Clinical trial results:
A Phase 1, Non-comparative, Open-label Study to Characterize the Pharmacokinetics of a Single Intravenous Dose of Ceftolozane/Tazobactam in Pediatric Patients Receiving Standard of Care Antibiotic Therapy for Proven or Suspected Gram-negative Infection or for Peri-operative Prophylaxis

Summary

EudraCT number	2014-003485-24
Trial protocol	Outside EU/EEA
Global end of trial date	15 June 2017

Results information

Result version number	v2 (current)
This version publication date	21 April 2018
First version publication date	24 December 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MK-7625A-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02266706
WHO universal trial number (UTN)	-
Other trial identifiers	Cubist Pharmaceuticals LLC Protocol Number: CXA-PEDS-13-08

Notes:

Sponsors

Sponsor organisation name	Cubist Pharmaceuticals LLC
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001142-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the pharmacokinetics (PK), safety, and tolerability of a single intravenous dose of ceftolozane/tazobactam (MK-7625A) in pediatric participants.

In each of the 6 age cohorts, an interim analysis of PK and safety data was conducted after approximately 3 participants had received the initially proposed dose. The interim analysis was to determine whether the initial dose was appropriate based on pre-defined criteria. If data from the interim analysis demonstrated that the initially proposed dose met the above criteria, enrollment was to continue with the same dose administered to approximately 3 additional participants of the same age range. However, if the interim analysis demonstrated that a new optimized dose was required, the new dose was to be administered to approximately 3 additional participants of the same age range.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measure(s) defined for this individual study was (were) in place for the protection of trial subjects: Interim analyses were conducted for each cohort to confirm absence of safety signals and acceptability of PK targets.

Background therapy:

Participants were receiving concurrent standard of care antibiotic therapy for proven or suspected gram-negative infection or for peri-operative prophylaxis.

Evidence for comparator: -

Actual start date of recruitment	17 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	43
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	2
Infants and toddlers (28 days-23 months)	19
Children (2-11 years)	16
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were males or non-pregnant females from birth to <18 years of age who were receiving standard of care antibiotic therapy for proven or suspected gram-negative infection or for peri-operative prophylaxis. Participants were recruited and treated as age cohorts.

Pre-assignment

Screening details:

Participants were screened for eligibility within 48 hours prior to study drug administration.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC

Arm description:

Participants ≥12 to <18 years of age received a single dose of ceftolozane/tazobactam (TOL/TAZ) 1000/500 mg FDC as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 1000 mg Tazobactam 500 mg FDC
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1

Arm title	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg

Arm description:

Participants ≥7 to <12 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 18 mg/kg Tazobactam 9 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1

Arm title	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg

Arm description:

Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental

Investigational medicinal product name	Ceftolozane 18 mg/kg Tazobactam 9 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1

Arm title	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg

Arm description:

Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 30 mg/kg Tazobactam 15 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1. Participants in this group enrolled after interim analysis for
Cohort 3.

Arm title	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg

Arm description:

Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 18 mg/kg Tazobactam 9 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1

Arm title	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg

Arm description:

Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 30 mg/kg Tazobactam 15 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1. Participants in this group enrolled after interim analysis for
Cohort 3.

Arm title	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg

Arm description:

Participants from birth (>32 weeks gestation, 7 days postnatal) to <3 months of age received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental

Investigational medicinal product name	Ceftolozane 20 mg/kg Tazobactam 10 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1. After interim analysis for Cohort 4, the original regimen of
TOL/TAZ 12/6 mg/kg for this group was changed to TOL/TAZ 20/10.

Arm title	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg

Arm description:

Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance of 20 - 49 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 12/6 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 12 mg/kg Tazobactam 6 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1

Arm title	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg

Arm description:

Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance ≥50 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftolozane 20 mg/kg Tazobactam 10 mg/kg
Investigational medicinal product code	
Other name	MK-7625A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 60-minute intravenous infusion administered on Day 1. Participants in this group enrolled after interim analysis for
Cohort 4.

Number of subjects in period 1	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Started	6	7	4
Treated	6	6	3
Completed	6	6	3
Not completed	0	1	1
Consent withdrawn by subject	-	1	1
Enrolled in another study	-	-	-
Screen failure	-	-	-

Number of subjects in period 1	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Started	4	1	7
Treated	3	1	5
Completed	3	1	5
Not completed	1	0	2
Consent withdrawn by subject	-	-	1
Enrolled in another study	1	-	-
Screen failure	-	-	1

Number of subjects in period 1	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Started	8	2	4
Treated	7	2	4
Completed	7	2	4
Not completed	1	0	0
Consent withdrawn by subject	-	-	-
Enrolled in another study	-	-	-
Screen failure	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC
Reporting group description:	
Participants ≥12 to <18 years of age received a single dose of ceftolozane/tazobactam (TOL/TAZ) 1000/500 mg FDC as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg
Reporting group description:	
Participants ≥7 to <12 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Reporting group description:	
Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Reporting group description:	
Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg
Reporting group description:	
Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Reporting group description:	
Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg
Reporting group description:	
Participants from birth (>32 weeks gestation, 7 days postnatal) to <3 months of age received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Reporting group description:	
Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance of 20 - 49 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 12/6 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Reporting group description:	
Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance ≥50 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.	

Reporting group values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Number of subjects	6	7	4
Age Categorical Units: Subjects			
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	7	4
Adolescents (12-17 years)	6	0	0

Age Continuous			
Units: years			
arithmetic mean	16.1	8.5	5.5
standard deviation	± 1.4	± 1.2	± 0.8
Gender Categorical			
Units: Subjects			
Female	5	3	2
Male	1	4	2

Reporting group values	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Number of subjects	4	1	7
Age Categorical			
Units: Subjects			
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	1	6
Children (2-11 years)	4	0	1
Adolescents (12-17 years)	0	0	0
Age Continuous			
Units: years			
arithmetic mean	4.8	0.9	0.9
standard deviation	± 1.8	± 0.0	± 0.7
Gender Categorical			
Units: Subjects			
Female	3	0	2
Male	1	1	5

Reporting group values	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Number of subjects	8	2	4
Age Categorical			
Units: Subjects			
Newborns (0-27 days)	2	0	0
Infants and toddlers (28 days-23 months)	6	2	4
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Age Continuous			
Units: years			
arithmetic mean	0.1	0.1	0.2
standard deviation	± 0.0	± 0.0	± 0.1
Gender Categorical			
Units: Subjects			
Female	4	0	3
Male	4	2	1

Reporting group values	Total		
Number of subjects	43		

Age Categorical Units: Subjects			
Newborns (0-27 days)	2		
Infants and toddlers (28 days-23 months)	19		
Children (2-11 years)	16		
Adolescents (12-17 years)	6		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	22		
Male	21		

End points

End points reporting groups

Reporting group title	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC
Reporting group description:	
Participants ≥12 to <18 years of age received a single dose of ceftolozane/tazobactam (TOL/TAZ) 1000/500 mg FDC as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg
Reporting group description:	
Participants ≥7 to <12 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Reporting group description:	
Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Reporting group description:	
Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg
Reporting group description:	
Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Reporting group description:	
Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg
Reporting group description:	
Participants from birth (>32 weeks gestation, 7 days postnatal) to <3 months of age received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Reporting group description:	
Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance of 20 - 49 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 12/6 mg/kg as a 60-minute infusion on Day 1.	
Reporting group title	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Reporting group description:	
Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance ≥50 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.	
Subject analysis set title	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants ≥12 to <18 years of age received a single dose of ceftolozane/tazobactam 1000/500 mg FDC as a 60-minute infusion on Day 1.	
Subject analysis set title	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants ≥7 to <12 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.	
Subject analysis set title	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a	

60-minute infusion on Day 1.

Subject analysis set title	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.

Subject analysis set title	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Subject analysis set title	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.

Subject analysis set title	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from birth (>32 weeks gestation, 7 days postnatal) to <3 months of age received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.

Subject analysis set title	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance of 20 - 49 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 12/6 mg/kg as a 60-minute infusion on Day 1.

Subject analysis set title	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance ≥50 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.

Primary: Maximum Plasma Concentration (Cmax) of Ceftolozane

End point title	Maximum Plasma Concentration (Cmax) of Ceftolozane[1]

End point description:

Blood was collected for the determination of Cmax of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. Cmax is expressed as 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.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: µg/mL				
geometric mean (confidence interval 95%)	63.5 (50.2 to 80.4)	56.2 (45.3 to 69.7)	51.4 (37.9 to 69.7)	96.6 (71.2 to 131)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: µg/mL				
geometric mean (confidence interval 95%)	50.5 (29.8 to 85.6)	91.3 (72.1 to 116)	45.0 (36.3 to 55.9)	34.9 (24.1 to 50.7)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: µg/mL				
geometric mean (confidence interval 95%)	45.2 (33.3 to 61.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of Tazobactam

End point title	Maximum Plasma Concentration (Cmax) of Tazobactam[2]

End point description:

Blood was collected for the determination of Cmax of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. Cmax is expressed as 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.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: µg/mL				
geometric mean (confidence interval 95%)	14.0 (8.59 to 22.9)	9.25 (5.92 to 14.5)	15.7 (8.36 to 29.6)	24.8 (13.2 to 46.6)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: µg/mL				
geometric mean (confidence interval 95%)	11.6 (3.88 to 34.7)	22.4 (13.8 to 36.6)	11.7 (7.48 to 18.3)	6.87 (3.17 to 14.9)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: µg/mL				
geometric mean (confidence interval 95%)	12.1 (6.43 to 22.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Plasma Concentration (Tmax) of Ceftolozane

End point title	Time to Maximum Plasma Concentration (Tmax) of

End point description:

Blood was collected for the determination of Tmax of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours				
median (full range (min-max))	1.02 (1.00 to 1.10)	1.07 (0.58 to 1.13)	1.02 (1.02 to 1.03)	1.03 (1.03 to 1.12)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours				
median (full range (min-max))	1.00 (1.00 to 1.00)	1.05 (0.58 to 1.95)	1.08 (0.95 to 1.90)	1.80 (1.03 to 2.57)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
median (full range (min-max))	1.07 (1.07 to 1.18)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Plasma Concentration (Tmax) of Tazobactam

End point title	Time to Maximum Plasma Concentration (Tmax) of

End point description:

Blood was collected for the determination of Tmax of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours				
median (full range (min-max))	1.00 (0.50 to 1.10)	1.07 (0.58 to 1.13)	1.02 (1.02 to 1.03)	1.03 (1.03 to 1.12)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours				
median (full range (min-max))	1.00 (1.00 to 1.00)	1.05 (0.58 to 1.95)	1.08 (0.95 to 1.33)	3.89 (1.03 to 6.75)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
median (full range (min-max))	1.07 (1.07 to 1.18)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration at the Last Quantifiable Concentration (Clast) of Ceftolozane

End point title	Plasma Concentration at the Last Quantifiable Concentration (Clast) of Ceftolozane[5]

End point description:

Blood was collected for the determination of Clast of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. Clast is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: µg/mL				
geometric mean (geometric coefficient of variation)	4.01 (± 40.4)	2.85 (± 37.3)	2.47 (± 29.1)	5.69 (± 59.5)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: µg/mL				
geometric mean (geometric coefficient of variation)	2.53 (± 0)	5.72 (± 96.1)	8.70 (± 49.1)	10.2 (± 49.2)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	6.26 (± 39.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration at the Last Quantifiable Concentration (Clast) of Tazobactam

End point title	Plasma Concentration at the Last Quantifiable Concentration (Clast) of Tazobactam[6]

End point description:

Blood was collected for the determination of Clast of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. Clast is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: µg/mL				
geometric mean (geometric coefficient of variation)	0.232 (± 52.2)	0.420 (± 188.6)	0.137 (± 24.1)	0.327 (± 62.7)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: µg/mL				
geometric mean (geometric coefficient of variation)	0.224 (± 0)	0.401 (± 90.5)	0.657 (± 169.2)	3.66 (± 57.6)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	0.266 (± 81.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of Last Sampling Point (Tlast) of Ceftolozane

End point title	Time of Last Sampling Point (Tlast) of Ceftolozane[7]

End point description:

Blood was collected for the determination of Tlast of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours				
median (full range (min-max))	6.00 (5.85 to 6.03)	6.01 (5.82 to 6.15)	6.08 (5.85 to 6.25)	5.77 (5.72 to 5.93)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours				
median (full range (min-max))	6.00 (6.00 to 6.00)	6.00 (5.72 to 6.75)	6.01 (5.88 to 6.18)	6.40 (6.05 to 6.75)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			

Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
median (full range (min-max))	5.85 (5.72 to 6.02)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of Last Sampling Point (Tlast) of Tazobactam

End point title	Time of Last Sampling Point (Tlast) of Tazobactam[8]

End point description:

Blood was collected for the determination of Tlast of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours				
median (full range (min-max))	4.15 (4.00 to 6.00)	3.10 (2.02 to 4.15)	5.85 (4.03 to 6.08)	5.72 (3.85 to 5.93)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours				
median (full range (min-max))	4.00 (4.00 to 4.00)	5.02 (4.02 to 5.75)	5.95 (2.18 to 6.10)	6.40 (6.05 to 6.75)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10			

	mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
median (full range (min-max))	5.85 (5.72 to 6.02)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve (AUClast) of Ceftolozane

End point title	Area Under the Plasma Concentration-Time Curve (AUClast) of Ceftolozane[9]

End point description:

Blood was collected for the determination of AUC from time zero to the last quantifiable concentration of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. AUC0-last is expressed as 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.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	124 (103 to 150)	102 (86.2 to 121)	94.2 (74.1 to 120)	172 (135 to 219)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	98.8 (65.1 to 150)	178 (148 to 214)	131 (111 to 155)	118 (88.2 to 159)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	119 (93.7 to 151)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve (AUClast) of Tazobactam

End point title	Area Under the Plasma Concentration-Time Curve (AUClast) of Tazobactam[10]

End point description:

Blood was collected for the determination of AUC from time zero to the last quantifiable concentration of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. AUC0-last is expressed as 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.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	17.3 (10.7 to 27.9)	9.69 (6.27 to 15.0)	17.6 (9.53 to 32.7)	28.5 (15.4 to 52.8)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	14.8 (5.08 to 42.9)	28.9 (18.0 to 46.6)	21.3 (13.8 to 33.0)	21.6 (10.2 to 45.9)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	21.9 (11.8 to 40.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve (AUC0-inf) of Ceftolozane

End point title	Area Under the Plasma Concentration-Time Curve (AUC0-inf) of Ceftolozane[11]

End point description:

Blood was collected for the determination of AUC from time zero extrapolated to infinity of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. AUC0-inf is expressed as 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.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	133 (104 to 171)	107 (85.7 to 135)	99.4 (72.2 to 137)	186 (135 to 255)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	103 (59.4 to 180)	202 (158 to 259)	164 (131 to 205)	165 (112 to 244)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	137 (99.6 to 189)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve (AUC0-inf) of Tazobactam

End point title	Area Under the Plasma Concentration-Time Curve (AUC0-inf) of Tazobactam[12]

End point description:

Blood was collected for the determination of AUC from time zero extrapolated to infinity of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. AUC0-inf is expressed as 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.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	3
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	17.5 (12.6 to 24.2)	10.2 (6.68 to 15.5)	17.8 (11.7 to 27.0)	28.9 (19.0 to 43.9)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	5	1
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	14.9 (7.21 to 30.9)	29.9 (21.6 to 41.4)	24.9 (18.0 to 34.4)	77.6 (37.5 to 161)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours*µg/mL				
geometric mean (confidence interval 95%)	22.3 (14.7 to 34.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Half-life (t1/2) of Ceftolozane

End point title	Elimination Half-life (t1/2) of Ceftolozane[13]

End point description:

Blood was collected for the determination of t1/2 of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. t1/2 is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: Hours				
geometric mean (geometric coefficient of variation)	1.45 (± 16.7)	1.29 (± 9.6)	1.34 (± 14.0)	1.48 (± 35.5)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: Hours				
geometric mean (geometric coefficient of variation)	1.30 (± 0)	1.63 (± 69.0)	2.21 (± 37.6)	3.14 (± 0.9)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
geometric mean (geometric coefficient of variation)	1.73 (± 29.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Half-life (t1/2) of Tazobactam

End point title	Elimination Half-life (t1/2) of Tazobactam[14]

End point description:

Blood was collected for the determination of t1/2 of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. t1/2 is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	3
Units: Hours				
geometric mean (geometric coefficient of variation)	0.702 (± 38.7)	0.544 (± 3.1)	0.719 (± 29.7)	0.770 (± 34.2)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	5	1
Units: Hours				
geometric mean (geometric coefficient of variation)	0.538 (± 0)	0.815 (± 85.1)	1.09 (± 32.0)	3.03 (± 0)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
geometric mean (geometric coefficient of variation)	0.875 (± 20.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution at Steady State (Vss) of Ceftolozane

End point title	Volume of Distribution at Steady State (Vss) of Ceftolozane[15]

End point description:

Blood was collected for the determination of Vss of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. Vss is expressed as

geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: L/kg				
geometric mean (geometric coefficient of variation)	0.274 (± 25.7)	0.296 (± 22.0)	0.331 (± 15.6)	0.312 (± 19.5)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: L/kg				
geometric mean (geometric coefficient of variation)	0.282 (± 0)	0.340 (± 21.1)	0.394 (± 12.6)	0.344 (± 36.6)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: L/kg				
geometric mean (geometric coefficient of variation)	0.388 (± 26.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution at Steady State (Vss) of Tazobactam

End point title	Volume of Distribution at Steady State (Vss) of Tazobactam[16]

End point description:

Blood was collected for the determination of Vss of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. Vss is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	3
Units: L/kg				
geometric mean (geometric coefficient of variation)	0.474 (± 69.6)	0.740 (± 30.2)	0.488 (± 32.0)	0.513 (± 49.2)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	5	1
Units: L/kg				
geometric mean (geometric coefficient of variation)	0.421 (± 0)	0.574 (± 36.2)	0.668 (± 19.8)	0.338 (± 0)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: L/kg				
geometric mean (geometric coefficient of variation)	0.667 (± 29.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Clearance (CL) of Ceftolozane

End point title	Plasma Clearance (CL) of Ceftolozane[17]

End point description:

Blood was collected for the determination of CL of ceftolozane. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. CL is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	3
Units: L/hour/kg				
geometric mean (geometric coefficient of variation)	0.146 (± 27.0)	0.168 (± 21.3)	0.181 (± 3.8)	0.162 (± 31.1)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	6	2
Units: L/hour/kg				
geometric mean (geometric coefficient of variation)	0.176 (± 0)	0.149 (± 43.2)	0.118 (± 36.0)	0.0723 (± 32.2)

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: L/hour/kg				
geometric mean (geometric coefficient of variation)	0.147 (± 6.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Clearance (CL) of Tazobactam

End point title	Plasma Clearance (CL) of Tazobactam[18]

End point description:

Blood was collected for the determination of CL of tazobactam. The pharmacokinetics population included enrolled participants who received a full dose of study drug and had blood samples with quantifiable plasma levels at Cmax and at least 2 time points after Cmax. CL is expressed as geometric mean and percent geometric coefficient of variation, CV% = 100*sqrt(exp(s^2)-1), where s^2 is the observed between-subjects variance on the natural log-scale. The geometric coefficient of variation for groups with N=1 cannot be calculated and is reported as '0' for the purpose of this report.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, and 6 hours after the start of infusion for Cohorts 1 to 4 and 1, 2, and 6 hours after start of infusion for Cohorts 5 and 6.

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned or conducted for between-group comparisons

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	3
Units: L/hour/kg				
geometric mean (geometric coefficient of variation)	0.556 (± 53.9)	0.886 (± 23.1)	0.506 (± 42.0)	0.519 (± 44.8)

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	5	1
Units: L/hour/kg				
geometric mean (geometric coefficient of variation)	0.611 (± 0)	0.502 (± 34.7)	0.385 (± 34.1)	0.0760 (± 0)

End point values	Cohort 6: birth to <3 months			

	TOL/TAZ 20/10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: L/hour/kg				
geometric mean (geometric coefficient of variation)	0.452 (± 24.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with One or More Adverse Events

End point title	Number of Participants with One or More Adverse Events

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The safety population was all enrolled participants who received study drug.

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	3	3
Units: Participants	2	1	1	1

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	7	2
Units: Participants	1	2	1	2

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			

Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Discontinued the Study due to an Adverse Event

End point title	Number of Participants who Discontinued the Study due to an Adverse Event

End point description:

An AE is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The safety population was all enrolled participants who received study drug.

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	3	3
Units: Participants	0	0	0	0

End point values	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	7	2
Units: Participants	0	0	0	0

End point values	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 10

Adverse event reporting additional description:

The safety population was all enrolled participants who received study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC

Reporting group description:

Participants ≥12 to <18 years of age received a single dose of ceftolozane/tazobactam (TOL/TAZ) 1000/500 mg FDC as a 60-minute infusion on Day 1.

Reporting group title	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg

Reporting group description:

Participants ≥7 to <12 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg

Reporting group description:

Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg

Reporting group description:

Participants ≥2 to <7 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg

Reporting group description:

Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 18/9 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg

Reporting group description:

Participants ≥3 months to <2 years of age received a single dose of ceftolozane/tazobactam 30/15 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg

Reporting group description:

Participants from birth (>32 weeks gestation, 7 days postnatal) to <3 months of age received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg

Reporting group description:

Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance of 20 - 49 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 12/6 mg/kg as a 60-minute infusion on Day 1.

Reporting group title	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg

Reporting group description:

Participants from birth (≤32 weeks gestation, 7 days postnatal) to <3 months of age with creatinine clearance ≥50 mL/min/1.73 m^2 received a single dose of ceftolozane/tazobactam 20/10 mg/kg as a 60-minute infusion on Day 1.

Serious adverse events	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1: ≥12 to <18 years TOL/TAZ 1000/500 mg FDC	Cohort 2: ≥7 to <12 years TOL/TAZ 18/9 mg/kg	Cohort 3: ≥2 to <7 years TOL/TAZ 18/9 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 3 (33.33%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Device dislocation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Device leakage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Waist circumference increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Weaning failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypokinesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin exfoliation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 3: ≥2 to <7 years TOL/TAZ 30/15 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 18/9 mg/kg	Cohort 4: ≥3 months to <2 years TOL/TAZ 30/15 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 1 (100.00%)	1 / 5 (20.00%)

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Device leakage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Investigations			
Waist circumference increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Weaning failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dizziness			

subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypokinesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin exfoliation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Metabolic acidosis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 5: birth to <3 months TOL/TAZ 20/10 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 12/6 mg/kg	Cohort 6: birth to <3 months TOL/TAZ 20/10 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	2 / 2 (100.00%)	0 / 4 (0.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Device leakage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Waist circumference increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Weaning failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypokinesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Skin exfoliation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2014	Amendment 1: clarified the study design, revised inclusion criteria, added exclusion criteria, updated nonclinical information, updated clinical trial background information, clarified timing of Screening procedures and PK time point, added new sections to clarify participant replacement, identification, and numbering, reduced the volume of blood required for PK samples, added new section to define a closely monitored event, and clarified expedited reporting.
19 August 2015	Amendment 2: added a possible interim analysis across Cohorts 5 and 6 which allowed for increased PK and safety evaluations for the youngest participants, revised inclusion criteria, allowed axillary temperature to assess participant temperature, revised clinical blood sampling to reduce the amount of blood required, and updated safety reporting contact information.
05 April 2016	Amendment 3: decreased creatinine clearance cutoff for Cohort 6.
16 February 2017	Amendment 4: for Cohort 6 only, revised inclusion from peri-operative prophylaxis only to any antibiotic prophylaxis and removed height and weight criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported