactic antibiotics).

Between the first dose of IV study medication and the TOC visit, 12.4% of participants in the C/T group and 11.1% in the MERO group, received at least 1 dose of concomitant non-study antibiotic therapy. Most of these were P034 participants who received protocol-allowed antibiotic prophylaxis after the EOT visit, based on site-level standard of care for participants at increased risk of recurrent cUTI.

Participants who received non-study antibiotics that were stopped on the same date as the first dose of IV study medication or started on the same date as the EOT or TOC visit date (for which a start or stop time for the non-study antibiotic was not recorded), were not included as having received concomitant non-study antibiotics.

Compliance with the overall treatment regimen (both IV and oral step-down) was high in both treatment groups in P034 and P035.

Phase 1 Study (P010)

Nineteen (51.4%) participants were male and 18 (48.6%) were female, and the majority of participants (67.6%) were white. Most participants (97.3%) were receiving antibiotics for a proven or suspected gram-negative bacterial infection.

4.6.2. Adverse events

Overview of Adverse Events

The overall incidence of Aes (all-causality and drug-related), SAEs, and Aes leading to discontinuation, was comparable between the C/T and MERO treatment groups.

The majority of participants experienced an AE; most of these were not considered by the investigator to be related to study treatment. There was a low incidence of SAEs, Aes leading to discontinuation, and SAEs leading to discontinuation. There were no drug-related SAEs, Aes leading to death, or discontinuations due to drug-related Aes, see overview table below.

Table 36: *Analysis of Adverse Event Summary All Participants as Treated Population Studies MK-7625A-034 and MK-7625A-035 Combined*

	C/T		MERO		Difference in % vs MERO
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	170		54		
with one or more adverse events	115	(67.6)	33	(61.1)	6.5 (-7.5, 21.6)
with no adverse event	55	(32.4)	21	(38.9)	-6.5 (-21.6, 7.5)
with drug-related[b] adverse events	27	(15.9)	8	(14.8)	1.1 (-11.7, 10.7)
with serious adverse events	11	(6.5)	2	(3.7)	2.8 (-6.5, 8.4)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0.0 (-6.7, 2.2)
who died	0	(0.0)	0	(0.0)	0.0 (-6.7, 2.2)
discontinued drug due to an adverse event	3	(1.8)	0	(0.0)	1.8 (-4.9, 5.1)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-6.7, 2.2)
discontinued drug due to a serious adverse event	2	(1.2)	0	(0.0)	1.2 (-5.5, 4.2)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-6.7, 2.2)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
AE=adverse event, CI=confidence interval, cIAI=complicated intra-abdominal infections, C/T=ceftolozane/tazobactam, IV=intravenous, MERO= meropenem.
Study treatment discontinuation refers to an AE leading to IV study medication withdrawn.
In the cIAI study, participants in the ceftolozane/tazobactam group also received metronidazole.

The AE summary profile was generally comparable between P034 and P035 studies for both C/T and MERO groups with the exceptions of the incidences of Aes and SAEs which were higher in the C/T+MTZ group for P035 compared with the MERO group for P035; however, the incidence of drug-related Aes was similar between treatment groups in both studies, see table below

Table 37: *Adverse Event Summary All Participants as Treated Population*

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	100		33		70		21		170		54	
with one or more adverse events	59	(59.0)	20	(60.6)	56	(80.0)	13	(61.9)	115	(67.6)	33	(61.1)
with no adverse event	41	(41.0)	13	(39.4)	14	(20.0)	8	(38.1)	55	(32.4)	21	(38.9)
with drug-related[a] adverse events	14	(14.0)	5	(15.2)	13	(18.6)	3	(14.3)	27	(15.9)	8	(14.8)
with serious adverse events	3	(3.0)	2	(6.1)	8	(11.4)	0	(0.0)	11	(6.5)	2	(3.7)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(1.0)	0	(0.0)	2	(2.9)	0	(0.0)	3	(1.8)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(2.9)	0	(0.0)	2	(1.2)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
C/T=ceftolozane/tazobactam, MERO= meropenem, MTZ=metronidazole.

The CHMP noted that the majority of participants experienced an AE. In total 115/170 (67.6%) patients in the C/T arm and 33/54 (61.1%) in the MERO treatment arm experienced one or more Aes, of which 15.9% and 14.8% were considered to be related to study treatment by the investigator. In the C/T group, 11 (6.7%) patients experienced SAEs, compared to 2 patients (3.7%) in the MERO group. However, none of these SAEs were considered related to treatment.

Three (3) patients in the C/T treatment arm vs. none in the MERO arm discontinued treatment due to Aes, however none were considered treatment-related. There were no drug-related SAEs, Aes leading to death, or discontinuations due to drug-related Aes.

The incidences of Aes and SAEs which were higher in the C/T+MTZ group for P035 compared with the corresponding MERO group; however, the incidence of *drug-related* Aes was similar between treatment groups in both studies.

Common Adverse Events

Most Frequently Reported Adverse Events

The incidence of individual reported Aes was generally comparable between treatment groups.

Overall, the most frequently reported Aes (>5%) were diarrhoea (11.2%), pyrexia (8.8%), thrombocytosis (7.6%), and AST increased (5.3%) in the C/T group, and diarrhoea (14.8%), thrombocytosis, pyrexia, nasopharyngitis, and urinary tract infection (each 7.4%), and AST increased and ALT increased (each 5.6%) in the MERO group, see table below.

Table 38: *Participants With Adverse Events by System Organ Class and Preferred Term (Incidence ≥ 5% in One or More Treatment Groups) All Participants as Treated Population*

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	100		33		70		21		170		54	
with one or more adverse events	59	(59.0)	20	(60.6)	56	(80.0)	13	(61.9)	115	(67.6)	33	(61.1)
with no adverse events	41	(41.0)	13	(39.4)	14	(20.0)	8	(38.1)	55	(32.4)	21	(38.9)
Blood and lymphatic system disorders	**16**	**(16.0)**	**4**	**(12.1)**	**18**	**(25.7)**	**2**	**(9.5)**	**34**	**(20.0)**	**6**	**(11.1)**
Anaemia	2	(2.0)	0	(0.0)	4	(5.7)	0	(0.0)	6	(3.5)	0	(0.0)
Neutropenia	5	(5.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(2.9)	0	(0.0)
Thrombocytosis	7	(7.0)	3	(9.1)	6	(8.6)	1	(4.8)	13	(7.6)	4	(7.4)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(8.6)**	**1**	**(4.8)**	**6**	**(3.5)**	**1**	**(1.9)**
Tachycardia	0	(0.0)	0	(0.0)	4	(5.7)	1	(4.8)	4	(2.4)	1	(1.9)
Gastrointestinal disorders	**10**	**(10.0)**	**6**	**(18.2)**	**33**	**(47.1)**	**7**	**(33.3)**	**43**	**(25.3)**	**13**	**(24.1)**
Abdominal pain	2	(2.0)	0	(0.0)	7	(10.0)	0	(0.0)	9	(5.3)	0	(0.0)
Diarrhoea	7	(7.0)	3	(9.1)	12	(17.1)	5	(23.8)	19	(11.2)	8	(14.8)
Vomiting	1	(1.0)	1	(3.0)	7	(10.0)	1	(4.8)	8	(4.7)	2	(3.7)
General disorders and administration site conditions	**10**	**(10.0)**	**3**	**(9.1)**	**17**	**(24.3)**	**4**	**(19.0)**	**27**	**(15.9)**	**7**	**(13.0)**
Pyrexia	6	(6.0)	1	(3.0)	9	(12.9)	3	(14.3)	15	(8.8)	4	(7.4)
Infections and infestations	**19**	**(19.0)**	**10**	**(30.3)**	**15**	**(21.4)**	**6**	**(28.6)**	**34**	**(20.0)**	**16**	**(29.6)**

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**19**	**(19.0)**	**10**	**(30.3)**	**15**	**(21.4)**	**6**	**(28.6)**	**34**	**(20.0)**	**16**	**(29.6)**
Nasopharyngitis	0	(0.0)	1	(3.0)	3	(4.3)	3	(14.3)	3	(1.8)	4	(7.4)
Rhinitis	2	(2.0)	2	(6.1)	0	(0.0)	0	(0.0)	2	(1.2)	2	(3.7)
Urinary tract infection	1	(1.0)	3	(9.1)	0	(0.0)	1	(4.8)	1	(0.6)	4	(7.4)
Vulvovaginitis	0	(0.0)	2	(6.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.7)
Injury, poisoning and procedural complications	**1**	**(1.0)**	**1**	**(3.0)**	**9**	**(12.9)**	**2**	**(9.5)**	**10**	**(5.9)**	**3**	**(5.6)**
Incision site pain	0	(0.0)	0	(0.0)	4	(5.7)	1	(4.8)	4	(2.4)	1	(1.9)
Investigations	**11**	**(11.0)**	**4**	**(12.1)**	**17**	**(24.3)**	**4**	**(19.0)**	**28**	**(16.5)**	**8**	**(14.8)**
Alanine aminotransferase increased	4	(4.0)	2	(6.1)	4	(5.7)	1	(4.8)	8	(4.7)	3	(5.6)
Aspartate aminotransferase increased	4	(4.0)	2	(6.1)	5	(7.1)	1	(4.8)	9	(5.3)	3	(5.6)
Platelet count increased	2	(2.0)	0	(0.0)	5	(7.1)	2	(9.5)	7	(4.1)	2	(3.7)
Metabolism and nutrition disorders	**5**	**(5.0)**	**0**	**(0.0)**	**6**	**(8.6)**	**1**	**(4.8)**	**11**	**(6.5)**	**1**	**(1.9)**
Renal and urinary disorders	**6**	**(6.0)**	**0**	**(0.0)**	**4**	**(5.7)**	**1**	**(4.8)**	**10**	**(5.9)**	**1**	**(1.9)**
Respiratory, thoracic and mediastinal disorders	**5**	**(5.0)**	**1**	**(3.0)**	**7**	**(10.0)**	**1**	**(4.8)**	**12**	**(7.1)**	**2**	**(3.7)**
Skin and subcutaneous tissue disorders	**9**	**(9.0)**	**4**	**(12.1)**	**4**	**(5.7)**	**2**	**(9.5)**	**13**	**(7.6)**	**6**	**(11.1)**
Vascular disorders	**2**	**(2.0)**	**2**	**(6.1)**	**7**	**(10.0)**	**0**	**(0.0)**	**9**	**(5.3)**	**2**	**(3.7)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole.

Overall, the Committee noted that the most frequently reported Aes (>5%) were diarrhoea (11.2%), pyrexia (8.8%), thrombocytosis (7.6%), and AST increased (5.3%) in the C/T group, these are all known ADRs with Zerbaxa. For the MERO group the most frequently reported Aes (>5%) were diarrhoea (14.8%), thrombocytosis, pyrexia, nasopharyngitis, and urinary tract infection (each 7.4%), and AST increased and ALT increased (each 5.6%).

The SOCs where Aes were reported most frequently (≥20% in the C/T arm): Gastrointestinal disorders (25.3% in the C/T arm vs. 24.1% in the MERO arm), Blood and lymphatic system disorders (20.0% vs. 11.1%), and Infections and infestations (20.0% vs. 29.6%).

Drug-related Adverse Events

Overall, the incidence of Aes considered as drug-related by the investigator was generally comparable between both treatment groups (C/T: 15.9%; MERO: 14.8%). The most frequently reported drug-related Aes (>2% of participants) were diarrhoea (C/T: 4.1%; MERO: 7.4%), AST increased (C/T: 3.5%; MERO: 3.7%), and ALT increased (C/T: 2.9%; MERO: 1.9%), see table below.

No Aes related to oral step-down treatment were reported.

Table 39: *Participants With Drug-Related Adverse Events (Incidence > 0% in One or More Treatment Groups) All Participants as Treated Population*

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	100		33		70		21		170		54	
with one or more drug-related adverse events	14	(14.0)	5	(15.2)	13	(18.6)	3	(14.3)	27	(15.9)	8	(14.8)
with no drug-related adverse events	86	(86.0)	28	(84.8)	57	(81.4)	18	(85.7)	143	(84.1)	46	(85.2)
Blood and lymphatic system disorders	**4**	**(4.0)**	**1**	**(3.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(2.4)**	**1**	**(1.9)**
Eosinophilia	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Leukaemoid reaction	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Neutropenia	3	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.8)	0	(0.0)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**0**	**(0.0)**	**1**	**(0.6)**	**0**	**(0.0)**
Tachycardia	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)
Gastrointestinal disorders	**3**	**(3.0)**	**4**	**(12.1)**	**5**	**(7.1)**	**1**	**(4.8)**	**8**	**(4.7)**	**5**	**(9.3)**
Diarrhoea	3	(3.0)	3	(9.1)	4	(5.7)	1	(4.8)	7	(4.1)	4	(7.4)
Frequent bowel movements	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Vomiting	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(2.9)**	**0**	**(0.0)**	**2**	**(1.2)**	**0**	**(0.0)**

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(2.9)**	**0**	**(0.0)**	**2**	**(1.2)**	**0**	**(0.0)**
Feeling cold	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**	**1**	**(1.9)**
Vulvovaginal mycotic infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(1.9)
Investigations	**4**	**(4.0)**	**1**	**(3.0)**	**5**	**(7.1)**	**1**	**(4.8)**	**9**	**(5.3)**	**2**	**(3.7)**
Alanine aminotransferase increased	2	(2.0)	0	(0.0)	3	(4.3)	1	(4.8)	5	(2.9)	1	(1.9)
Aspartate aminotransferase increased	2	(2.0)	1	(3.0)	4	(5.7)	1	(4.8)	6	(3.5)	2	(3.7)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	2	(2.9)	0	(0.0)	2	(1.2)	0	(0.0)
C-reactive protein increased	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)
Neutrophil count decreased	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Red blood cell sedimentation rate increased	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)
Metabolism and nutrition disorders	**3**	**(3.0)**	**0**	**(0.0)**	**1**	**(1.4)**	**0**	**(0.0)**	**4**	**(2.4)**	**0**	**(0.0)**
Increased appetite	3	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.8)	0	(0.0)
Metabolic disorder	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.6)	0	(0.0)

	P034 C/T		P034 MERO		P035 C/T+MTZ		P035 MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(2.9)**	**0**	**(0.0)**	**2**	**(1.2)**	**0**	**(0.0)**
Dysgeusia	0	(0.0)	0	(0.0)	2	(2.9)	0	(0.0)	2	(1.2)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(1.0)**	**1**	**(3.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.6)**	**1**	**(1.9)**
Pruritus	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Urticaria	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)
Vascular disorders	**0**	**(0.0)**	**1**	**(3.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.9)**
Phlebitis	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole.
This table only includes IV drug related Adverse Events.

Overall, the incidence of Aes considered as drug-related by the investigator was considered by the Committee comparable between both treatment groups (C/T: 15.9%; MERO: 14.8%), corresponding to 27 vs. 8 patients, respectively.

The most frequently reported drug-related Aes (>1%) were neutropenia (C/T 1.8%; MERO: 0%), diarrhoea (C/T: 4.1%; MERO: 7.4%), AST increased (C/T: 3.5%; MERO: 3.7%), and ALT increased (C/T: 2.9%; MERO: 1.9%), blood alkaline phosphatase increased (C/T: 1.2%; MERO: 0%), increased appetite (C/T: 1.8%; MERO: 0%), and dysgeusia (C/T: 1.2%; MERO: 0%). All but three of these ADRs are well

known for Zerbaxa for the adult population, but neutropenia, increased appetite and dysgeusia seems to be new ADRs for this product. All the ADRs presented here are reflected in the proposed SmPC in a separate table concerning paediatric safety data. However, a separate table was not acceptable. The MAH was requested to consider merging the adverse reactions (from the proposed paediatric table) into a single table, i.e. insert new ADRs into the already approved table based on adult safety data. In case of paediatric-specific frequencies or adverse reactions, this was indicated by footnotes, as already performed for the specific therapeutic indications for adults. However, after assessing MAH's proposal for modifications, the CHMP reconsidered the request. The MAH was therefore asked to reinsert the approved version of the table (which is based on adult data). In addition, to keep in with the paediatric data and with reference to the SmPC guideline, a paediatric sub-section was recommended to be included *below* the table.

Any co-medication use will hamper the safety evaluation of C/T treatment in the children. The majority of paediatric patients in both studies did receive both prior and/or concomitant medications, including non-antibiotics and antibiotics. This issue was not discussed by the MAH. However, based on data provided, and presence of many different medications, any trend would be difficult to see, reason for which the issue was not pursued.

Adverse Events by Maximum Intensity

Most Aes were generally mild to moderate and comparable between both treatment groups. The individual Aes within each intensity category were also generally comparable between both treatment groups.

The incidence of severe Aes was low for both treatment groups (C/T: 5.9%; MERO: 1.9%). No severe AE was reported in >2 participants. The most commonly reported severe Aes (>1% of participants), were neutropenia (1.2%) in the C/T group, and hypertension (1.9%) in the MERO group.

Events of Clinical Interest (ECIs)

No predefined ECIs of elevated liver enzymes meeting specific DILI criteria or events of overdose of C/T were reported in P034 or P035.

Analysis of Adverse Events by Organ System or Syndrome

Select Aes of hypersensitivity, severe skin reaction, *Clostridioides difficile*-associated diarrhea (CDAD), renal impairment, and hemolysis were reviewed, as they are potentially associated with the β-lactam antibiotic class. No Aes of hypersensitivity, severe skin reactions, or CDAD, were reported in P034 or P035.

<u>Adverse Events of Acute Renal Failure</u>

Based on the SMQ of Acute Renal Failure, there was 1 AE of oliguria reported in the C/T+MTZ group in P035. The event was non-serious, not considered related to study treatment, resolved, and the participant did not discontinue study treatment.

Although not considered part of the SMQ of Acute Renal Failure, an AE of exacerbation of chronic kidney disease occurred in a participant in the C/T group in P034 which caused the participant to discontinue study treatment. The event was non-serious, not considered related to study treatment, and resolved.

<u>Adverse Events of Hemolytic Disorders</u>

Based on the SMQ of Hemolytic Disorders, there was 1 AE of transfusion reaction reported in the C/T +MTZ group in P035. The participant had a negative Coombs' test at screening and a positive Coombs' test at EOIV. The event was non-serious, did not cause the participant to discontinue study treatment, and was not considered related to study treatment.

Phase 1 Study (P010)

In P010, 11 participants (29.7%) experienced at least 1 AE and all Aes were either mild or moderate in intensity. Three participants (8.1%) experienced SAEs; 2 participants (5.4%) experienced drug-related Aes. No severe Aes, deaths, or Aes leading to discontinuation of study treatment were reported.

Anemia, diarrhea, and hypokalemia were the only Aes reported for >1 participant (n=2 each).

Specific SAEs that occurred were: pneumonia, infective pulmonary exacerbation of cystic fibrosis, and device-related sepsis. Each of the SAEs began several days after study treatment administration and were considered by the investigator to be unrelated to study treatment.

Specific drug-related Aes that occurred were: 1 dizziness (1 participant), bradycardia and tachycardia (1 participant). Each of the drug-related Aes were mild in severity and resolved.

There were no events indicative of hypersensitivity reactions or hemolytic disorders, or any events involving *Clostridiodes difficile*.

The CHMP noted that most Aes were generally mild to moderate and comparable between both treatment groups. The incidence of severe Aes was 5.9% (10 pts) for the C/T arm and 1.9% (1 patient) for the MERO arm, which corresponds to 10 patients vs. 1 patient in the treatment groups, respectively. No severe AE was reported in >2 participants. The most commonly reported severe Aes were neutropenia (1.2%, 2 patients) in the C/T group, and hypertension (1.9%, one patient) in the MERO group.

Within the Renal and urinary disorders SOC, renal impairment and renal failure are already stated ADR for Zerbaxa based on adult safety data (Zerbaxa SmPC). With regards to Acute Renal Failure or the associated SOC, there was 1 AE of oliguria reported in the C/T+MTZ group in P035 and one AE of exacerbation of chronic kidney disease that occurred in a participant in the C/T group in P034. None of these non-serious events was considered related to treatment by the investigator.

In study P010, specific drug-related Aes that occurred were: 1 dizziness (1 participant), bradycardia and tachycardia (1 participant). Each of the drug-related Aes were mild in severity and resolved.

4.6.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in P034 or P035.

Serious Adverse Events

The overall incidence of SAEs was low for the treatment groups (C/T: 6.5% vs. MERO: 3.7%, i.e. 11 patients vs. 2 patients, respectively). The most frequently reported SAEs (>1%) were pneumonia (2 patients, 1.2%) in the C/T group, and pyrexia and hypertension (both 1.9%) in the MERO group. All SAEs resolved except for 1 (hypertension), which resolved with sequelae. No SAEs were considered to be related to study treatment.

The Committee noted that the overall incidence of SAEs was somewhat higher in the C/T group (6.5%, 11 pts) than in the MERO group (3.7%, 2 pts). Of the 11 patients with SAEs in the C/T group, SAEs were reported in 3 patients in P034 (all within the SOC Infections and infestations), and in 8 patients in P035 (4 in each of the SOCs Infections and infestations, and Gastrointestinal disorder). The most frequently reported SAEs (>1%) were pneumonia (1.2%, i.e. in two patients) in the C/T group, and pyrexia and hypertension (both 1.9%, i.e. one patient each) in the MERO group.

No SAEs were considered to be related to study treatment.

4.6.4. Laboratory findings

Clinical laboratory evaluations

Phase 2 Studies (P034, P035, and Integrated Data)

Mean changes from baseline over time were generally comparable between the treatment groups for clinical chemistry and hematology. No clinically meaningful changes from baseline over time in any laboratory parameters were observed.

The proportion of participants with post-baseline hematology and chemistry measurements that worsened from baseline was generally comparable between treatment groups.

Few participants from either treatment group had elevated liver function test results. The data show no DILI and no pattern of elevated liver function tests. Most of the elevations occurred at screening or during follow-up and appeared to be transient in nature.

Seroconversion of direct Coombs' test from negative to positive is a known side effect of β-lactam exposure. A higher proportion of participants in the C/T group compared to the MERO group seroconverted from a negative result at baseline to a positive direct Coombs' test result at EOIV. No Aes or laboratory abnormalities suggestive of drug-induced hemolytic anemia were reported for these participants.

In clinical studies, there was no evidence of haemolysis in patients who developed a positive direct Coombs test in any treatment group (Zerbaxa SmPC). Based on the SMQ of Hemolytic Disorders, there was 1 AE of transfusion reaction reported in the C/T +MTZ group in P035, and this participant had a negative Coombs' test at screening and a positive Coombs' test at EOIV. This event was non-serious and not considered related to treatment.

The CHMP considered that Coombs test positive are already identified as an ADR for Zerbaxa, and there is text in section 4.4 and 4.8 of the Zerbaxa SmPC describing this in more detail; "The development of a positive direct antiglobulin test (DAGT) may occur during treatment with ceftolozane/tazobactam (see section 4.8). In clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment."

Phase 1 Study (P010)

No participants had abnormal liver function test results that met the criteria for closely monitored events.

In general, small mean changes in chemistry and hematology parameters from Baseline to Day 2 were observed in all dosage groups.

One participant from Group 2 with a negative baseline Coombs' test had a positive test result on Day 2. This participant did not experience an AE of anemia but had an SAE of cystic fibrosis pulmonary exacerbation that began on Study Day 4. From Baseline to Day 2, no other participant experienced a shift from negative to positive in direct Coombs' test results.

Vital signs, physical findings, and other observations related to safety

Phase 2 Studies (P034, P035, and Integrated Data)

There were no clinically meaningful findings in the vital signs measurements. The mean changes in heart rate, respiratory rate, temperature and systolic and diastolic blood pressure from baseline across scheduled visits were small and generally comparable between both treatment groups.

Phase 1 Study (P010)

In general, mean changes in vital signs from Baseline to Day 1 (post-dose) and Day 2 were observed in all dosage groups, including Groups 5 and 6. For any vital sign value not in the expected range, investigators had to confirm or update the value to ensure it was accurate. From Baseline to Day 1, no clinically significant shifts in ECG parameters were observed in the dosage groups.

4.6.5. Safety in special populations

Intrinsic Factors

The incidence of Aes by the intrinsic factors of age and gender for the integrated P034 and P035 studies are provided below. Intrinsic factors of renal function, body weight, or race/ethnicity were not assessed.

Age

The incidences of AE summary measures by age group were generally comparable between the C/T and MERO treatment groups, se table below.

Table 40: Adverse Event Summary By Age group All Participants as Treated Population Studies MK-7625A-034 and MK-7625A-035 Combined

	Group 1 12 to <18 y C/T		Group 1 12 to <18 y MERO		Group 2 6 to <12 y C/T		Group 2 6 to <12 y MERO		Group 3 2 to <6 y C/T		Group 3 2 to <6 y MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	31		10		54		17		44		14	
with one or more adverse events	22	(71.0)	7	(70.0)	39	(72.2)	10	(58.8)	29	(65.9)	8	(57.1)
with no adverse event	9	(29.0)	3	(30.0)	15	(27.8)	7	(41.2)	15	(34.1)	6	(42.9)
with drug-related[a] adverse events	4	(12.9)	0	(0.0)	13	(24.1)	2	(11.8)	3	(6.8)	2	(14.3)
with serious adverse events	0	(0.0)	1	(10.0)	4	(7.4)	0	(0.0)	5	(11.4)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	1	(1.9)	0	(0.0)	2	(4.5)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.5)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	Group 4 3 mo to <2 y C/T		Group 4 3 mo to <2 y MERO		Group 5 Birth to < 3 mo C/T		Group 5 Birth to < 3 mo MERO		Total C/T		Total MERO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	25		7		16		6		170		54	
with one or more adverse events	15	(60.0)	5	(71.4)	10	(62.5)	3	(50.0)	115	(67.6)	33	(61.1)
with no adverse event	10	(40.0)	2	(28.6)	6	(37.5)	3	(50.0)	55	(32.4)	21	(38.9)
with drug-related[a] adverse events	3	(12.0)	3	(42.9)	4	(25.0)	1	(16.7)	27	(15.9)	8	(14.8)
with serious adverse events	1	(4.0)	1	(14.3)	1	(6.3)	0	(0.0)	11	(6.5)	2	(3.7)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.8)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.2)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
cIAI=complicated intra-abdominal infections, C/T=ceftolozane/tazobactam, MERO=meropenem.
In the cIAI study, participants in the ceftolozane/tazobactam group also received metronidazole.

There were no clinically meaningful differences identified in patterns of specific Aes or AE intensity between treatment groups in the incidences of Aes within age categories. These results are consistent with those in the overall population.

As shown in the table above, the distribution of treatment-emergent Aes is given for different age cohorts or categories (group 1-5). For the integrated population (P034+P035), the frequency of Aes (participants

with one or more Aes) in general is either similar or ~10% difference within each age group; for the age cohorts, these frequencies are given (C/T vs. MERO), from oldest to youngest: group 1 (71.0% vs. 70.0%), group 2 (72.2% vs. 58.8%), group 3 (65.9% vs. 57.1%), group 4 (60.0% vs. 71.4%) and group 5 (62.5% vs. 50.0%). No apparent trends can be found. Having in mind that the age groups are constituted of a quite small number of paediatric patents, especially in the MERO groups (randomisation for C/T:MERO is 3:1), the frequency will inherently be uncertain and must be interpreted with caution.

When looking at the *treatment-related* Aes and age cohorts, the Aes considered related to Zerbaxa treatment and hence, of most importance, the numbers are even more uncertain. Number of patients with events out of total number of patients within each age group are as follows: (C/T vs. MERO), from oldest to youngest: group 1 (4/31 vs. 0/10 patients), group 2 (13/54 vs. 2/17), group 3 (3/44 vs. 2/14), group 4 (3/25 vs. 3/7) and group 5 (4/16 vs. 1/6).

As stated by the MAH, there were no clinically meaningful differences identified in patterns of specific Aes or AE intensity between treatment groups in the incidences of Aes within age categories. The CHMP considered these results consistent with those in the overall population.

Gender

The incidences of AE summary measures by gender were generally comparable between the C/T and MERO treatment groups.

There were no clinically meaningful differences identified in patterns of specific Aes or AE intensity between treatment groups in the incidences of Aes within the gender categories. These results are consistent with those in the overall population.

Extrinsic Factors

Geographic Region

The incidences of AE summary measures by geographic region were generally comparable between the C/T and MERO treatment groups. Higher incidences of Aes (in both treatment groups) and SAEs (in the C/T group) were reported for participants in North America compared with Europe; however, within these regions, the incidence of Aes was comparable between the C/T and MERO treatment groups.

There were no clinically meaningful differences identified in patterns of specific Aes or AE intensity between treatment groups in the incidences of Aes by geographic region. These results are consistent with those in the overall population.

The CHMP noted that there were no clinically meaningful differences identified in patterns of specific Aes or AE intensity between treatment groups in the incidences of Aes within age or gender categories or by geographic region. These results are consistent with those in the overall population.

4.6.6. Safety related to drug-drug interactions and other interactions

No new DDI studies were provided in support of this application. Therefore, Aes by drug interaction were not evaluated. The CHMP however considered that data assessed in previous Zerbaxa procedures indicate a low risk of DDIs during C/T treatment, and it is reasonable that the low DDI potential observed in adults can be extended to the paediatric population.

4.6.7. Discontinuation due to adverse events

Adverse Events Leading to Study Drug Discontinuation

Three participants (1.8%), all from the C/T group, discontinued study treatment due to an AE. None of the Aes leading to discontinuation were considered by the investigator to be drug-related.

In P034, one participant discontinued due to chronic kidney disease. In P035, 1 participant discontinued due to pneumonia, and 1 participant discontinued due to pneumonia and abdominal sepsis.

The CHMP noted that, in total, 3 patients (1.8%) in the C/T treatment arm discontinued drug due to an AE (chronic kidney disease, pneumonia, pneumonia and abdominal sepsis). None of these were considered related to treatment by the investigator.

4.6.8. Post marketing experience

Ceftolozane/tazobactam (C/T) was first approved in the United States on 19-DEC-2014 (international birth date) and has been approved in adults in 76 countries as of 19-DEC-2020. There are no records of any registration being revoked or withdrawn for safety reasons.

Based on the above calculations, the estimated cumulative number of patients through 19-DEC-2020 exposed to ceftolozane and tazobactam for all indications was within the range of 63,286 to 443,004 patients, depending on the indication and duration of treatment.

The Applicant's safety database was queried for valid, spontaneous and non-interventional study reports of C/T from 19-DEC-2014 to 19-DEC-2020.

A total of 2,178 reports containing 3,754 events were identified. By number of events, the 3 most commonly affected SOCs were: Injury, poisoning and procedural complications; General disorders and administration site conditions; and Infections and infestations.

Of the 2,178 reports, 55 reports or cases concerned paediatric patients (4 non-interventional study reports and 51 spontaneous). The 55 reports contained 117 events: 12 (10%) were considered serious and 105 (90%) were non-serious. Of the 55 reports, 16 were female patients, 10 were male patients, and 29 were of unidentified gender. The median age was 11 years (range: 91 days-17 years). The 3 most commonly reported current conditions were: hospitalization (n=15), Pseudomonas infection (n=13), and pneumonia (n=9).

By number of events, the 3 most commonly affected SOCs in paediatric reports were: Injury, poisoning and procedural complications (55 cases including 77 events); General disorders and administration site conditions (13 cases, 13 events); and Infections and infestations (4 cases, 6 events).

• The Injury, poisoning and procedural complications SOC contained 77 (66%) of all events: All events were non-serious. By number of events (n, % of all events), the 3 most common PTs in this SOC were: off-label use (n=26, 22%), product use issue (n=21, 18%) and product use in unapproved indication (n=20, 17%), reflecting unapproved use in paediatric patients.

• The General disorders and administration site conditions SOC contained 13 events (11%): 2 were considered serious and 11 non-serious. By number of events (n, % of all events), the 2 most common PTs in this SOC were no adverse event (n=5, 4%) and drug effective for unapproved indication (n=2, 2%). All other events were reported once.

• The Infections and infestations SOC contained 6 events (5%), all of which were considered serious. By number of events (n, % of all events), the most commonly reported PT in this SOC was pathogen resistance (n=3, 3%). All other events were reported once.

Of the 117 events, 12 events were considered serious. The 12 events occurred within 8 reports and were listed as the following PTs: pathogen resistance (n=3), bone operation (n=1), osteomyelitis (n=1), dehiscence (n=1), multiple organ dysfunction syndrome (n=1), Pseudomonas infection (n=1),

Clostridioides difficile infection (n=1), diarrhea (n=1), neutropenia (n=1), and hepatocellular injury (n=1).

The Aes by age group (<2 years, ≥2 to <6 years, ≥6 to <12 years, ≥12 to <18 years) were similar.

An analysis of the post marketing data did not identify any safety issues in paediatric patients. Based on this analysis, the safety profile in paediatric patients is consistent with the overall safety profile.

Of the 2,178 reports of C/T from 19-DEC-2014 to 19-DEC-2020 (including 3,754 events), 55 reports concerned paediatric patients (4 non-interventional study reports and 51 spontaneous). The 55 reports contained 117 events: 12 (10%) were considered serious and 105 (90%) were non-serious. Of the 117 events, 12 events were considered serious. The 12 events occurred within 8 reports and were listed as the following PTs: pathogen resistance (n=3), bone operation (n=1), osteomyelitis (n=1), dehiscence (n=1), multiple organ dysfunction syndrome (n=1), Pseudomonas infection (n=1), *Clostridioides difficile* infection (n=1), diarrhea (n=1), neutropenia (n=1), and hepatocellular injury (n=1).

It can be agreed by the MAH that reported events are consistent with the known safety profile of C/T; no new risks have been identified in the post marketing setting in paediatric patients.

4.6.9. Discussion on clinical safety

Safety analysis of the pooled phase 2 paediatric studies in cUTI (including pyelonephritis) and cIAI (in combination with MTZ) comprising 170 paediatric patients from birth to <18 years of age exposed to intravenous ceftolozane/tazobactam has been conducted. All randomised patients who received any amount of IV study therapy (C/T±MTZ) were included. In addition, data from a Phase 1 study (P010) to characterize the PK of a single IV dose of C/T in 37 paediatric patients, was submitted for support (The P010 study was submitted as an Article 46 application, and CHMP review was completed in January 2018). The safety analysis population for each of the 3 studies was the ApaT population consisting of all randomized participants who received any amount of study treatment.

Dose: Paediatric participants from 12 to <18 years of age with cIAI and AP/cUTI received the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam); children <12 years of age, including neonates, received a weight-based dosing regimen of 30 mg/kg C/T (20 mg/kg ceftolozane and 10 mg/kg tazobactam) that did not exceed the adult fixed dose of 1.5 g C/T (1 g ceftolozane and 0.5 g tazobactam).

Overall, in the Phase 2 Studies (studies P034 and P035), the disposition of participants was generally comparable between 5 age groups (12 to < 18 years, 6 to < 12 years, 2 to < 6 years, 3 months to < 2 years and birth to < 3 months). It should be noted that there were less children in the youngest age group, and only one (1) patient in each of group 4 and 5 (birth to <2 years of age) in the cIAI study (P035), which might be due to the condition of cIAI being less common at very young age.

With regard to duration of IV therapy, overall in the APaT population, the median duration of exposure was generally comparable between treatment groups (C/T was 5.4 days [range: 0.3 to 14.0 days], and MERO was 5.0 days [range: 1.0 to 9.7]). Study treatment duration for IV therapy was, however, shorter in the AP/cUTI study (P034) compared with cIAI (P035), because a larger proportion of participants discontinued from study treatment due to no qualifying pathogen in the P034 study. Concomitant medications were in widespread use, and the majority of patients in both treatment groups (C/T: 86/170; MERO: 32/54) received prior or concomitant medications; including oral step-down antibacterial medication. This was considered acceptable, although may hamper the assessment of possible association of AEs to the medicinal product.

The majority of participants in P034+P035 experienced AEs: 115/170 (67.6%) patients in the C/T arm and 33/54 (61.1%) in the MERO arm. The AE summary profile was generally comparable between the P034 and P035 studies for both the C/T and MERO groups, with the exceptions of the incidences of AEs and SAEs in P035, which were higher in the C/T+MTZ group compared with the MERO group. In the C/T+MTZ group in P035, AEs and SAEs were distributed over a variety of preferred terms and SOCs without clustering to suggest a specific safety signal. With regard to the different age cohorts, there is no apparent trend regarding AE frequency, however, the numbers of participants are very small when dividing into age subsets. The incidence of individual reported AEs was generally comparable between treatment groups. Overall, the most frequently reported AEs (>5%) were diarrhoea (11.2%), pyrexia (8.8%), thrombocytosis (7.6%), and AST increased (5.3%) in the C/T group, all known ADRs with Zerbaxa. In comparison, the most frequently reported AEs (>5%) were diarrhea (14.8%), thrombocytosis, pyrexia, nasopharyngitis, and urinary tract infection (each 7.4%), and AST increased and ALT increased (each 5.6%) in the MERO group.

Overall, the incidence of AEs considered as *drug-related* by the investigator was generally comparable between both treatment groups (C/T: 15.9% (27 pts); MERO: 14.8% (8 pts)). The most frequently reported *drug-related* AEs (>1%) were neutropenia (C/T 1.8%; MERO: 0%), diarrhoea (C/T: 4.1%; MERO: 7.4%), AST increased (C/T: 3.5%; MERO: 3.7%), and ALT increased (C/T: 2.9%; MERO: 1.9%), blood alkaline phosphatase increased (C/T: 1.2%; MERO: 0%), increased appetite (C/T: 1.8%; MERO: 0%), and dysgeusia (C/T: 1.2%; MERO: 0%). All but three of these ADRs are well known for Zerbaxa for the adult population; neutropenia, increased appetite and dysgeusia seems to be new ADRs for this product. After reconsideration, the MAH is asked to reinsert the approved version of the table of ADRs (based on adult data) rather than merging paediatric data into it. In addition, to keep in with the paediatric data and with reference to the SmPC guideline, a paediatric sub-section is suggested to be included below this table.

Most AEs were generally mild to moderate and comparable between both treatment groups. The incidence of severe AEs for the treatment groups were C/T: 5.9% and for MERO: 1.9%. No severe AE was reported in >2 participants. The most commonly reported severe AEs were neutropenia (1.2%, 2 patients) in the C/T group, and hypertension (1.9%, 1 patient) in the MERO group.

No deaths were reported in P034 or P035. There was a low incidence of SAEs for the treatment groups, however, it is noted that the overall incidence of serious adverse events in studies 034 and 035 (combined) was higher in the C/T group; 11 (6.7%) patients experienced SAEs, compared to 2 patients (3.7%) in the MERO group. Among the 13 total SAEs that were reported, 4 occurred while participants were receiving IV therapy; the remainder occurred either during oral step-down therapy or during the post treatment follow-up period. All SAEs resolved except for 1 (hypertension), which resolved with sequelae. However, none of these SAEs was considered related to treatment. Three (3) patients in the C/T treatment arm vs. none in the MERO arm discontinued treatment due to AEs, of which none considered treatment-related. In summary, there were no drug-related SAEs, AEs leading to death, or discontinuations due to drug-related AEs.

The incidences of AEs and SAEs which were higher in the C/T+MTZ group compared with the MERO group in P035 (cIAI); however, the incidence of *drug-related* AEs was similar between treatment groups in both studies.

No predefined Events of Clinical Interest (ECIs) of elevated liver enzymes meeting specific DILI criteria or events of overdose of C/T were reported in P034 or P035.

Select AEs of hypersensitivity, severe skin reaction, *Clostridioides difficile*-associated diarrhea (CDAD), renal impairment, and hemolysis were reviewed, as they are potentially associated with the β-lactam antibiotic class. No AEs of hypersensitivity, severe skin reactions, or CDAD, were reported in P034 or

P035. However, these are uncommon reactions and would not be expected to occur in this small number of patients treated. With regard to Acute Renal Failure or Renal and urinary disorders SOC in general, there was 1 AE of oliguria reported in the C/T+MTZ group in P035 and an AE of exacerbation of chronic kidney disease occurred in a participant in the C/T group in P034. However, none of the two (both non-serious) events was considered related to treatment. In addition, one AE of hemolysis (transfusion reaction) was reported (see below).

Seroconversion of direct Coombs' test from negative to positive is a known side effect of β-lactam exposure, and the development of a positive direct Coombs test may occur during treatment with Zerbaxa. In clinical studies, there was no evidence of haemolysis in patients who developed a positive direct Coombs test in any treatment group (see Zerbaxa SmPC). A higher proportion of participants in the C/T group compared to the MERO group seroconverted from a negative result at baseline to a positive direct Coombs' test result at EOIV. No AEs or laboratory abnormalities suggestive of drug-induced hemolytic anemia were reported for these participants. Based on the SMQ of Hemolytic Disorders, there was 1 AE of transfusion reaction reported in the C/T +MTZ group in P035, and this participant had a negative Coombs' test at screening and a positive Coombs' test at EOIV. This event was non-serious and not considered related to treatment.

There were no clinically meaningful differences identified in patterns of specific AEs or AE intensity between treatment groups in the incidences of AEs within age or gender categories or by geographic region. These results are consistent with those in the overall population.

Specific *drug-related* AEs that occurred in the single-dose study P010 were: 1 dizziness (1 participant), bradycardia and tachycardia (1 participant). Each of the drug-related AEs were mild in severity and resolved.

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure. However, based on the known safety profile of cephalosporins/beta-lactamase inhibitors with extensive use in the paediatric populations, a different safety profile for ceftolozane/tazobactam in patients < 18 years old compared with adults is not anticipated. Notwithstanding this, three new ADR were reported for C/T in the AP/cUTI and cIAI pooled paediatric population; neutropenia, increased appetite and dysgeusia, which are considered manageable and not concerning. Besides these ADRs, no new safety concerns were observed in the paediatric studies in AP/cUTI or cIAI, or from post-marketing data.

4.6.10. Conclusions on clinical safety

Safety analysis of the pooled phase 2 paediatric studies in cUTI, AP and cIAI (in combination with MTZ) comprising 170 paediatric patients from birth to <18 years of age exposed to intravenous ceftolozane-tazobactam has been conducted. All randomised patients who received any amount of IV study therapy (C/T±MTZ) were included. About two thirds (115 patients, 67.6%) of the patients treated with C/T±MTZ experienced Aes, of which 27 patients (15.9%) had Aes that were considered treatment related.

The overall safety profile in paediatric patients seems to be in line with the expected safety profile for C/T in adults, however three new ADRs are reported in the paediatric population (neutropenia, increased appetite and dysgeusia), which are considered manageable. Besides these, no new safety issues have been identified in the two studies performed. However, the data on safety is limited based on the small number of patients included. In particular safety data from patients <2 years of age with serious cIAIs are limited. Routine Pharmacovigilance measures, such as PSUR reporting, are expected to generate the safety follow-up.

It is concluded that the submitted clinical data provides overall clinical evidence that C/T has an

acceptable safety profile for use in paediatric patients from birth to <18 years of age with cUTI, AP and cIAI.

4.6.11. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4.6.12. Direct Healthcare Professional Communication

Not applicable.

5. Risk management plan

The MAH submitted an updated RMP version 4.0 dated 1 November 2021 with the response to the first RSI within this application. The (main) proposed RMP changes were the following:

Part I. Product overview

The table has been updated to include the information concerning proposed indication and posology (in paediatric population).

Part II. Safety Specification

Module SI. EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) section has been updated to include the following information (new text in blue):

Complicated intra-abdominal infections

Incidence:

(…)

In community and hospital settings, UTIs are among the most common infections encountered in paediatric patients [Ref. 5.4: 04L9BT, 047LSV, 045QPR]. The epidemiology of UTI during childhood varies by age, gender, geographic region and other factors [Ref. 5.4: 044G96]. The incidence of UTI is highest in the first year of life for all children (1%) but decreases among boys after infancy [Ref. 5.4: 06CXBN].

In the US, paediatric UTIs account for over 1 million annual office visits, and 500,000 emergency department (ED) visits. Nearly 50,000 children are hospitalized annually with a UTI, representing ~1.8% of all paediatric hospitalizations [Ref. 5.4: 05Q0Y9]. A population-based study from Scandinavia reported a cumulative UTI incidence rate of 7.8% for girls [Ref. 5.4: 06CX9L] by the age of 7 years, In Sweden, a retrospective population-based study investigated the incidence rate of first-time symptomatic UTI in children under 6 years of age. The cumulative incidence rate of UTI was 3 times greater in girls (6.6%) than boys (1.8%) [Ref. 5.4: 06CXC2]. Literature on complicated paediatric UTI is limited.

The main existing treatment options:

(…)

In paediatric patients, fluoroquinolones are generally avoided due to their association with musculoskeletal toxicity including tendinopathies [Ref. 5.4: 03V6FR], further limiting treatment options. Resistance to aminopenicillins and first generation cephalosporins limit their utility as empiric treatments.

Second or third generation cephalosporins are recommended empiric treatment options [Ref. 5.4: 04L9R3].

Antibiotic resistance in paediatric patients with cUTI is attributed to recurrent infection, instrumentation, and exposure to multiple courses of antibiotics [Ref. 5.4: 044QP8].

Natural history of the indicated condition in the population, including mortality and morbidity:

(…)

UTIs in paediatric patients are associated with significantly higher morbidity and more severe long-term sequelae, including impaired renal function and progression to end-stage renal disease, in comparison to UTIs in adult patients [Ref. 5.4: 03V6FR]. Renal scarring represents the most significant difference in disease pathophysiology between the adult and paediatric populations; paediatric patients younger than 2 years of age are more likely to be predisposed to renal damage, given their developmental stage. Sequelae associated with renal scarring can include hypertension, proteinuria, renal damage, and chronic renal failure, which may necessitate dialysis treatment in adulthood [Ref. 5.4: 04L9R3].

Across all paediatric age groups, E. coli is the most common cause of UTI, followed by Klebsiella spp., Proteus mirabilis, other Enterobacterales, Enterococcus spp., P. aeruginosa, and Staphylococcus saprophyticus [Ref. 5.4: 04L9BV, 04L9RH]. Uncomplicated UTIs are most commonly caused by E. coli, whereas a broader range of microorganisms may be responsible for cUTIs [Ref. 5.4: 044QP8, 04L9RC].

Furthermore, cUTIs are associated with an increased likelihood of drug resistance in the infecting microorganisms, which can further complicate treatment and lead to high mortality rates [Ref. 5.4: 044QP8]. In a retrospective study (2008-2009) conducted in Turkey of 344 paediatric outpatients diagnosed with UTI due to E coli and Klebsiella, ESBL-producing bacteria was isolated from 148 (43%) of these patients who all had at least 1 episode of pyelonephritis[Ref. 5.4: 05NG4F].

Complicated Intraabdominal Infections (cIAIs)

Incidence:

(…)

Data from the US and EU has shown that appendicitis is overwhelmingly the most common cause of paediatric cIAIs, with an annual incidence rate ranging from 1-6/10,000 children for 0-4 years to 19-28/10,000 for children younger than 14 years, and accounts for ~90% of paediatric cIAIs in children from 1 month to 15 years old[Ref. 5.4: 04474R, 06D2GN]. Complicated appendicitis due to a gangrenous or perforated appendix accounts for ~25,000 paediatric hospital admissions annually in the US and is more common in younger children; 57%, 87% and 100% of such cases occurring in children <6 years old, <5 years and < 1 year respectively [Ref. 5.4: 04LGYL, 05Q0XX]

Demographics of the population and risk factors for the disease:

(…)

In paediatric patients cIAI, characterized by extension of infection from an abdominal organ into the peritoneal space, is associated with a variety of causes including intussusception, volvulus, Necrotizing Enterocolitis (NEC), trauma, post-surgical complication and appendicitis [Ref. 5.4: 03RBW3]. In neonates, NEC, an inflammatory bowel necrosis that generally prents within the first 2 weeks of life and affects the terminal ileum, is the most common cause of cIAI [Ref. 5.4: 04LF78].

The main existing treatment options:

(…)

For paediatric patients, the commonly recommended antibiotic options for empiric therapy of suspected or confirmed cIAI include carbapenems (imipenem/cilastatin or meropenem), piperacillin/tazobactam, ticarcillin/clavulanate, or an extended spectrum cephalosporin (cefotoxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole [Ref. 5.4: 044GPV].

Module SII was updated as follows:

In the Table SII.1: Summary of Important Safety Findings from Non-clinical Studies the information has been updated, to include also juvenile toxicity studies findings.

Module SIII CLINICAL TRIALS EXPOSURE has been updated. The following new information has been added.

(…)

To support local registration, several additional studies have been completed in support of the adult cUTI and cIAI indications. These include: 2 Phase 3 open-label, noncomparative, local registration studies of ceftolozane and tazobactam for treatment of cUTI and cIAI which enrolled a total of 214 Japanese subjects, and 1 Phase 3 randomized, double-blind, active comparator-controlled local registration study of ceftolozane and tazobactam for treatment of cIAI in Chinese subjects. A total of 268 subjects were randomized in the Chinese Phase 3 cIAI study 1:1 to receive ceftolozane and tazobactam 1.5 g every 8 hours or meropenem 1 g every 8 hours; all subjects received study drug.

The paediatric development program for ceftolozane/tazobactam includes a paediatric PK and safety trial of ceftolozane/tazobactam, and two randomized, double-blind, active comparator-controlled Phase 2 studies in paediatric patients with cUTI or cIAI. CXA-PEDS-13-08 (MK-7625A-010) was a Phase 1, multicenter, single-dose, noncomparative, open-label trial of age- and weight-based dosing of ceftolozane/tazobactam up to 1.5 g IV in 36 subjects. Neonates, infants, young children, and adolescents were enrolled in 6 age groups to receive a single IV dose of ceftolozane/tazobactam. MK-7625A-034 and MK-7625A-035 were two randomized, double-blind, active comparator-controlled Phase 2 studies completed in paediatric patients with cUTI or cIAI which enrolled patients from birth (defined as ≥7 days postnatal) to <18 years of age. The paediatric Phase 2 cUTI study (MK-7625A-034) included 134 subjects randomized 3:1 across 5 age groups to receive ceftolozane/tazobactam either 1.5 g (participants ≥12 years of age) or 20 mg/kg ceftolozane and 10 mg/kg tazobactam (max 1.5 g, participants <12 years of age) every 8 hours, or meropenem 20 mg/kg (maximum 1.0 g, all age groups) every 8 hours; 133 subjects received study drug. The paediatric Phase 2 cIAI study (MK-7625A-035) included 94 subjects randomized 3:1 across 5 age groups to receive ceftolozane/tazobactam plus metronidazole either 1.5 g (participants ≥12 years of age) or 20 mg/kg ceftolozane and 10 mg/kg tazobactam (max 1.5 g, participants <12 years of age) plus metronidazole 10 mg/kg every 8 hours, or meropenem 20 mg/kg (maximum 1.0 g, all age groups) plus placebo every 8 hours; 91 subjects received study drug. Both paediatric Phase 2 studies were multinational, including sites in North and South America, Eastern and Western Europe, Asia, and South Africa.

The current clinical development program for ceftolozane and tazobactam includes one ongoing clinical study, a Phase 1, open-label, non-comparative study of ceftolozane/tazobactam in paediatric subjects with NP.

The tables related to duration of exposure, age group and gender, dose, ethnic origin were updated to include current data.

PART II: Module SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS was updated in relation to paediatric development programme.

In the table SIV.3 current exposure of patients with renal impairment has been provided. Paediatric data was also listed here.

PART II: Module SV - POST-AUTHORIZATION EXPERIENCE has been updated to include current data.

No changes to the list of safety concerns were introduced.

The list is as follows:

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

No additional pharmacovigilance activities nor risk minimisation measures are in place for ceftolozane/tazobactam.

5.1. Overall conclusion on the RMP

The changes to the RMP are acceptable. RMP Version 4.0 is approved with this procedure.

6. Changes to the Product Information

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

In addition, the list of local representatives in the PL is being revised.

See Annex 1 for the full Product Information

6.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The changes in the package leaflet are minor. Paragraphs are added concerning the paediatric population. Design, layout and format are continued. Key messages concerning safe use is not affected.

6.1.2. Additional monitoring

Not applicable

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

The MAH has applied for an extension of indication to broaden the current indications of Zerbaxa to include treatment of paediatric patients from birth to <18 years with the following infectious diseases:

- Complicated intra-abdominal infection (cIAI)

- Complicated urinary tract infection (cUTI)

- Acute pyelonephritis (AP)

7.1.2. Available therapies and unmet medical need

cIAI - available therapies

According to IDSA guideline 2017, selection of specific antimicrobial therapy for paediatric patients with cIAI should be based on considerations of the origin of infection (community vs health care), severity of illness, and safety of the antimicrobial agents in specific paediatric age groups.

Acceptable broad-spectrum antimicrobial regimens for paediatric patients with cIAI include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole.

AP/cUTI - available therapies

The EAU/ESPU guidelines 2015 for UTI in children recommend therapy with an antimicrobial regimen for paediatric AP/cUTI patients, such as an aminoglycoside with or without amoxicillin, or a second or third generation cephalosporin, or an extended-spectrum penicillin with or without an aminoglycoside. The most frequently used agents for treatment of paediatric UTI are parenteral cephalosporins (e.g., cefotaxime, ceftazidime and ceftriaxone) or oral cephalosporins (such as cefexime and cefuroxime axetil), trimethoprim and trimethoprim-sulphamethoxazole, ampicillin, amoxicillin, amoxicillin/clavulanic acid, piperacillin, aminoglycosides (i.e., tobramycin and gentamycin), ciprofloxacin, and nitrofurantoin. The dosing regimen selected should be based on local resistance data and urine culture results.

Unmet medical need

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

7.1.3. Main clinical studies

P035MK7625A (P035) – cIAI

Clinical phase 2 study to evaluate safety, tolerability and efficacy of ceftolozane/tazobactam (C/T) when given in combination with metronidazole (MTZ), compared with meropenem (MERO), in children from birth to less than 18 years of age with complicated intra-abdominal infections (cIAIs).

Of the 98 enrolled patients, 94 were randomised in a 3:1 ratio to receive C/T + MTZ or MERO and 91 received treatment (70 were treated in the C/T+MTZ group and 21 were treated in the MERO group).

The paediatric age groups who received C/T+MTZ were as follows: 12 to <18 years (n= 16), 6 to < 12 years (n=30), 2 to < 6 years (n= 22), 3 months to < 2 years (n=1) and birth to < 3 months (n=1).

P034MK7625A (P034) – AP/cUTI

Clinical phase 2 study to evaluate safety, tolerability and efficacy of ceftolozane/tazobactam (C/T) compared to meropenem (MERO) in children from birth to less than 18 years of age with AP and cUTIs.

Of the 143 enrolled patients, 134 were randomised in a 3:1 ratio to receive C/T or MERO and 133 patients received treatment (100 were treated in the C/T group and 33 were treated in the MERO group).

The paediatric age groups who received C/T were as follows: 12 to <18 years (n= 15), 6 to < 12 years (n= 24), 2 to < 6 years (n= 22), 3 months to < 2 years (n= 24) and birth to < 3 months (n=15).

7.2. Favourable effects

Efficacy measures were defined as secondary endpoints in the Phase 2 studies and evaluation of efficacy was based on descriptive statistics only. Extrapolation of efficacy against an infectious disease from adults to paediatric patients is possible based on similar pathophysiology of the infectious disease and a spectrum of activity of the antibacterial agent that includes pathogens relevant across the target age groups. This situation applies to the majority of infectious diseases that occur both in adults and in one or more paediatric age sub-groups, including

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI)
- Acute pyelonephritis (AP).

<u>cIAI indication</u>

Clinical cure rates were 80.0% (56/70) in the C/T+MTZ treatment arm and 100.0% (21/21) in the MERO arm in the MITT population at TOC.

In the CE population, the cure rates were 89.7% (52/58) in the C/T+MTZ arm and 100.0% (19/19) in the MERO arm at TOC.

<u>cUTI and AP indication</u>

Clinical cure rates were 88.7% (63/71) in the C/T treatment arm and 95.8% (23/24) in the MERO arm in the mMITT population at TOC.

The per-participant microbiological eradication rates were 84.5% (60/71) in the C/T treatment arm and 87.5% (21/24) in the MERO arm in the mMITT population at TOC.

In the ME population, the per-participant microbiological eradication rates were 90.9% (40/44) in the C/T treatment arm and 88.2% (15/17) in the MERO arm at TOC.

For all indications, the response rates for C/T±MTZ at the EOIV visit were in line with the response rates reported at the EOT and TOC visits. For the EOIV visit the main proportion of patients were partially improved reflecting that they were not in need of further IV antibiotic treatment for their infection, but additional treatment in the form of oral step-down therapy was still required.

PK data was collected in the paediatric population in two Phase 2 studies (**P034** and **P035**) and one Phase 1 study (**P010**). Comparable PK of ceftolozane and tazobactam in paediatric patients to adults was demonstrated for most patient groups, using a population-PK modelling approach based on sparse sampling in the three studies and PTA simulations. Although some trends are observed in the steady-state ceftolozane and tazobactam plasma PK parameter values, the presented data are within the range of observations in the adults with cUTI, AP and cIAI.

7.3. Uncertainties and limitations about favourable effects

The primary objective of the two phase 2 studies was to evaluate safety and tolerability of ceftolozane/tazobactam ± metronidazole. Hence, the studies were not powered for a statistical analysis of efficacy.

Updated population-PK analyses (082HY8) were conducted to assess the PK of C/T in paediatric patients and to support the proposed paediatric dose recommendations as well as to support the PK bridging for extrapolation of efficacy and safety. Clinical PK data in paediatric patients with AP, cUTI and cIAI is available for validation of the paediatric population-PK models, but the data is sparse and not fully covering all factors that are known to influence PK exposure (age, weight, type of infection, renal function). During the initial assessment, the respective model evaluations indicated reasonable fit for the ceftolozane model and model misspecifications for tazobactam. Newly provided graphical presentations indicates no major misspecification in the tazobactam model, and overall, the additional presentations submitted, indicates that the tazobactam population-PK model fit to the paediatric data reasonably well, also at the lower age range. Still the model is considered as of low credibility, particularly for the lowest age ranges (below 3 months for AP/cUTI and below 2 years for cIAI). Limited clinical data exists from paediatric patients with CrCL <50 mL/min/1.73m^2, and the paediatric population PK-model for ceftolozane did not adequately describe the influence of renal function. Consequently, no dosing recommendations could be provided for paediatric patients with AP, cUTI or cIAI with immature renal function or moderate/severe renal impairment (eGFR $\leq$50 mL/min/1.73 m^2) with this procedure. A population-PK model has been submitted to support dose selection for paediatric NP patients at a higher dose compared to AP, cUTI and cIAI.

At the dose regimens clinically tested in study **P034** and **P035**, some trends were observed in PK measures that deviated from the adult population. The estimated exposure of both ceftolozane and tazobactam (AUC_{0-8} and C_{eoi}) in paediatric AP- and cUTI patients trended lower (except Group 1 (12 to <18 years) where both ceftolozane and tazobactam were comparable, and Group 5 (birth to <3 months where elevated exposure of tazobactam was observed) compared to that in adults with AP and cUTI. The estimated AUC_{0-8} of both ceftolozane and tazobactam in paediatric patients with cIAI also trended lower compared to adults with cIAI. While ceftolozane C_{eoi} was comparable to adult values, tazobactam values trended higher in paediatric patients. There are few patients included in the lower age groups which brings uncertainties to the estimates. No PK data from cIAI patients <2 years were included in the population-PK dataset on which the exposure and PTA predictions were based.

The PTA simulations, using the joint PK/PD target, demonstrated joint PTA achievement of >90% at the dose regimen clinically tested in study **P034** and **P035**, and at the proposed dose regimens, for all paediatric subgroups with cIAI, AP and cUTI. The credibility of the tazobactam population-PK model is low, particularly for the lowest age ranges (<3 months for AP/cUTI and <2 years for cIAI), where the

model overpredicts the tazobactam exposures. This impacts the derived exposure metrics, and the PTA simulations will likely be overestimated. Even so, considering the tazobactam target of fraction of time above 1mg/mL at 20%, the observed exposure data indicate that patients are above this limit.

7.4. Unfavourable effects

The majority of participants in P034+P035 experienced AEs: 115/170 (67.6%) patients in the C/T arm and 33/54 (61.1%) in the MERO arm. The incidence of individual reported AEs was generally comparable between treatment groups. Overall, the most frequently reported AEs (>5%) were diarrhoea (11.2%), pyrexia (8.8%), thrombocytosis (7.6%), and AST increased (5.3%) in the C/T group, all known ADRs with Zerbaxa.

Overall, the incidence of AEs considered as *drug-related* by the investigator was generally comparable between both treatment groups (C/T: 15.9% (27 pts) MERO: 14.8% (8 pts)). The most frequently reported *drug-related* AEs (>1%) were neutropenia (C/T 1.8%), diarrhoea (C/T: 4.1%), AST increased (C/T: 3.5%), and ALT increased (C/T: 2.9%), blood alkaline phosphatase increased (C/T: 1.2%), increased appetite (C/T: 1.8%), and dysgeusia (C/T: 1.2%). Three (3) new ADR were reported in the paediatric population in AP/cUTI and cIAI; neutropenia, increased appetite and dysgeusia, which are proposed added to the SmPC section 4.8.

Most AEs were generally mild to moderate and comparable between both treatment groups. The incidence of severe AEs was 5.9% for C/T arm. No severe AE was reported in >2 participants. The most commonly reported severe AE were neutropenia (1.2%, 2 patients) in the C/T group.

No deaths were reported in P034 or P035. In the C/T group, 11 (6.7%) patients experienced SAEs. However, none of these SAEs was considered related to treatment. Three (3) patients in the C/T treatment arm discontinued treatment due to AEs, of which none considered treatment-related.

The incidences of AEs and SAEs which were higher in the C/T+MTZ group compared with the MERO group in P035 (cIAI); however, the incidence of *drug-related* AEs was similar between treatment groups in both studies.

No predefined Events of Clinical Interest (ECIs) of elevated liver enzymes meeting specific DILI criteria or events of overdose of C/T were reported in P034 or P035.

Select AEs of hypersensitivity, severe skin reaction, *Clostridioides difficile*-associated diarrhoea (CDAD), renal impairment, and hemolysis were reviewed, as they are potentially associated with the β-lactam antibiotic class. No AEs of hypersensitivity, severe skin reactions, or CDAD, were reported in P034 or P035. With regard to Acute Renal Failure or Renal and urinary disorders SOC in general, there was 1 AE of oliguria reported in the C/T+MTZ group in P035 and an AE of exacerbation of chronic kidney disease occurred in a participant in the C/T group in P034. However, none of these two non-serious events was considered related to treatment.

Based on the SMQ of Hemolytic Disorders, there was 1 AE of transfusion reaction reported in the C/T +MTZ group in P035, and this participant had a negative Coombs' test at screening and a positive Coombs' test at EOIV. This event was non-serious and not considered related to treatment.

Seroconversion of direct Coombs' test from negative to positive is a known side effect of β-lactam exposure. A higher proportion of participants in the C/T group compared to the MERO group seroconverted from a negative result at baseline to a positive direct Coombs' test result at EOIV. No AEs or laboratory abnormalities suggestive of drug-induced hemolytic anemia were, however, reported for these participants.

As mentioned, three (3) new ADR were reported in the paediatric population in AP/cUTI and cIAI;

neutropenia, increased appetite and dysgeusia. Besides these ADRs, no new safety concerns were observed in the paediatric studies in AP/cUTI or cIAI, or from post-marketing data.

7.5. Uncertainties and limitations about unfavourable effects

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency. Overall, the number of children included is limited and can only contribute to detect common AEs.

With regard to the different age cohorts, there is no apparent trend regarding AE frequency, however, the numbers of participants are very small when dividing into age subsets, so any differences must be interpreted with caution.

Few details regarding safety data collection are found in the documentation, and the documentation is to a less degree critical.

The paediatric safety data are to a small degree compared to adult data in the documentation by the applicant. This hampers the comparison and hence, evaluation of, the new data with the already approved safety database.

Any co-medication use hampers the safety evaluation of C/T treatment in the children, which was not discussed by the MAH.

As only two children below the age of 2 years old were recruited into the paediatric cIAI study (both in C/T+MTZ arm) submitted in the present application, i.e. one child >3 months and up to 2 years of age and one child below 3 months of age, there is an uncertainty with respect to the risk of exposing the youngest children with cIAI to C/T. Dosing recommendations and safety in children with moderate and severe renal impairment were lacking, which is reflected in SmPC section 4.2. It is expected that a variation application is submitted when data from the ongoing study **MK-7625A-036** become available, to include in section 4.2 and 5.2 of the SmPC (and other sections as relevant) dosing recommendations to paediatric patients with AP, cUTI or cIAI with reduced renal function, if supported by the data. To support this variation the MAH is recommended to submit full results of updated/relevant population PK model(s).

7.6. Benefit-risk assessment and discussion

7.6.1. Importance of favourable and unfavourable effects

Assuming that similar PK exposure to adults should lead to similar response to ceftolozane and tazobactam, a population PK modelling approach was employed to identify appropriate doses of ceftolozane/tazobactam to be used in paediatric patients <18 years of age. Therefore, the extension of the proposed indications to the paediatric patients depends on the adequacy of the proposed dose regimens in different age subgroups based on the comparability of PK to adults and whether the paediatric safety profile is acceptable.

Acceptable similarity of PK in paediatric patients to adults was demonstrated for most patient groups, using population-PK modelling and PTA simulations. It is reassuring that acceptable joint PTAs of >90% were achieved at the proposed dose regimens using the same joint PK/PD target as that employed in the original MAA for adults. This was shown for all paediatric subgroups with cIAI, AP and cUTI. The low credibility of the tazobactam population-PK model impacts and brings uncertainties to the PTA simulations, which will likely be overestimated. Even so, considering the tazobactam target of fraction of time above 1µg/mL at 20%, the observed exposure data indicate that patients are above this limit.

Few patients are included in the lower age groups which brings uncertainties to the estimates in these groups. No PK data from cIAI patients <2 years were included in the population-PK dataset on which the exposure and PTA predictions were based.

Since ceftolozane and tazobactam both are renally excreted, dosing recommendations in renal impairment is generally required. Considering the low GFR expected in new-born and preterm neonates, the proposed eGFR cutoff will most likely exclude a large proportion of the youngest patients born at term and possibly all the youngest preterm patients from treatment with C/T. Consequent to the limitations in the collected paediatric data with regards to representing the expected range of renal functions and the lack of a reliable paediatric population PK model for renal impairment, dosing recommendations for paediatric patients with reduced or immature renal function cannot be provided at this time.

Safety and tolerability of the fixed combination of C/T are the primary objectives in both paediatric studies of patients with cIAI, AP and cUTI. The overall safety profile in paediatric patients seems to be in line with the expected safety profile for C/T in adults, however three new ADRs are reported in the paediatric population (neutropenia, increased appetite and dysgeusia), which are considered manageable. Besides these, no new safety issues have been identified in the two paediatric studies performed. The data on safety is, however, limited based on the small number of patients included, in particular is safety in patients <2 years of age with cIAIs limited. The safety in children with moderate and severe renal impairment could not be evaluated.

According to Draft guideline EMA/187859/2017 "Addendum to guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements", no appropriately powered efficacy studies are required in the paediatric population as efficacy can be extrapolated from adults provided similar exposure is achieved in the paediatric population.

7.6.2. Balance of benefits and risks

The data on safety is limited based on the small number of patients included. However, based on the known safety profile of cephalosporins/beta-lactamase inhibitors with extensive use in the paediatric populations, a different safety profile for ceftolozane/tazobactam in patients < 18 years old compared with adults is not anticipated.

The totality of the data allows for concluding that the proposed dosing recommendations are adequate for both ceftolozane and tazobactam for the majority of the paediatric patients and that the exposures are sufficiently similar to allow extrapolation of safety and efficacy from adults for cIAI, AP and cUTI infections in paediatric patients with eGFR >50 mL/min/1.73m^2. Routine Pharmacovigilance measures, such as PSUR reporting, are expected to generate safety follow-up.

The clinical safety data provides overall clinical evidence that C/T has an acceptable safety profile for use in paediatric patients from birth to <18 years of age with cUTI, AP and cIAI.

7.6.3. Additional considerations on the benefit-risk balance

Not applicable

7.7. Conclusions

The data on safety is limited based on the small number of patients included. However, based on the known safety profile of cephalosporins/beta-lactamase inhibitors with extensive use in the paediatric populations,

a different safety profile for ceftolozane/tazobactam in patients < 18 years old compared with adults is not anticipated.

The totality of the data allows for concluding that the proposed dosing recommendations are adequate for both ceftolozane and tazobactam for the majority of the paediatric patients and that the exposures are sufficiently similar to allow extrapolation of safety and efficacy from adults for cIAI, AP and cUTI infections in paediatric patients with eGFR >50 mL/min/1.73m^2.

The overall B/R of Zerbaxa is considered positive for the extension of indication to broaden the current indications to include treatment of paediatric patients with cIAIs, AP and cUTIs with eGFR >50 mL/min/1.73m^2.