Official Protocol Title:	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
NCT number:	NCT02266706
Document Date:	09-Feb-2017

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CEFTOLOZANE/TAZOBACTAM

CXA-PEDS-13-08

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

Study Drug:	ceftolozane/tazobactam
IND Number:	104,490
Protocol Number:	CXA-PEDS-13-08 (MK-7625A PN010)
Sponsor:	Cubist Pharmaceuticals LLC (formerly known as Cubist Pharmaceuticals, Inc.), an indirect wholly-owned subsidiary of Merck & Co., Inc. and with a principal place of business address of: Weystrasse 20 - 6000 Lucerne 6 Switzerland
Dose Form:	Intravenous
Medical Monitor:	PPD
Version:	5.0
Amendment:	4.0
Date:	09 February 2017

STATEMENT OF CONFIDENTIALITY

The confidential information in the following document is provided to you as an investigator, potential investigator, or consultant, for review by you, your staff, and applicable institutional review board(s). It is understood that the information will not be disclosed to others without written authorization from Cubist Pharmaceuticals, LLC, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

PROTOCOL Approval

Protocol Title:	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
Protocol Number:	CXA-PEDS-13-08
Protocol Date:	09 February 2017

PPD

PPD

Date

PPD

PPD

Date

PPD

PPD

Date

Investigator's Agreement

I have received and read the Investigator's Brochure for ceftolozane/tazobactam. I have read the CXA-PEDS-13-08 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SUMMARY OF CHANGES

PRIMARY REASONS FOR THIS AMENDMENT:

Section Numbers	Section Titles	Description of Changes	Rationale
Synopsis, 1.4.1, 3.1, 4.1	Synopsis Study Rationale Overall Study Design Subject Inclusion Criteria	For Group 6 only, Inclusion Criterion 6 was expanded from peri-operative prophylaxis only to any antibiotic prophylaxis.	For Group 6 subjects born at ≤32 weeks gestation who are <3 months of age, surgery is commonly delayed due to immaturity and their small size. These subjects may still be receiving antibiotic prophylaxis and be appropriate candidates for the study despite not being in a peri-operative period.
Synopsis, 4.2	Synopsis, Subject Exclusion Criteria	For Group 6 only, height and weight criteria were removed from Exclusion Criterion 6.	For Group 6 subjects born at ≤32 weeks gestation who are <3 months of age, there are no validated or standardized tools to assess percentiles for height or weight. In addition, height is accounted for in the calculation of creatinine clearance using the Schwartz equation.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Numbers	Section Titles	Description of Changes	Rationale
Title Page, Protocol Approval Page	Title Page, Protocol Approval Page	Medical Monitor name was changed.	Administrative change.
Throughout the document	Throughout the document	Minor stylistic and typographical edits were made.	To align with Merck style, improve clarity, or both.

SYNOPSIS

Name of Sponsor/Company: Cubist Pharmaceuticals, LLC
Name of Investigational Product: ceftolozane/tazobactam
Name of Active Ingredient: ceftolozane/tazobactam
Title of Study: 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
Phase of Development: 1
Objectives: **Primary:** To evaluate the pharmacokinetics (PK) of a single dose of intravenous ceftolozane/tazobactam in pediatric patients from birth to <18 years receiving standard of care antibiotic therapy for proven or suspected gram-negative infection, including patients receiving peri-operative prophylactic antibiotics. **Secondary:** To assess the safety and tolerability of a single dose of intravenous ceftolozane/tazobactam in pediatric patients from birth to <18 years receiving standard of care antibiotic therapy for proven or suspected gram-negative infection, including patients receiving peri-operative prophylactic antibiotics.
Study Rationale: Ceftolozane/tazobactam is a novel antibacterial consisting of ceftolozane, a unique antipseudomonal cephalosporin, with tazobactam, a well-established β-lactamase inhibitor. This antibacterial has activity against *Pseudomonas aeruginosa,* including drug-resistant strains, and other common gram-negative pathogens including extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. Ceftolozane/tazobactam is being developed in adults for the treatment of serious gram-negative bacterial infections including complicated urinary tract infections, complicated intra-abdominal infections, and nosocomial pneumonia. This is the first study investigating the use of ceftolozane/tazobactam in pediatric patients. Current guidance documents for pediatric PK studies focus on appropriate dosing in the pediatric population based on PK data. The PK of a drug in the pediatric population usually cannot be precisely predicted from that in adults. Therefore, PK studies are needed to identify the appropriate pediatric dosing. In general, the initial pediatric doses of ceftolozane/tazobactam were chosen based on adult PK data, with the objective of achieving the therapeutic exposure levels seen in adults. However as, ceftolozane/tazobactam is primarily renally eliminated the initial doses for each age group will take into account the stage of development of their renal function and body weight. This study is designed to assess the PK, safety, and tolerability of a single intravenous dose of ceftolozane/tazobactam in pediatric patients.

Methodology:

This is a Phase 1, single-dose, non-comparative, open-label study to characterize the PK, safety, and tolerability of ceftolozane/tazobactam in male and female pediatric patients from birth to <18 years receiving concurrent standard of care antibiotic therapy for proven or suspected gram-negative infection including patients receiving peri-operative prophylactic antibiotics.

Thirty-six eligible patients will be enrolled into one of six age groups (6 patients planned per age group):

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

In Groups 5 and 6, birth has been defined as at least 7 days postnatal due to the fact that neonatal renal function is closely related to both gestational age and postnatal age. Fluctuations in serum creatinine occur in the first week of life and as a result, the Schwartz equation, which will be used to calculate renal function in this population, is not recommended for use until after the first week of life. Because ceftolozane/tazobactam is primarily renally eliminated, it is necessary to limit enrollment in Groups 5 and 6 only to those patients who have undergone the fluctuation in serum creatinine observed during the first week of life, hence the requirement for 7 days postnatal. A subanalysis of Groups 5 and 6 will be conducted in patients aged 7-28 days and those aged 29 days - <3 months.

All patients will receive a single age-based IV dose of ceftolozane tazobactam as a 60 (± 10) minute infusion.

In each age group, an interim analysis of PK and safety data will be conducted after 3 patients have received the initially proposed dose. For Groups 5 and 6, an additional interim analysis will be conducted after a total of 3 patients across both groups have been dosed. This additional interim analysis will only be performed if the first 3 patients span across both groups, and will not be required if the first 3 patients are consecutively enrolled into either Group 5 or Group 6. Depending on the results of the interim analysis, dosing will either continue at the initial dose, or a new optimized dose targeted at achieving the exposure levels seen in adult patients.

In subsequent groups, the initial dose is also subject to change based upon the results of the interim analysis in previous groups.

Enrollment will begin with Groups 1-4 at study start. Enrollment of Groups 5-6 will occur following interim analysis of Group 4, and will be based on preliminary PK assessments, PK variability, and patient safety data.

Screening assessments, including medical and surgical history, medication history, nursing mothers' medication history, demographics, physical examination, vital signs, ECG, urinalysis, and clinical laboratory tests (hematology, chemistry, urinalysis, serum creatinine, and direct Coombs' test) will be performed within 48 hours prior to dosing.

Blood samples for plasma PK determination of ceftolozane, tazobactam, and tazobactam M1 (the single major metabolite of tazobactam) plasma levels will be collected in all patients.

Patients will be monitored for safety 24 hours post study-drug infusion, including assessments of adverse events (AEs), physical examination, vital signs, and clinical laboratory tests.

The site will contact the patient and/or parent (or appropriate legal representative) at Study Day 8 (± 2 days) for assessment of AEs and concomitant medications and procedures.

Number of Patients (planned):

Thirty-six patients concurrently receiving standard of care antibiotic therapy for proven or suspected gram-negative infection or for peri-operative prophylaxis are planned to be enrolled into one of six age groups: ≥12 to <18 years, ≥7 to <12 years, ≥2 to <7 years, ≥3 months to <2 years, birth (>32 weeks gestation, 7 days postnatal) to <3 months, and birth (≤32 weeks gestation, 7 days postnatal) to <3 months.

Inclusion Criteria:

To be eligible for enrollment, a patient must fulfill all of the following inclusion criteria:

1. Provide written parental (or appropriate legal representative) informed consent and age-appropriate assent prior to any study-related procedure not part of normal medical care;
2. Male or female from birth (defined as at least 7 days postnatal) to <18 years of age;
3. Able to comply with the protocol for the duration of the study;
4. For female patients who have undergone menarche:
    - Is not pregnant (as confirmed by the serum pregnancy test at Screening) and not planning to become pregnant within 30 days of last study drug administration, AND
    - Is non-lactating, AND
    - Is abstinent OR utilizes one of the following for at least 1 month prior to screening: hormonal contraceptives (injectable, oral, patch, or vaginal ring), intrauterine device (IUD), or barrier method (diaphragm). This method must be used in combination with a barrier method of contraception for their male partner (condom). Patients must be willing to practice these methods for at least 30 days after study drug administration;
5. For male patients who are sexually active with female partners who have undergone menarche: patient must be using and willing to continue using medically acceptable forms of contraception (abstinence, or male condom for patients plus an additional method of contraception for their female partners) from Screening and for at least 30 days after study drug administration;
6. For Groups 1-5:
    - Receiving standard of care antibiotic therapy for suspected or diagnosed gram-negative infection or for peri-operative prophylaxis

    For Group 6:
    - Receiving standard of care antibiotic therapy for suspected or diagnosed gram-negative infection or as antibiotic prophylaxis;
7. For Groups 1–4:
    - Have a calculated creatinine clearance rate (CL_{CR}) ≥ 80 mL/min/1.73m^2 as determined by the Schwartz (2009) equation at baseline.

    For Group 5:
    - Have a calculated creatinine clearance rate (CL_{CR}) ≥ 50 mL/min/1.73m^2 as determined by the Schwartz (2009) equation at baseline.

    For Group 6:
    - Have a calculated creatinine clearance rate (CL_{CR}) ≥ 20 mL/min/1.73m^2 as determined by the Schwartz (2009) equation at baseline.

Exclusion Criteria

To be eligible for enrollment, a patient must not meet any of the following exclusion criteria:

1. Known allergy/hypersensitivity to any β-lactam antibacterial;

2. History of clinically significant renal, hepatic, or hemodynamic instability (defined as a requirement for pharmacological intervention to manage blood pressure in the 24-hour window prior to enrollment);
3. Planned use of cardiopulmonary bypass or dialysis;
4. Planned blood transfusion within 24 hours of study drug administration;
5. Clinically significant abnormal laboratory test results not related to the underlying infection, as determined by Investigator;
6. For Groups 1-5 only:
    - Height or weight outside of the 5th to 95th percentile;
7. Receipt of piperacillin/tazobactam within 24 hours of study drug administration;
8. Use of any medications known to inhibit tubular secretion of renally-excreted drugs;
9. Known use of illicit drugs or abuse of alcohol or cigarettes;
10. Patients likely to be at risk of hemodynamic disturbance (as determined by Investigator) following collection of the required PK blood samples;
11. Use of any investigational drug or participation in any experimental procedure in the 30 days preceding study entry.
12. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of study data.

Investigational Product, Dosage and Mode of Administration:

Single IV dose of ceftolozane/tazobactam based on age and weight infused over 60 (±10) minutes. The doses below are 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:

- Group 1 (Ages ≥12 to <18 years): 1.5 g fixed dose of ceftolozane/tazobactam (comprising 1000 mg ceftolozane and 500 mg tazobactam)
- Group 2 (Ages ≥7 to <12 years): 18 mg/kg ceftolozane and 9 mg/kg tazobactam
- Group 3 (Ages ≥2 to <7 years): 18 mg/kg ceftolozane and 9 mg/kg tazobactam
- Group 4 (Ages ≥3 months to <2 years): 18 mg/kg ceftolozane and 9 mg/kg tazobactam
- Group 5 (Ages birth [>32 weeks gestation, 7 days postnatal] to <3 months): 12 mg/kg ceftolozane and 6 mg/kg tazobactam
- Group 6 (Ages birth [≤32 weeks gestation, 7 days postnatal] to <3 months): 12 mg/kg ceftolozane and 6 mg/kg tazobactam

Varying age-appropriate volumes from a fixed concentration, not to exceed 15 mg/mL, of ceftolozane/tazobactam will be administered to achieve the intended dose in each pediatric patient.

Duration of Treatment:

Patients will be screened for eligibility within 48 hours prior to study drug administration and monitored at least 24 hours post-dose.

The patient and/or parent (appropriate legal representative) will be contacted via telephone on Study Day 8 (± 2 days) post-infusion for assessment of AEs and concomitant medications and procedures.

Criteria for Evaluation:

Analysis Populations:

- *Pharmacokinetic (PK) population:* All patients who receive one full dose of study drug and have blood samples with quantifiable plasma levels at the C_{max} (the 1 hour post infusion start time point) and at least two time points after C_{max} (the 2, 4, or 6 hour post infusion start time points), to allow an estimation of area under the concentration versus time curve (AUC).

- *Safety population:* All patients who receive any dose (including partial doses) of any study medication.

Pharmacokinetics:

Pharmacokinetic data will be summarized by descriptive statistics, including number of subjects (n), mean, standard deviation (SD), median, coefficient of variation (CV%), minimum, maximum, geometric mean, and geometric CV, and presented for each time point by group for plasma concentrations of ceftolozane, tazobactam, and M1. Individual and mean ceftolozane, tazobactam, and M1-plasma concentration-time profiles will be plotted. Exploratory analyses may be conducted using graphical and/or regression methods.

The following PK parameters will be determined: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), concentration at last sampling point (C_{last}), time of last sampling point (T_{last}), area under the plasma concentration-time curve from 0 to last sample collected ($AUC_{0\text{-}last}$), area under the plasma concentration-time curve from 0 to infinity ($AUC_{0\text{-}\infty}$), elimination half-life ($t_{1/2}$), volume of distribution at steady state (V_{ss}), and plasma clearance (CL).

Safety:

Although confounded by the use of other concomitant antibiotics, safety and tolerability will be evaluated by examining the incidence, severity, and type of adverse events, changes in clinical laboratory tests (including chemistry/hematology, urinalysis, serum creatinine, and direct Coombs' test), and changes from baseline in vital signs.

The type and incidence of all adverse events and serious adverse events will be tabulated, and events occurring within 72 hours of dosing will be analyzed separately. Special attention will be given to local tolerability events occurring at time of study drug administration and to those patients who discontinue due to an adverse event or a serious adverse event. In addition, hypersensitivity reactions, events indicative of hemolytic disorders, and events involving *Clostridium difficile* will be summarized separately. Laboratory data will be summarized by type of laboratory test. Descriptive statistics of laboratory values, vital signs and changes from baseline will be summarized. Abnormalities detected during the physical examination will be summarized in frequency tables.

Statistical Methods:

Statistical methods are primarily descriptive in nature and will be used to guide decisions as to the clinical relevance of findings. No formal statistical analysis is planned.

Safety analyses will include a summarization of exposure, AEs, tabulation of changes from baseline in clinical laboratory data and vital signs and concomitant medications.

Characterization of the PK of single dose ceftolozane/tazobactam will be evaluated by analyzing plasma concentration data by non-compartmental pharmacokinetic analysis, and generating standard pharmacokinetic parameters. In addition, PK data obtained from all groups will be pooled for a population PK analysis, as allowed by the data. These results will be reported separately.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-24}	Area under the curve from 0 to 24 hours
$AUC_{0-\infty}$	Area under the curve from 0 to infinity
AUC_t	Area under the concentration time curve from the time of the dose to the T_{last}
β	Beta
BLI	β-lactamase inhibitor
BLQ	Below limit of quantification
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
cIAI	Complicated intra-abdominal infections
CL	Plasma clearance
C_{last}	Last quantifiable plasma concentration
CL_{CR}	Creatinine clearance
C_{max}	Maximum concentration
CRO	Contract research organization
Cr_{serum}	Serum creatinine
Cubist	Cubist Pharmaceuticals LLC
cUTI	Complicated urinary tract infections
%CV	% Coefficient of variation
CXA-101	Ceftolozane
CXA-201	Ceftolozane/tazobactam
CYP	Cytochrome
CYP450	Cytochrome P450
DCSI	Developmental Core Safety Information
EC	Ethics Committee

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
ESBL	Extended spectrum β-lactamase
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
h	Hour
ICH	International Conference on Harmonization
IP	Intraperitoneal
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
kg	Kilogram
L	Liter
m	Meter
M1	Tazobactam metabolite
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram
MIC	Minimum inhibitory concentration
min	Minute
mL	Milliliter
NOAEL	No observed adverse effect level
PBP	Penicillin-binding protein
PD	Pharmacodynamic
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
PND	Postnatal day

Abbreviation or Specialist Term	Explanation
PT	Preferred term
PTA	Probability of target attainment
q8h	Every 8 hours
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Terminal elimination half-life
t>MIC	Time above the minimum inhibitory concentration
T_{max}	Time of maximum concentration
TOC	Test of cure
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
WBC	White blood count
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Ceftolozane/tazobactam

Ceftolozane/tazobactam (formerly known as CXA-201), is a novel antibacterial consisting of ceftolozane, a unique antipseudomonal cephalosporin, with tazobactam, a well-established beta (β)-lactamase inhibitor (BLI). Ceftolozane/tazobactam is being developed by Cubist Pharmaceuticals, LLC (Cubist) for the treatment of serious bacterial infections in adult patients, including complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), and nosocomial pneumonia. Ceftolozane alone was previously referred to as CXA-101 or FR264205.

Like other members of the cephalosporin class, ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell wall synthesis and subsequent cell death. Tazobactam is an inhibitor of most Class A and some Class C β-lactamases, with well-established in vitro and in vivo activity in combination with active β-lactams.

Ceftolozane displays potent antibacterial activity against common gram-negative and selected gram-positive organisms, such as *P. aeruginosa, E. coli*, *K. pneumoniae, Enterobacter* spp., streptococci, *H. influenzae*, *Moraxella catarrhalis*, the majority of pathogenic enteric bacilli, and select gram-positive anaerobic species. Ceftolozane exhibits limited activity against staphylococci and enterococci, insufficient for reliable treatment of this pathogen. In general, the gram-positive and gram-negative spectrum of activity of ceftolozane is similar to ceftazidime, but the antipseudomonal activity of ceftolozane is the most potent among all currently available β-lactams, including the carbapenems. Most importantly, ceftolozane has been shown to be active against strains of *P. aeruginosa* that are resistant to carbapenems, cephalosporins, fluoroquinolones, and aminoglycosides, including many multidrug resistant isolates.

Tazobactam increases the *in vitro* activity of ceftolozane against the majority of extended spectrum β-lactamase (ESBL)-producing gram-negative bacilli and some AmpC over-expressing Enterobacteriaceae. The addition of tazobactam has no significant impact on the antipseudomonal activity of ceftolozane, since *P. aeruginosa* rarely produces ESBLs. Both ceftolozane and ceftolozane/tazobactam show time-dependent bactericidal activity against various gram-negative organisms, with ceftolozane/tazobactam being more potent than piperacillin/tazobactam against Enterobacteriaceae (both ESBL-negative and ESBL-positive isolates) and *P. aeruginosa*.

In summary, ceftolozane is a novel cephalosporin antibiotic which, in combination with the potent BLI, tazobactam, has broad-spectrum antibacterial coverage against β-lactam-resistant Enterobacteriaceae and multidrug resistant *P. aeruginosa*.

1.2 Nonclinical Experience

Ceftolozane/tazobactam has been well characterized in a comprehensive series of in vitro and in vivo nonclinical studies that have defined key safety findings, including test-article related effects, and the reversibility of these changes.

1.2.1 Safety Pharmacology

Ceftolozane showed no potential to affect the functioning of the cardiovascular, respiratory, and central nervous systems across rats and dogs at clinically relevant blood concentrations. Safety pharmacology studies with tazobactam were not conducted by the Sponsor. The safety of tazobactam is supported by its long history of clinical use.

1.2.2 Absorption, Distribution, Metabolism, Excretion, and Drug-Drug Interactions

Ceftolozane and tazobactam, both alone and in combination, exhibited dose-proportional intravenous (IV) pharmacokinetics (PK) in rats and dogs with no gender differences and no change in systemic exposure with repeat dosing. Ceftolozane was distributed to tissues and exhibited low plasma protein binding, a predominantly renal route of elimination, and minimal metabolism following IV administration. Tazobactam exhibited low plasma protein binding and is metabolized to a single major metabolite, M1, which lacks pharmacologic activity.

No PK interactions were observed between ceftolozane and tazobactam when administered to rats or dogs in combination. In vitro, ceftolozane, tazobactam, and the M1 metabolite of tazobactam demonstrated low potential for drug-drug interactions involving cytochrome (CYP) enzymes and/or transporters at clinically relevant concentrations.

1.2.3 Repeat Dose Toxicity

No target organ toxicities were identified for ceftolozane alone or in combination with tazobactam. Effects associated with ceftolozane and tazobactam treatment alone were primarily limited to non-adverse changes in the kidney and liver, respectively. Ceftolozane-related effects in the kidney were limited to the microscopic presence of hyaline droplets in proximal renal tubule epithelium in the absence of toxicologically meaningful degeneration or necrosis with no effects on renal function noted as determined by the absence of biologically relevant changes in serum blood urea nitrogen (BUN), creatinine, inorganic phosphorus, urine volume, or presence of cellular/granular casts [Studies GLR050690 and CX.101.TX.031]. A corresponding increase in kidney weight was observed in rats [Studies GLR050690 and CX.101.TX.031] but not dogs [Study GLR050729]. The no-observed-adverse-effect level (NOAEL) for rats was considered 1000 milligram (mg)/kilogram (kg)/day, the highest dose level assessed [Studies GLR050690 and CX.101.TX.031and Report CX.101.TX.032]. The NOAEL of 300 mg/kg/day for dogs was based on the observation of the cephalosporin-induced, histamine-related adverse clinical signs at 1000 mg/kg/day (namely, flush of the auricular and oral mucosa, swelling of the head, emesis, salivation, as well as lateral position and non-kidney-related effects) [Study GLR050729 and Report CX.101.TX.032]. Ceftolozane safety margins for cIAI and cUTI based on general repeated dose toxicity studies conducted in rats and dogs with ceftolozane alone range from approximately 3 fold to 10-fold based on area under the curve (AUC) and approximately 13 fold to 141-fold based on maximum concentration (C_{max}).

The primary effect for tazobactam in rats and dogs was observed in the liver. Microscopic evidence of reversible glycogen accumulation was detected in hepatocytes following twice daily repeat intraperitoneal (IP) or IV administration of tazobactam to rats [1] and dogs [2], respectively, for 6 months at dose levels of 80 and 160 mg/kg/day. A correlating reversible

increase in liver weights was evident at 80 and 160 mg/kg/day in rats. Other reversible tazobactam-related effects noted only in rats included a dose-independent increase in food consumption in males and females, an increase in reticulocytes in females at 80 and 160 mg/kg/day, decreased triglycerides in males at 160 mg/kg/day, decreased serum triglyceride levels in all females administered tazobactam, and cecal enlargement in females at 160 mg/kg/day. Tazobactam administration alone was associated with an increase in smooth endoplasmic reticulum and glycogen granules from bile canaliculi and hepatocyte nuclei at 160 mg/kg/day in dogs. The NOAEL determined for both species was 40 mg/kg/day.

Importantly, no new effects or unexpected toxicities were observed when ceftolozane was combined with tazobactam. Ceftolozane safety margins for cIAI and cUTI based on general repeated dose toxicity studies conducted in rats and dogs with ceftolozane in combination with tazobactam range from approximately 3- to 5-fold based on AUC and approximately 16- to 41-fold based on C_{max}. Tazobactam safety margins for cIAI based on general repeated dose toxicity studies conducted in rats and dogs with ceftolozane in combination with tazobactam range from approximately 1- to 7-fold based on AUC and approximately 10- to 15-fold based on C_{max}. Tazobactam safety margins for cUTI are not calculated because clinical PK data for tazobactam were not collected in cUTI patients. While modest, the tazobactam safety margins support clinical use because tazobactam is a component of a currently marketed drug (piperacillin/tazobactam) whose mode of action, PK, and safety profile has been well characterized and established in animals and humans.

1.2.4 Genotoxicity

The weight of evidence suggests that ceftolozane alone and in combination with tazobactam has a low potential for genotoxicity.

Ceftolozane/tazobactam was negative when tested in a mouse lymphoma assay [Study CXA201-T-003] and did not induce the formation of micronucleated erythrocytes in rat bone marrow [Study CXA201-T-004]. In an in vitro cytogenetics (Chinese Hamster Ovary cells) ceftolozane/tazobactam was positive for structural aberrations at doses ≥ 500/250 microgram (µg)/milliliter (mL) for ceftolozane and tazobactam, respectively [Study CXA201-T-002].

Ceftolozane was negative when tested in a variety of in vitro assays including a microbial mutagenicity assay [Study GLR050752], a chromosomal aberration assay using Chinese Hamster Lung fibroblasts [Study GLR050845], and a UDS assay [Study GLR040362]. Ceftolozane was positive in a mouse lymphoma assay [Study GLR050528]. Ceftolozane did not induce the formation of micronucleated erythrocytes in mouse blood [Study GLR050847].

Tazobactam was negative in a variety of in vitro assays including a microbial mutagenicity assay, a UDS assay, a mammalian point mutation (Chinese hamster ovary cell HPRT) assay, a BALB/c-3T3 cell transformation assay, a chromosomal aberration (Chinese hamster lung cell) assay [3]. In another mammalian point mutation (mouse lymphoma cell) assay, tazobactam was positive [3]. In vivo, tazobactam did not induce the formation of micronucleated erythrocytes in rat bone marrow [3].

1.2.5 Reproductive Toxicity

Standard definitive fertility and embryo/fetal development studies conducted with ceftolozane in mice and/or rats have demonstrated that ceftolozane is neither a developmental nor reproductive toxicant.

Ceftolozane showed no effect upon fertility or early embryonic development in rats up to 1000 mg/kg/day, the highest dose level assessed [Study CX.101.TX.002]. The calculated area under the curve from 0 to 24 hours (AUC_{0-24}) values associated with this dose are approximately 3-fold and 4-fold greater than the mean calculated daily AUC values in cUTI and cIAI patients, respectively, receiving the clinically relevant dose of 1000 mg of ceftolozane thrice-daily. Studies in rats and mice revealed no embryo/fetal toxicity related to ceftolozane administration at doses of up to 1000 and 2000 mg/kg/day, respectively, the highest dose tested [Studies CX.101.TX.001 and CXA101.T-006]. The calculated AUC from 0 to infinity ($AUC_{0-\infty}$) values associated with this dose range from approximately 4- to 10-fold greater than the mean calculated daily AUC values in cUTI and cIAI patients receiving the clinically relevant dose of 1000 mg of ceftolozane thrice-daily. Administration of ceftolozane to pregnant rats from gestation day 6 through lactation day 20 did not affect pre or post-natal development of the pups with the exception of a decrease in auditory startle response on postnatal day (PND) 60 at maternal doses of 300 and 1000 mg/kg/day [Study CX.101.TX.012]. No effect was noted at 100 mg/kg/day. A dose of 300 mg/kg/day is associated with a daily AUC value approximately equivalent to the daily clinical exposure based on mean daily clinical ceftolozane AUC values for cUTI and cIAI.

Reproduction studies performed with tazobactam in rats revealed no evidence of impaired fertility due to tazobactam administered at doses up to 4 times the maximum recommended human daily dose based on body-surface area (mg/meter $[m]^2$) [3]. Teratology studies performed with tazobactam in mice and rats and have revealed no evidence of harm to the fetus due to tazobactam administered at doses up to 8 and 19 times, respectively, the human dose based on body-surface area (mg/m^2) [3]. Twice daily IP administration to female rats for 15 days prior to mating, during the mating, and throughout the gestation and lactation period was associated with a decrease in the numbers of implantations and live litter size and an increase in the number of still births were evident along with reversible delays in renal development at a dose of 640 mg/kg/day following repeat administration to rats [4]. In a separate study, twice daily IP administration of tazobactam to female rats from gestation day 17 through PND 21 at dose levels of 40, 320, and 1280 mg/kg/day was associated with decreased pup body weight during the lactation period at doses ≥320 mg/kg/day with an increase in stillbirths and a decrease in body weights early postweaning at a dose of 1280 mg/kg/day [5]. Tazobactam, co-formulated with piperacillin, is currently approved for use in pediatric patients down to two months of age.

1.2.6 Neonatal and Juvenile Development

Once daily subcutaneous administration of ceftolozane/tazobactam to PND4 neonatal Sprague Dawley rats for 14 days was associated with clinical observations (decreased motor activity, list/impaired righting reflex, ataxia), increased liver and kidney weight, as well as microscopic evidence of centrilobular hepatocellular hypertrophy and cytoplasmic vacuolation in the proximal convoluted tubular epithelium of the kidney at a dose of

1000/500 mg/kg/day [Study CX.101.TX.033]. Hyaline droplets (males only), and basophilic tubules and fibrosis in the kidney were also noted at this dose level. A dose of 300/150 mg/kg/day was associated with increased liver and kidney weight with correlating microscopic evidence of centrilobular hepatocellular hypertrophy and cytoplasmic vacuolation in the proximal convoluted tubular epithelium of the kidney. No effects were observed at a dose of 50/25 mg/kg/day.

The NOAEL for this study was considered to be 300/150 mg/kg/day, which correlated with mean PND17 ceftolozane/tazobactam $AUC_{0-\infty}$ and C_{max} values of 657/145 µg•h/mL and 416/184 µg/mL, respectively. Daily ceftolozane and tazobactam exposure values were approximately 2-fold greater on day 1 of treatment as compared to day 14. In a pivotal 28-day Good Laboratory Practice toxicity study (Study CX.101.TX.038), once daily subcutaneous administration of ceftolozane in combination with tazobactam in a 2 to 1 ratio to neonatal Sprague-Dawley rats for 28 days (PNDs 4 through 31) was associated with clinical observations of decreased motor activity and/or impaired righting reflex at dosages of 300/150 and 1000/500 mg/kg/day and were considered adverse at 1000/500 mg/kg/day. A non-adverse decrease in erythrocytes, hemoglobin, and hematocrit values was noted in male and female rats in the 1000/500 mg/kg/day dose group on PND 32. Non-adverse centrilobular hypertrophy of hepatocytes was observed in the 1000/500 mg/kg/day dose group. These effects had reversed or were in the process of reversing following a 28 day recovery period. Based on the adverse clinical signs observed at 1000/500 mg/kg/day, the NOAEL for this study was considered to be 300/150 mg/kg/day, which correlated with mean PND 4 AUC_{last} and C_{max} values of 1520/426 µg•h/mL and 525/257 µg/mL, respectively, and mean PND 31 AUC_{last} and C_{max} values of 296/33.0 µg•h/mL and 294/59.8 µg/mL, respectively. Ceftolozane AUC_{last} and C_{max} were approximately 5- and 2 fold lower, respectively, on PND 31 as compared to PND 4. Tazobactam AUC_{last} and C_{max} were approximately 9- to 15-fold lower and 3- to 4-fold lower, respectively, on PND 31 as compared to PND 4.

1.2.7 Other Studies

Ceftolozane showed a potential for local tolerance effects in mice and rats, a low potential for antigenicity, and no potential for phototoxicity, immunotoxicity, or hemolytic activity.

Overall, the nonclinical data package collected on ceftolozane/tazobactam supports clinical investigation for pediatric use. Further information is available in the ceftolozane/tazobactam Investigator's Brochure.

1.3 Clinical Experience with Ceftolozane/tazobactam

Ceftolozane alone or ceftolozane/tazobactam has been evaluated in adults in ten completed Phase 1 studies, a Phase 2 study in cUTI, a Phase 2 study in cIAI, and two Phase 3 clinical studies (one in cUTI and one in cIAI). A Phase 3 study in nosocomial pneumonia is ongoing.

1.3.1 Pharmacokinetics

The results from the adult Phase 1 and Phase 2 studies demonstrated ceftolozane/tazobactam PK characteristics are generally consistent with those of other renally-excreted β-lactam

antibiotics. Ceftolozane/tazobactam had linear PK across a wide range of doses (250 to 3000 mg for ceftolozane and 100 to 1500 mg for tazobactam); and its volume of distribution at steady state (V_{ss}), approximately 11 to 18 liters (L), was roughly equivalent to the extracellular fluid volume. The plasma protein binding was low; approximately 16 to 21% and 30% for ceftolozane and tazobactam, respectively. The terminal elimination half-life ($t_{½}$) for ceftolozane and tazobactam was 2 to 3 hours and approximately 1 hour, respectively, independent of dose, and with little or no accumulation after multiple dosing every 8 hours or every 12 hours. Ceftolozane/tazobactam was primarily cleared from the systemic circulation into the urine by glomerular filtration, but tazobactam was also partly cleared by tubular secretion. About 20% of the tazobactam dose is converted to a single inactive metabolite (M1) via hydrolysis of the β-lactam ring while >95% for ceftolozane was eliminated as unchanged parent drug, suggesting minimal potential for cytochrome P450 (CYP450) mediated metabolism. Co-administration of ceftolozane/tazobactam given as 1-hour IV infusions in a fixed 2:1 ratio of ceftolozane to tazobactam did not change the PK profiles of either drug, nor of the tazobactam M1 metabolite.

Systemic clearance was linearly related to creatinine clearance (CL_{CR}), but no other significant intrinsic factors affecting the PK of ceftolozane/tazobactam were identified. A drug-drug interaction study suggested a low potential for any CYP450 or transporter-mediated PK interaction, and there is a low potential for PK interaction with other drugs eliminated primarily by glomerular filtration, such as tobramycin and vancomycin.

1.3.2 Safety

In adult patients, two Phase 1 and one Phase 2 clinical studies were completed with ceftolozane alone, and eight Phase 1, one Phase 2, and two Phase 3 clinical studies in two indications were completed with ceftolozane/tazobactam. A total of 145 subjects in these clinical studies received ceftolozane alone, and 1044 received ceftolozane/tazobactam.

Phase 1 studies suggested ceftolozane/tazobactam was safe and well tolerated. The most common adverse events (AEs) in Phase 1 studies were mainly gastrointestinal in origin (nausea, vomiting, constipation and diarrhea), as well as headache and infusion site reactions. Multiple dose studies (CXA-101-01, CXA-201-01, and CXA-MD-11-07) demonstrated that doses of ceftolozane/tazobactam up to 9000 mg daily (3000 mg every 8 hours [q8h]) were well tolerated in adults for durations of up to 10 days. The thorough QT study (CXA-QT-10-02) demonstrated at therapeutic and 3-fold supra-therapeutic dose of ceftolozane/tazobactam did not increase QTc, QTcF and QTcB intervals, and no findings indicated an effect of ceftolozane/tazobactam on cardiac repolarization. Only one serious adverse event (SAE) was reported in the ten Phase 1 studies for ceftolozane or ceftolozane/tazobactam. One patient in study CXA-REN-11-01 reported an unrelated SAE of thrombosis of arteriovenous fistula on study day 44, requiring hospitalization for heparinization and catheter replacement. Adverse events leading to discontinuation of ceftolozane/tazobactam in the Phase 1 studies were rare. One subject in study CXA-QT-10-02 discontinued due to an unrelated AE of fever, one subject in study CXA-MD-11-07 discontinued due to an AE of vomiting assessed by the Investigator as related, and one subject in study CXA-EB-13-05 discontinued due to an AE of acute drug eruption assessed by the Investigator as related.

In Phase 2 studies of ceftolozane in cUTI (CXA-101-03) and ceftolozane/tazobactam in cIAI (CXA-IAI-10-01), the most common AEs across both studies were pyrexia, nausea, constipation, sleep disorder, anemia, headache, vomiting, diarrhea and insomnia. In study CXA-101-03, there was an imbalance in the incidence of hyperglycemia severity grade shifts which was neither associated with ongoing abnormalities in serum glucose nor reported as adverse events. In study CXA-IAI-10-01, there was an imbalance in the incidence of hemoglobin severity grade shifts in the ceftolozane/tazobactam group; however the decreases in hemoglobin appeared to be related to complicated surgical procedures in high-risk subjects or the subject's underlying condition. Collectively, three subjects experienced a shift from negative direct Coombs' test at baseline to positive at the test of cure (TOC) visit, but none were associated with a report of hemolytic anemia.

No deaths were reported in the ceftolozane/tazobactam treatment arm, and no subjects met laboratory criteria for Hy's rule in study CXA-101-03. However, in study CXA-IAI-10-01, three subjects died in the ceftolozane/tazobactam arm; all were unrelated to study drug and occurred following study drug discontinuation. In the same study, one ceftolozane/tazobactam subject met the laboratory criteria for Hy's rule on therapy. These liver enzyme elevations were likely related to the underlying condition and surgical procedure as all levels declined during continued treatment.

In the integrated Phase 3 studies of ceftolozane/tazobactam in cUTI and cIAI (CXA-cUTI-10-04, CXA-cUTI-10-05, CXA-cIAI-10-08, and CXA-cIAI-10-09), 1015 adult patients received treatment with ceftolozane/tazobactam. The most common AEs from these trials were nausea, headache, diarrhea, pyrexia, constipation, hypertension, insomnia, and, vomiting. Overall SAE rates were 5.3% and 5.2% in the ceftolozane/tazobactam and comparator arms, respectively. Drug discontinuation rates due to AEs were similar, with 2% of patients who discontinued ceftolozane/tazobactam and 1.9% of patients who discontinued comparator drug. Drug-related SAEs with ceftolozane/tazobactam were limited to only two cases of *Clostridium difficile* colitis compared to one case with comparator drug. In cUTI, there was 1 death in the ceftolozane/tazobactam treatment arm and none in the comparator arm. In cIAI, there were 11 deaths in the ceftolozane/tazobactam arm and 8 deaths in the comparator arm. All of the deaths reported in these Phase 3 studies were deemed unrelated to study therapy by the Investigator.

An open-label Phase 3 study in nosocomial pneumonia was electively terminated by the Sponsor after enrollment of 4 patients, in order to devote all resources in initiating and completing the larger registration study being conducted as part of the clinical development program for nosocomial pneumonia. Two patients experienced SAEs, 1 in each arm, and the 1 in the ceftolozane/tazobactam treatment arm resulted in death. Neither event was deemed to be related to study drug. The Phase 3 registration study in nosocomial pneumonia is ongoing.

1.4 Rationale

1.4.1 Study Rationale

This is the first study investigating the use of ceftolozane/tazobactam in pediatric patients.

Current guidance documents for pediatric PK studies focus on appropriate dosing in the pediatric population based on PK data [6]. The PK of a drug in the pediatric population usually cannot be precisely predicted from that in adults. Therefore, PK studies are needed to identify the appropriate pediatric dosing.

This study will be conducted to investigate the PK and safety of a single IV dose of ceftolozane/tazobactam in pediatric patients from birth to <18 years of age receiving standard of care antibiotics either for treatment of suspected or proven gram-negative infection or for peri-operative prophylaxis (For Group 6 only, patients will be eligible if receiving antibiotic prophylaxis outside of a peri-operative period). Patients will be recruited into one of six age groups.

1.4.2 Dose Rationale

The initial pediatric doses of ceftolozane/tazobactam were chosen based on adult PK data, with the objective of achieving the therapeutic exposure levels seen in adults.

Ceftolozane/tazobactam is primarily renally eliminated; therefore, initial doses for each age group will take into account the stage of development of their renal function. In each age group, an interim analysis of the PK and safety data will be conducted when half of the group has received the initially proposed dose. For Groups 5 and 6, an additional interim analysis will be conducted after a total of 3 patients across both groups have been dosed. This additional interim analysis will only be performed if the first 3 patients span across both groups, and will not be required if the first 3 patients are consecutively enrolled into either Group 5 or Group 6. Depending on the results of the interim analysis, dosing will either continue at the initial dose, or a new optimized dose targeted at achieving the exposure levels seen in adult patients.

The initial dose selected for each group was supported by population PK analysis incorporating allometric scaling by body weight and renal function maturation for pediatric patients. Monte Carlo simulations were conducted to calculate the probability of target attainment (PTA) ≥90% for the PK/pharmacodynamic (PD) driver of approximately 30% time above the minimum inhibitory concentration (t>MIC) of 8 μg/mL. In addition, these simulations restricted the total daily ceftolozane AUC within the limits demonstrated to be safe in adults
(approximately 1100 μg*hr/mL). The proposed doses will target a ceftolozane AUC of approximately 200 μg*hr/mL, similar to the target therapeutic AUC in the adult population. Varying age-appropriate volumes of a fixed concentration of ceftolozane/tazobactam will be administered intravenously to achieve the intended dose in each pediatric patient. The same IV formulation will be used across all age groups.

2.0 TRIAL OBJECTIVES AND PURPOSE

2.1 Primary Objective

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

2.2 Secondary Objective

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

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is an open-label, non-comparative study of a single IV dose of ceftolozane/tazobactam in male and female pediatric patients 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 (For Group 6 only, patients will be eligible if receiving antibiotic prophylaxis outside of a peri-operative period).

Thirty-six eligible patients will be enrolled into one of six age groups (6 patients planned per age group):

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

The study design, as described in Section 3.1.1 and illustrated in Figure 1, will be used with enrollment beginning with Groups 1, 2, 3, and 4.

In Groups 5 and 6, birth has been defined as at least 7 days postnatal, due to the fact that neonatal renal function is closely related to both gestational age and postnatal age. Fluctuations in serum creatinine occur in the first week of life and as a result, the Schwartz equation, which will be used to calculate renal function in this population, is not recommended for use until after the first week of life. Because ceftolozane/tazobactam is primarily renally eliminated, it is necessary to limit enrollment in Groups 5 and 6 only to those patients who have undergone the fluctuation in serum creatinine observed during the first week of life, hence the requirement for 7 days postnatal.

Subject participation will require a minimum commitment of 6 days and a maximum of 12 days. Screening assessments will occur within 48 hours of study drug administration (Day 1). Baseline assessments will be performed following eligibility verification based on screening assessments. Patients will be monitored for safety 24 hours post study drug infusion. The site will contact the patient and/or parent (or appropriate legal representative) via telephone at Study Day 8 (± 2 days) for assessment of AEs and concomitant medications and procedures.

Blood samples for plasma PK determination will be collected in all patients. Details of the PK sample collection procedures can be found in Section 7.1.

Table 2 presents the full Schedule of Assessments.

3.1.1 Dosing and the Interim PK Assessment

All patients will receive a single age and weight-based IV dose of ceftolozane tazobactam as a 60 (±10) minute (min) infusion (Table 1). The doses below are 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.

Table 1 Ceftolozane/Tazobactam Dosing

Age Group	Age Range	Ceftolozane/Tazobactam Dose[a] (60 (±10) min infusion)
1	≥12 to <18 years	1.5 g fixed dose of ceftolozane/tazobactam (comprising 1000 mg ceftolozane and 500 mg tazobactam)
2	≥7 to <12 years	18 mg/kg ceftolozane and 9 mg/kg tazobactam
3	≥2 to <7 years	
4	≥3 months to <2 years	
5	Birth (>32 weeks gestation, 7 days postnatal) to <3 months	12 mg/kg ceftolozane and 6 mg/kg tazobactam
6	Birth (≤32 weeks gestation, 7 days postnatal) to <3 months	

[a] 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.

In each age group, an interim analysis of PK and safety data will be conducted after 3 patients have received the initially proposed dose. For Groups 5 and 6, an additional interim analysis will be conducted after a total of 3 patients across both groups have been dosed. This additional interim analysis will only be performed if the first 3 patients span across both groups, and will not be required if the first 3 patients are consecutively enrolled into either Group 5 or Group 6. The interim analysis will determine whether this initial dose was appropriate based on meeting the following criteria:

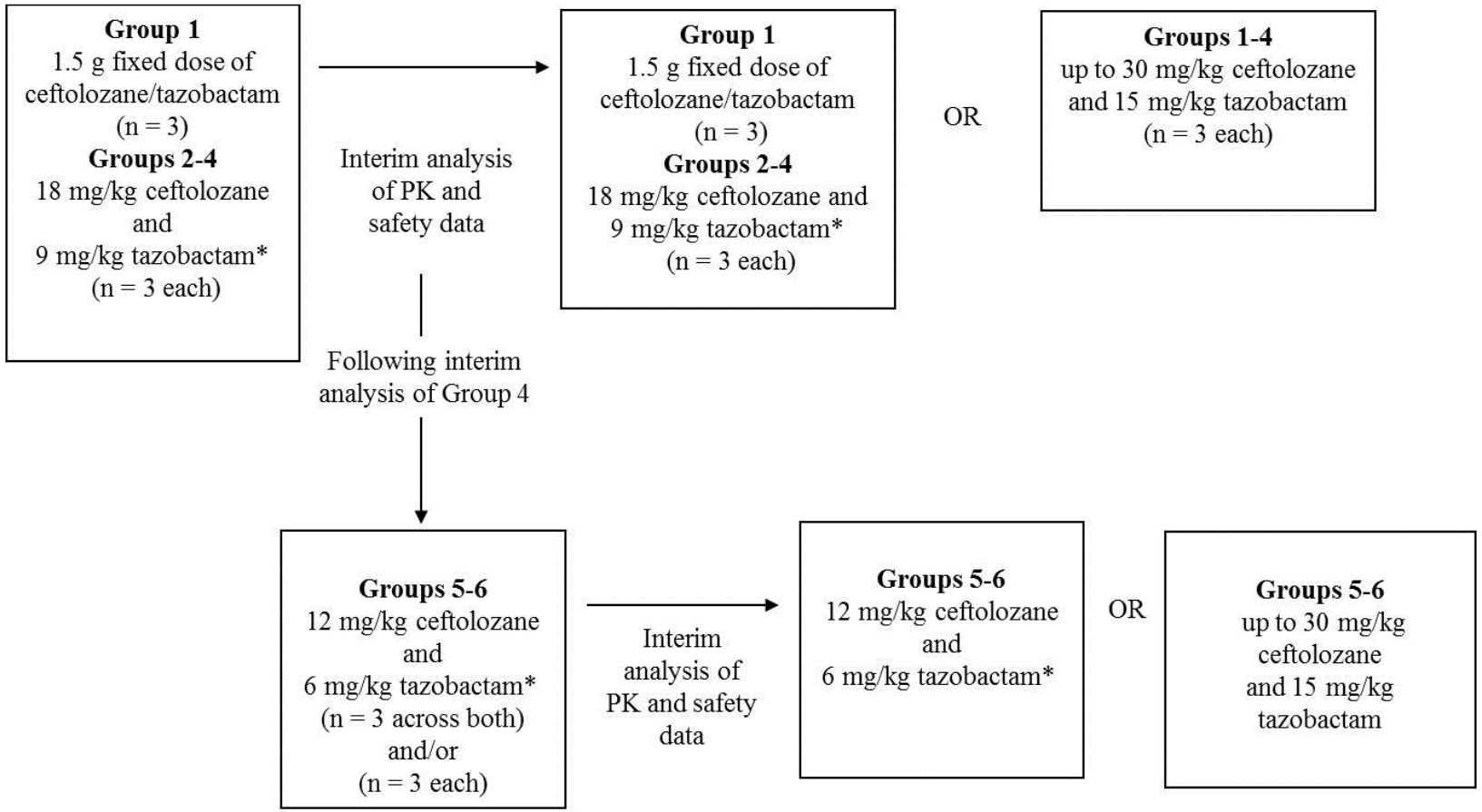
- absence of a safety signal (e.g., no SAE that is related to study drug or two reports of the same non-serious AE considered to be related to the study drug), and
- acceptable target attainment (excluding outliers and including at least 2 out of 3 patients) for PK/PD driver of approximately 30%T>MIC of 8 μg/mL, and
- targeted single dose ceftolozane $AUC_{0-\infty}$ of approximately 200 μg*hr/mL (which is a similar AUC to the proposed clinical adult dose) and does not exceed a steady-state ceftolozane AUC of approximately 1100 μg*hr/mL total daily exposure (which is the maximum exposure that has been previously demonstrated as safe in adults).

If data from the interim analysis demonstrates that the initially proposed dose meets the criteria above, enrollment will continue with the same dose administered to 3 additional patients. However, if the interim analysis demonstrates that a new optimized adjusted dose (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) is required, because one or more of the above criteria were not met, the new adjusted dose will be administered to 3 additional patients of the same age range.

In subsequent groups, the initial dose is also subject to change based upon the results of the interim analysis in previous groups. For example, at interim analysis of Group 4 if the initially proposed dose results in over or under exposure of study drug, then a new adjusted dose will be used for the remainder of the group. In this case, the initially proposed dose in Group 5 may also be adjusted, based on the knowledge obtained from the Group 4 interim analysis. See Figure 1.

Enrollment of Groups 1-4 will begin at study start. Enrollment of Groups 5-6 will occur following interim analysis of Group 4, and will be based on preliminary PK assessments, PK variability, and patient safety data.

Figure 1 Study Design



* 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

3.2 Study Visits

The schedule of events for the study is summarized in Table 2.

Screening assessments will occur within 48 hours of study drug administration (Day 1). Baseline assessments will be performed following eligibility verification based on screening assessments. Patients will be monitored for safety 24 (± 6) hours post study drug infusion (Day 2). The site will contact the patient and/or parent (or appropriate legal representative) via telephone on study day 8 (± 2 days) for assessment of AEs and concomitant medications and procedures.

3.3 Study Procedures

The schedule of events for the study is summarized in Table 2.

3.3.1 Clinical Assessments

- Full medical and surgical history
- Prior and concomitant medications, including those in the mothers of breast-fed patients, as detailed in Section 5.2
- Complete physical examination (Skin, Eyes, Ears/Nose/Throat, Head/Neck, Chest, Heart/Vascular, Abdomen, Neurological [sensory and motor], Musculoskeletal, and Extremities)
- Vital sign assessment including blood pressure, heart rate, respiratory rate and temperature (oral, axillary, tympanic, forehead or core)
- Height and weight
- 12-lead electrocardiogram (ECG)
    - In the event a patient is being continuously monitored with a cardiorespiratory monitor, an ECG waveform printout may be used
- Estimate the patient's CL_{CR} using the patient's serum creatinine (Cr_{serum}) value (mg/dL), height (cm), and the appropriate Schwartz (2009) equation:

  Glomerular filtration rate [GFR] (mL/min per 1.73 m^2) = 0.413 * height/Cr_{serum}
- Concomitant procedures
- Assessment of AEs, as detailed in Section 8.0, with a separate assessment of infusion-related reactions on Day 1

3.3.2 Laboratory Assessments

- Blood samples for hematology (hemoglobin, hematocrit, white blood cell [WBC] count with differential, and platelet count), serum chemistry (alkaline phosphatase, albumin, blood urea nitrogen [BUN], creatinine, non-fasting serum glucose, potassium, alanine aminotransferase, aspartate aminotransferase, sodium, total bilirubin, total protein) and coagulation (prothrombin time) evaluation
- Blood sample for direct Coombs' test
- Serum pregnancy test for female patients who have undergone menarche
- Urinalysis from patients who are either toilet trained and able to provide a specimen, catheterized, or fitted with a urine collection bag

For patients less than 3 months of age (Groups 5 and 6), study-specific blood draws for coagulation (prothrombin time) and the direct Coombs' test should be done at the discretion of the investigator based on safety and risks to the patient.

3.3.3 Pharmacokinetic Sampling

- Collect blood samples as detailed in Section 7.1.

3.4 Number of Subjects

Thirty-six patients are planned to be enrolled, with 6 patients planned in each of the 6 age groups: ≥12 to <18 years, ≥7 to <12 years, ≥2 to <7 years, ≥3 months to <2 years, birth (>32 weeks gestation, 7 days postnatal) to <3 months, and birth (≤32 weeks gestation, 7 days postnatal) to <3 months.

3.5 Treatment Assignment

All patients will receive a single IV dose of ceftolozane/tazobactam on Day 1.

3.6 Criteria for Study Termination

The Sponsor reserves the right to terminate the study at any time. Reasons for termination at any particular site includes, but are not limited to, the following: safety or AE finding that poses a potentially significant risk to the patients, site non-compliance with protocol and regulatory requirements, institutional review board (IRB)/ethics committee (EC) or the Investigator's decision to terminate or suspend the study at the investigative site.

Table 2 Schedule of Events

Procedure	Screening[a]	Study Day 1	Study Day 2[b] or Early Termination	Study Day 8[c] (Follow-up)
Informed Consent and Minors' Assent [d]	X			
Medical/Surgical and Medication History [e]	X			
Inclusion/Exclusion	X			
Safety				
Physical Examination	X	X[f]	X	
Vital Signs	X[g]	X[h]	X	
Serum Pregnancy Test [i]	X			
ECG [j]	X	X[k]		
Chemistry/Hematology [l]	X		X	
Direct Coombs' Test [l]	X		X	
Urinalysis [m]	X			
Concomitant Medications and Procedures	X	X	X	X
Adverse Event Assessment		X	X	X
Assessment of Infusion-Related Reactions		X[k]		
Pharmacokinetics				
Ceftolozane/tazobactam Administration		X		
Plasma PK Sampling (venous or arterial samples) [n]		X		

ECG: electrocardiogram; PK: pharmacokinetic

a. With the exception of Informed Consent and Minors' Assent, all must be completed within 48 hours prior to dosing.
b. Study Day 2 evaluations to occur 24 (± 6) hours after completion of study drug infusion.
c. Site to contact patient and/or parent (or appropriate legal representative) via telephone on Study Day 8 (± 2 days).
d. Written parental (or appropriate legal representative) informed consent and age-appropriate assent.
e. Includes medication history of the mothers of breast-fed patients.
f. Physical examination before dosing.
g. Includes height and weight.
h. Vital sign assessments (blood pressure, heart rate, and temperature [oral, axillary, tympanic, forehead or core]) will be conducted within 2 hours prior to dosing and within 15 minutes after the end of the ceftolozane/tazobactam infusion.
i. For female patients who have undergone menarche.
j. If a patient is being continuously monitored with a cardiorespiratory monitor, an ECG waveform printout may be used
k. To be conducted on Study Day 1 after completion of study drug infusion
l. For patients less than 3 months of age (Groups 5 and 6), study-specific blood draws for coagulation (prothrombin time) and the direct Coombs' test should be done at the discretion of the investigator based on safety and risks to the patient
m. Urine will be collected from patients who are either toilet trained and able to provide a specimen, catheterized, or fitted with a urine collection bag.
n. PK blood samples will be collected at up to the following six time points: 0 h, 0.5 h (± 5 minutes), 1 h (end of the study drug infusion + 5 minutes), 2 h (± 10 minutes), 4 h (± 10 minutes), 6 h (± 20 minutes) after start of infusion. In the youngest pediatric patients (<3 months), PK samples will be collected at the following three time points: 1 h (end of the study drug infusion + 5 minutes), 2 h (± 10 minutes), 6 h (± 20 minutes) after start of infusion

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Inclusion Criteria

To be eligible for enrollment, a patient must fulfill all of the following inclusion criteria:

1. Provide written parental (or appropriate legal representative) informed consent and age-appropriate assent prior to any study-related procedure not part of normal medical care;
2. Male or female from birth (defined as at least 7 days postnatal) to <18 years of age;
3. Able to comply with the protocol for the duration of the study;
4. For female patients who have undergone menarche:
    - Is not pregnant (as confirmed by the serum pregnancy test at Screening) and not planning to become pregnant within 30 days of last study drug administration, AND
    - Is non-lactating, AND
    - Is abstinent OR utilizes one of the following for at least 1 month prior to screening: hormonal contraceptives (injectable, oral, patch, or vaginal ring), intrauterine device (IUD), or barrier method (diaphragm). This method must be used in combination with a barrier method of contraception for their male partner (condom). Patients must be willing to practice these methods for at least 30 days after study drug administration;
5. For male patients who are sexually active with female partners who have undergone menarche: patient must be using and willing to continue using medically acceptable forms of contraception (abstinence, or male condom for patients plus an additional method of contraception for their female partners) from Screening and for at least 30 days after study drug administration;
6. For Groups 1-5:
    - Receiving standard of care antibiotic therapy for suspected or diagnosed gram-negative infection or for peri-operative prophylaxis;

    For Group 6:
    - Receiving standard of care antibiotic therapy for suspected or diagnosed gram-negative infection or as antibiotic prophylaxis;
7. For Groups 1-4:
    - Have a calculated creatinine clearance rate (CL_{CR}) $\geq$ 80 mL/min/1.73m^2 as determined by the Schwartz (2009) equation at baseline.

For Group 5:

- Have a calculated creatinine clearance rate (CL_{CR}) ≥ 50 mL/min/1.73m^2 as determined by the Schwartz (2009) equation at baseline.

For Group 6:

- Have a calculated creatinine clearance rate (CL_{CR}) ≥ 20 mL/min/1.73m^2 as determined by the Schwartz (2009) equation at baseline.

4.2 Subject Exclusion Criteria

To be eligible for enrollment, a patient must not meet any of the following exclusion criteria:

1. Known allergy/hypersensitivity to any β-lactam antibacterial;
2. History of clinically significant renal, hepatic, or hemodynamic instability (defined as a requirement for pharmacological intervention to manage blood pressure in the 24-hour window prior to enrollment);
3. Planned use of cardiopulmonary bypass or dialysis;
4. Planned blood transfusion within 24 hours of study drug administration;
5. Clinically significant abnormal laboratory test results not related to the underlying infection, as determined by Investigator;
6. For Groups 1-5 only:
   - Height or weight outside of the 5th to 95th percentile;
7. Receipt of piperacillin/tazobactam within 24 hours of study drug administration;
8. Use of any medications known to inhibit tubular secretion of renally-excreted drugs;
9. Known use of illicit drugs or abuse of alcohol or cigarettes;
10. Patients likely to be at risk of hemodynamic disturbance (as determined by Investigator) following collection of the required PK blood samples;
11. Use of any investigational drug or participation in any experimental procedure in the 30 days preceding study entry.
12. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the study data.

4.3 Subject Withdrawal Criteria

Patients may withdraw from the study at any time without prejudicing their medical care and are not obliged to state their reasons. In addition, patients may be withdrawn, if deemed necessary for their health and safety, by the Investigator or the Sponsor. Subjects that discontinue for any reason should be asked to provide the reason(s) for discontinuation, and assessments should be performed as outlined in the Schedule of Assessments for Study Day 2/Early Termination [ET] visit (Table 2). Reasons for withdrawal from the study will be summarized. Any discontinuations must be fully documented in the electronic case report form (eCRF).

4.4 Replacement of Patients

Patients who are withdrawn from the study before receiving the full dose of ceftolozane/tazobactam or with insufficient samples to be eligible for the PK analysis may be replaced in order to enroll a total of 36 PK evaluable patients. Patient identification numbers will not be reused.

5.0 TREATMENT OF SUBJECTS

5.1 Description of Study Drug

Study medication will be supplied by the Sponsor for use in this protocol and is for investigational use only. Please refer to the current Investigator's Brochure for additional information.

Product Name:	ceftolozane/tazobactam
Dosage Form:	IV infusion over 60 (±10) minutes
Route of Administration:	Intravenous
Physical Description:	When a 1.5 g dose of ceftolozane/tazobactam lyophilized powder is reconstituted and diluted into an IV bag for use, ceftolozane/tazobactam contains 1000 mg of active ceftolozane and tazobactam sodium at a quantity equivalent of 500 mg of tazobactam free acid. Inactive ingredients include sodium chloride as a stabilizer and L-arginine and citric acid for pH adjustment.
Manufacturer:	Cubist Pharmaceuticals, LLC

5.2 Concomitant Medications

All medications given, to the patient and to the mothers of breast-fed patients, within 7 days prior to the first dose of study drug through the last study evaluation (Study Day 8) must be recorded in the appropriate section of the eCRF.

The use of piperacillin/tazobactam or any medication that is known to inhibit the tubular secretion of renally excreted drugs within 24 hours of study drug administration is prohibited (for example: piperacillin, probenecid, cimetidine, diclofenac, indomethacin, mycophenolate, olmesartan).

5.3 Patient Identification and Numbering

At time of consent, patients will receive a unique identification number specific to the site. The full Patient Identification Number will consist of a three-digit site number and a four-digit patient number separated by a hyphen (e.g.: XXX-XXXX). The first digit of the four-digit patient number will represent the patient's age group (1-6). For example, Age Group 1 will begin with 1001, Age Group 2 will begin with 2001, Age Group 3 will begin with 3001, Age Group 4 will begin with 4001, Age Group 5 will begin with 5001, and Age Group 6 will begin with 6001.

6.0 STUDY DRUG MATERIALS AND MANAGEMENT

6.1 Study Drug

Study medication will be supplied by the Sponsor for use in this study and is for investigational use only.

6.2 Study Drug Packaging, Labeling and Storage

Labeling and packaging of study medication will meet applicable regulatory requirements. Study medication must be stored in a secure, limited access area, and may be dispensed only by specifically authorized personnel. Refer to the Pharmacy Manual for further details on packaging, labeling, and storage.

6.3 Study Drug Preparation

Refer to the Pharmacy Manual for step-by-step directions for ceftolozane/tazobactam preparation.

6.4 Administration

Patients will receive a single IV dose of ceftolozane/tazobactam as a 60 (±10) minute IV infusion. Varying age-appropriate volumes from a fixed concentration, not to exceed 15 mg/mL, of ceftolozane/tazobactam will be administered to achieve the intended dose in each pediatric patient. This approach will minimize the infusion volume in younger groups. Infusion rates will differ based on the volume of each dose in each patient.

6.5 Study Drug Accountability

The site will maintain accurate inventory and dispensing records. Unused study medication must not be discarded nor used for any purpose other than the present study. The study monitor will review the drug accountability forms prior to arranging for return or destruction of all study medication. Refer to the Pharmacy Manual for further details on study drug accountability.

7.0 PHARMACOKINETIC ASSESSMENTS

For complete details and timing of procedures and assessments, please refer to the Schedule of Assessments (Table 2).

7.1 Blood Sample Collection

Blood samples (at least 0.5 mL per sample) for plasma PK determination of ceftolozane, tazobactam, and tazobactam M1 plasma levels will be collected in all patients.

For patients in Groups 1-4 (≥3 months of age), samples will be collected at up to the following six time points: 0 h, 0.5 h (± 5 minutes)*, 1 h (end of the study drug infusion + 5 minutes), 2 h (± 10 minutes), 4 h (± 10 minutes), and 6 h (± 20 minutes) after the start of infusion.

> * Collection of the 0.5 hour time point sample is optional in cases where a second IV line (or comparable means of access) is not available.

For patients in Groups 5-6 (<3 months of age), samples will be collected at the following three time points: 1 h (end of the study drug infusion + 5 minutes), 2 h (± 10 minutes), and 6 h (± 20 minutes) after the start of the infusion.

> **NOTE:** The 1 hour time point is equivalent to the end of the study drug infusion. This PK blood sample should be taken **just after** the total dose is administered and the infusion line is flushed with 2-3 mL of normal saline or per site standard of care.

The method of sampling for PK blood draws is at the discretion of the Investigator (e.g., peripherally inserted central catheter [PICC] line, indwelling catheter access, individual peripheral phlebotomies, peri-operatively placed arterial line). Samples taken via an IV line (or comparable means of access) are preferred, however, in instances where samples are unable to be obtained from a second line, alternative methods (such as heel sticks or finger sticks) are allowed.

In circumstances in which the blood draw and study medication infusion must occur in the same limb, the blood must be drawn more distally in the vein (approximately 3-5 inches) from the infusion site.

In cases where obtaining a second IV line (or comparable means of access) is unsuccessful, a single IV line (or comparable means of access) is acceptable for both drug administration and sample collection at the 0, 1 (end of infusion), 2, 4, and 6 hour time points. Prior to obtaining PK samples, the line must be flushed with 2-3 mL of normal saline or per site standard of care to ensure the total dose is administered.

7.2 Sample Analysis

Refer to the Laboratory Manual for directions for sample analysis.

8.0 ASSESSMENT OF SAFETY

Safety will be assessed through collection of AEs, laboratory evaluations (hematology, chemistry and coagulation), vital signs, and physical examinations.

Adverse events and SAEs will be collected from administration of the first dose of study medication through the last study contact.

8.1 Definitions for Adverse Events

8.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical trial subject 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 (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- Adverse events may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency.
- Adverse events may be clinically significant changes from baseline in laboratory tests or other diagnostic investigations, and abnormal physical examination findings.

Pregnancy is not an AE; however, if a subject or female partner of a male subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures in Section 8.5.2.

8.1.2 Serious Adverse Event

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death;
- Life-threatening experience;
  - Note: "Life-threatening" refers to a situation in which the subject was at risk of death *at the time of the event.* It does not refer to an event which might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
  - Note: Adverse events requiring hospital admissions that are less than 24 hours in duration do not meet this criterion. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is considered to be an important medical event.
  - Note: Important medical events are those that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

8.1.3 Overdose

For this study, an overdose of ceftolozane/tazobactam is considered to be any dose that is higher than the protocol-specified dose for the patient's age group. Any overdose must be reported to the Sponsor as described in Section 8.5.

8.1.4 Closely Monitored Event

A closely monitored event is a non-serious AE or occurrence that is designated to be an event of special interest which must be reported to the Sponsor as though it were a SAE as described in Section 8.5.

The following events are considered closely monitored for this trial:

- Any of the following abnormal laboratory parameters or clinical findings suggesting unacceptable hepatic toxicity (Hy's Law criteria):
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 x upper limit of normal (ULN)
    - ALT or AST > 3 x ULN **and** Total Bilirubin > 2 x ULN or INR > 1.5
    - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Serum ALT, AST, alkaline phosphatase, total bilirubin and/or INR values are to be measured every 48-72 hours and repeated until medically stable. These data should also be reported to the Sponsor as follow-up information as described in Section 8.5.

If the site cannot identify an alternative etiology for these laboratory abnormalities, these test results should be reported as an SAE. The causality will be assessed as related to study drug, either by the Investigator or the Sponsor. Hy's Law cases that meet any seriousness criteria should be reported as SAEs as they require expedited reporting to authorities like Suspected Unexpected Serious Adverse Reactions (SUSARs) as per local regulatory requirements.

8.2 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, beginning immediately after administration of the first dose of study medication. Each subject will be followed for safety monitoring until the last follow-up visit in the trial as described in the schedule of events (see Table 2).

Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator.

Adverse events, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all SAEs and AEs that require the subject to be discontinued from the trial, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

8.3 Monitoring of Laboratory Assessments

All laboratory assessments will be performed at a local laboratory. The clinical laboratory values will be reported to the Investigator who will review them for clinical significance and consideration as an AE.

8.4 Assessment of Adverse Events

8.4.1 Assessment of Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of AEs will be assessed according to the following definitions:

- **Mild**: the AE is noticeable to the subject and/or the Investigator, but does not interfere with routine activity.
- **Moderate**: the AE interferes with routine activity, but responds to symptomatic therapy or rest.
- **Severe**: the AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy.

8.4.2 Assessment of Causality

A medically-qualified Investigator must assess the relationship of any AE (including SAEs) to the use of a study drug, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- **Dechallenge**: the AE resolved or improved with stopping use of the investigational product. Judgment should be used if multiple products are discontinued at the same time.

- **Rechallenge**: the AE recurred or worsened upon re-exposure to the investigational product.

The causal relationship between a study drug and the AE will be assessed using one of the following categories:

Not Related: An AE is not associated with study drug if:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); **or**
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments); **or**
- Dechallenge was either not clinically indicated or did not result in clinical improvement; or
- AE did not reoccur upon rechallenge (if applicable).

Related: An AE is attributed to the study drug if:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication); **and**
- The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with current knowledge of the investigational product or the class of the investigational product), or
- The event resolved on dechallenge
- The event re-occurred upon rechallenge (if applicable).

8.4.3 Reference Safety Information for the Assessment of Expectedness of AEs

The Reference Safety Information (RSI) for assessing the expectedness of an adverse event for ceftolozane/tazobactam in this trial can be found in the Developmental Core Safety Information (DCSI) section of the most recent Investigator's Brochure for ceftolozane/tazobactam.

8.5 Reporting Safety Observations by the Investigator to the Sponsor

8.5.1 Reporting of Nonserious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded on the AE page of the eCRF.

8.5.2 Reporting of Drug Exposure During Pregnancy

If the subject or the female partner of a male subject becomes pregnant after receiving study medication during the course of study, the Investigator must report this to Merck Pharmacovigilance using the Pregnancy Reporting Form within 24 hours of becoming aware of the event.

If the female partner of a male subject becomes pregnant, the Investigator must attempt to obtain consent to collect pregnancy information (including the status of the newborn, if applicable) before reporting information to the Sponsor.

If not all information on the Pregnancy Reporting Form is available at the time of the initial report, follow-up Pregnancy Reporting Forms will be completed and submitted within 24 hours of becoming aware of new information. The Investigator is required to attempt follow-up on the pregnancy until the completion of the pregnancy. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of the Investigator becoming aware.

8.5.3 Reporting of Expedited Safety Observations by the Investigator

Any occurrence of the following events or outcomes in a subject in the trial must be reported within 24 hours of becoming aware of the event by the Investigator or qualified designee to the Merck Pharmacovigilance department:

- SAE;
- Pregnancy;
- Overdose
- Closely monitored events

The investigator is to report any Expedited Safety Observations from the list above to Merck Pharmacovigilance using the appropriate reporting form within **24 hours** of becoming aware of the event.

MERCK PHARMACOVIGILANCE

Email: PPD

Fax: PPD

Any observation reported to Merck Pharmacovigilance that is also an AE is to be recorded in the eCRF, as well as in the subject's source documentation along, with any actions taken. If not all information is available at the time of the initial report, follow-up reports will be completed and submitted.

The Investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. Resolution is defined as:

- Resolved with or without residual effects (sequelae);
- A return to baseline for a pre-existing condition;
- The Investigator does not expect any further improvement or worsening of the event;
- Fatal outcome: If an autopsy is performed on a deceased subject, the autopsy report must be provided to the sponsor as soon as it is available.

8.6 Expedited Reporting by the Sponsor to the FDA

Merck Pharmacovigilance will monitor the data for safety. All SAEs that are considered unexpected and related to the study agent (SUSAR) will be reported by the Sponsor or designee as expedited (i.e., 7/15-Day) reports to the United States Food and Drug Administration (FDA) and to all participating investigators. In addition, the Sponsor or designee follows all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB responsible for reviewing the study at their site.

8.7 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience associated with the use of the study medication that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The Investigator will promptly inform the IRB of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

9.0 STATISTICAL CONSIDERATIONS

9.1 Data Collection, Processing and Reporting

The site will be supplied with the following data collection tool: a web browser address for an Electronic Data Capture (EDC) system database that has been fully validated and conforms to 21 Code of Federal Regulations (CFR) Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. The EDC system database will be maintained by a Contract Research Organization (CRO).

The trained Investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture forms as needed) into the EDC system. All information on the eCRFs must be traceable to these source documents. Data recorded directly on the eCRFs will be defined before study start.

eCRFs will be completed for all patients. Informed consent, demography, inclusion/exclusion and end of study eCRF pages are needed for patients who are enrolled but not treated. A clinical monitor will review the eCRFs entered by investigational staff for completeness and accuracy.

Automatic validation programs or manual checks for data discrepancies in the eCRFs may result in electronic queries generated for resolution by the investigational site. Designated investigator site staff is required to respond to these queries and make any necessary changes to the data.

All treatment-emergent AEs (events occurring from the first dose of study medication through the last study evaluation) will be recorded. Medical and surgical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Audits for quality assurance of the database may be performed according to relevant Standard Operating Procedures within the CRO or at the request of the Sponsor's Quality Assurance department.

9.2 Population for Analysis

9.2.1 PK Population

The PK population will include patients who receive one full dose of study drug and have blood samples with quantifiable plasma levels at the C_{max} (the 1 hour post infusion start time point) and at least two time points after C_{max} (the 2, 4, or 6 hour post infusion start time points), to allow an estimation of area under the concentration versus time curve (AUC).

9.2.2 Safety Population

The Safety population will include patients who receive any dose (including partial doses) of any study medication.

10.0 PHARMACOKINETIC ANALYSIS PLAN

A Pharmacokinetic Analysis Plan with further details will be prepared, and will be finalized before database lock and analysis of the data.

10.1 Primary Endpoint Analysis

The primary endpoints are AUC and C_{max} for ceftolozane, tazobactam and the M1 metabolite of tazobactam as data allow.

10.1.1 Below Limit of Quantification Values/Missing Values

All pre-dose below limit of quantification (BLQ) values in period 1 will be set to zero. Missing or BLQ values obtained after the first quantifiable concentration will be replaced by a period.

Sampling Times

Actual blood draw times will be used to calculate PK parameters. For the final analysis, tables for the PK calculations will be based on actual times.

10.1.2 Pharmacokinetic Parameters

The pharmacokinetic parameters will be determined by non-compartmental pharmacokinetic analysis. The PK parameters for all analytes (ceftolozane, tazobactam and M1 metabolite of tazobactam, except as noted below) may include but are not limited to:

- C_{max} – Maximum observed plasma concentration over the entire sampling interval
- t_{max} – Time of C_{max}
- C_{last} – Last quantifiable plasma concentration
- T_{last} – Time of C_{last}

- AUC_t – Area under the concentration time curve from the time of the dose to the T_{last} (single dose)
- $AUC_{0-\infty}$ – Area under the concentration versus time curve from zero to infinity (single dose)
- $t_{½}$ – Half-life
- V_{ss} – Volume of distribution at steady state (ceftolozane and tazobactam only)
- CL – Plasma clearance (ceftolozane and tazobactam only)

If PK data are sparse, alternate PK data analysis methodology such as non-compartmental analysis based on a composite profile may be used.

In addition, PK data obtained from all groups will be pooled for a population PK analysis, as allowed by the data. These results will be reported separately.

10.1.3 Pharmacokinetic/Pharmacodynamic Analysis

The PK/PD (exposure-safety) analysis may be explored if any trends are observed. Exploratory analyses may be conducted using graphical and/or regression methods.

10.2 Presentation of Data

Data will be presented in tables and listings. Listings may include but are not limited to: subject ID, dose administered, body weight, drug concentrations, time points and individual derived PK parameters. Summary tables may include but are not limited to the number of subjects, arithmetic means, standard deviations (SD), % coefficient of variation (%CV), minimum, median and maximum values, and geometric mean for individual parameters.

10.3 Pharmacokinetic Data Reporting

The clinical study report will provide the following information:

- Deviations from described PK analysis, if any
- Results and discussion of the pharmacokinetic parameters
- Study conclusions

10.4 Data Displays

Data displays may include but are not limited to:

<u>In-text tables</u>

- Summary statistics (n, mean, %CV, median, min-max and geometric mean) of PK parameters Dose and age groups
- Summary statistics (n, mean, %CV, median, min-max and geometric mean) of plasma concentration-time values by Dose and age groups

In-text graphs

- Mean plasma concentration time profiles (with error bar) by Dose and age groups
- AUC and C_{max} box plots by Dose and age groups

Appendix

- Individual plasma concentration-time profiles (linear-linear and log-linear)
- Summary statistics (n, mean, SD, %CV, median, min, max and geometric mean) for plasma concentration-time data by Dose and age groups
- Listing of individual pharmacokinetic parameters by subject, age group, and dose
- Summary statistics (n, mean, SD, %CV, median, min, max and geometric mean) of pharmacokinetic parameters by Dose and age groups

11.0 STATISTICAL ANALYSIS PLAN

A Statistical Analysis Plan with further details will be prepared, and will be finalized before database lock and analysis of the data.

11.1 General Methodology

The safety and tolerability of single IV doses ceftolozane/tazobactam in pediatric patients from birth to <18 years will be evaluated in the Safety population. Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation, median, minimum and maximum. Categorical variables will include number and percent of the subjects in each category. Adverse event data will be tabulated by age group and dose (if not all subjects received the same dose). Clinical laboratory data will be presented at baseline and at study Day 2. Vital signs data will be presented at baseline, Day 1, and Day 2.

A subanalysis of Groups 5 and 6 will be conducted in patients aged 7 to 28 days and those aged 29 days to < 3 months.

Descriptive statistics will be used to guide decisions as to the clinical relevance of findings. No formal hypothesis tests are planned. Table and listing shells will be provided in a separate document.

11.1.1 Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug, unless otherwise specified.

11.1.2 Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation of PK and safety endpoints. No formal statistical hypotheses testing will be performed.

11.1.3 Computing Environment

All statistical analyses will be performed using SAS statistical software Version 9.1.3., unless otherwise noted. Adverse events will be coded using the MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary.

11.1.4 Subject Disposition

Subject disposition data will be summarized for all subjects by age group. Number and percent of subjects enrolled, subjects who received initial dose of study drug, subjects who received adjusted dose of study drug, subjects who completed the study, subjects who discontinued treatment, and subjects who discontinued from the study will be tabulated together with the reasons for premature discontinuation of study medication and discontinuation from study participation by age group. A listing of all subjects, along with data on their disposition, will be provided.

11.1.5 Demographics and Baseline Data

Demographic information and baseline clinical data will be summarized by age group. Demographic and baseline characteristics variables will be presented in listings and in summary tables. Medical history, medication history, and screening laboratory tests will be presented in listings only.

Baseline will be defined as the most recent measurement prior to the administration of study drug, unless otherwise specified.

11.1.6 Study Drug Exposure

Dosing information for each subject will be summarized as descriptive statistics for the total amount of study drug received by age group. Also number and percentage of subjects receiving initial dose or adjusted dose will be summarized by age group, if relevant. A data listing of the dosing information for each subject, including dose interruptions, will also be provided.

11.1.7 Secondary Endpoint Analysis

The safety and tolerability of single doses of IV ceftolozane/tazobactam in pediatric patients will be evaluated in the Safety population. The safety evaluation will be based on clinical review of the following safety parameters:

- Incidence of AEs and SAEs
- AEs and SAEs by relationship to study drug
- AEs and SAEs by severity
- Deaths
- Premature discontinuation from the study due to an AE, regardless of relationship to study medication;
- Clinical laboratory data;

- Vital signs;
- Concomitant medications

11.1.8 Adverse Events

All AEs will be coded using MedDRA and displayed in tables and data listings by system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE with onset after the administration of study medication through the end of the study, or any event that was present at baseline but worsened in intensity or frequency. In this study, only treatment-emergent AEs are captured in the database.

The number and percentage of subjects with the following treatment-emergent adverse event categories will be summarized by age group: at least 1 adverse event, AEs by maximum severity, AEs by greatest relationship to study drug, at least 1 treatment-related severe AE, at least 1 SAE, at least 1 treatment related SAE, at least 1 AE leading to premature treatment discontinuation, at least 1 treatment-related AE leading to premature treatment discontinuation, at least 1 AE leading to early study withdrawal, at least 1 treatment-related AE leading to early study withdrawal, AE leading to death and treatment-related AE leading to death. In addition, summary tables will be provided for all AEs by SOC and PT, AEs by severity and AEs by relationship to study drug. For all summary tables of AE incidences, SOC and PTs will be presented in alphabetical order.

The type and incidence of all AEs and SAEs will be tabulated, and events occurring within 72 hours of dosing will be analyzed separately. Special attention will be given to local tolerability events occurring at time of drug administration and to those patients who discontinue due to an adverse event or a serious adverse event. In addition, hypersensitivity reactions, events indicative of hemolytic disorders, and events involving *Clostridium difficile* will be summarized separately.

In the event of missing data, a conservative approach will be taken. For example, if the relationship of an AE is not recorded in the eCRF the event will be considered to be treatment related, or if the severity of the event is missing the event will be considered severe.

All AE summaries will be presented by age group.

No formal hypotheses testing of AE incidence rates will be performed.

All AEs occurring on-study will be listed in subject data listings.

By-patient AE listings will be provided for the following subsets, as applicable: patient deaths; serious adverse events; and adverse events leading to premature study drug discontinuation.

11.1.9 Laboratory Data

Clinical laboratory values will be expressed in SI units.

The actual value and change from baseline study Day 2 will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. In the event of repeat values, the last non-missing value per visit will be used.

All laboratory data will be provided in data listings. Laboratory results outside the normal ranges will be flagged in these listings.

11.1.10 Vital Signs

The actual value and change from baseline to each on-study evaluation (Day 1 and Day 2) will be summarized for vital signs. Vital sign measurements will be presented for each subject in a data listing.

11.1.11 Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. The use of concomitant medications will be included in a by-subject data listing. A separate listing for concomitant medications in the mothers of breast-fed patients will also be included. Tabular summaries will be presented.

11.1.12 Sample Size and Power Considerations

Thirty-six will participate in this study: 6 subjects are planned in each of the 6 age groups. The sample size was chosen based primarily on empirical considerations and feasibility, and is considered sufficient to meet the study objectives.

11.1.13 Evaluation Criteria

Safety will be assessed through monitoring adverse events from the start time of study drug administration to the end of study. Any serious adverse events that occur during the study will be reported and recorded.

12.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will be responsible for the accuracy of the data entered in the eCRFs. The Investigator will allow designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify the data reported in the eCRFs. Source documents are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the subject and substantiate the integrity of the data collected during the trial (e.g., including, but not limited to, the subject's medical record). Source documents should be available to support all the data recorded in the eCRF, unless this is otherwise specified by the Sponsor.

12.1 Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will assess the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives.

This will be documented in a Clinical Study Agreement between the Sponsor and the investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

12.1.1 Protocol Deviations/Amendments

Any deviation from the protocol that has not been approved by the Sponsor and the IRB/EC could result in a discontinuation from the study of the center involved. Both the Sponsor and the IRB/EC that granted the original approval of the study prior to their implementation (unless only logistical or administrative aspects of the trial are involved) must approve any amendment(s) to the protocol.

However, in the event of any medical emergency, the Investigator is free to institute any medical procedure s/he deems appropriate for proper management of the subject. Such events must be promptly reported to the Sponsor and recorded in the source documents.

12.1.2 Discontinuation of the Study

The Sponsor may stop the study at any time on the basis of new information regarding safety or efficacy. Additionally, the Sponsor may terminate the study if progress is unsatisfactory.

12.2 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/EC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory

requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

Audits for quality assurance of the database may be performed according to relevant Standard Operating Procedures at the request of the Sponsor's Quality Assurance department.

12.3 Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the study protocol and any amendments, the Informed Consent Form and any other written documents to be provided to the subject, and recruitment materials must be maintained by the Investigator and made available for inspection.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

14.0 ETHICS

14.1 Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The investigator must submit written approval to the Sponsor before he or she can enroll any patient/subject into the study.

The Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/EC upon receipt of amendments and annually, in accordance with local regulations.

The Investigator is also responsible for providing the IRB/EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/EC according to local regulations and guidelines.

14.2 Ethical Conduct of the Study

The study will be performed in accordance with the protocol, ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline, 21 CFR 312.120, and any applicable local regulations.

14.3 Written Informed Consent

The Investigator(s) at each center will ensure that the patient (or appropriate legal representative) is given full and adequate oral and written information about the nature,

purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's (or appropriate legal representative's) signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient or to the legally acceptable representative signing the form and the original retained in the source documents of the study participant.

15.0 DATA HANDLING AND RECORDKEEPING

15.1 Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.2 Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or health authorities to review any documentation relating to the study, the Investigator must permit access to such records.

16.0 PUBLICATION POLICY

The Sponsor may publish the results of company-sponsored studies in a timely manner, regardless of whether the outcomes are perceived as positive, neutral, or negative. Publications will adhere to external guidelines, including the guidelines adopted by the International Society for Medical Publication Professionals and the International Committee of Medical Journal Editors, subject to taking appropriate steps to protect the Sponsor's intellectual property rights.

17.0 REFERENCES

1. Hayashi T, Yada H, Anai M, Umano T, Kawazu K, Anai S, Kaziwara T, Yamasaki K. Single dose toxicity studies of tazobactam/piperacillin and tazobactam. J Toxicol Sci. 1994a;19 Suppl 2:145-53.
2. Hayashi T, Yada H, Auletta C, Daly I, Knezevich A, Cockrell B. A six-month intraperitoneal repeated dose toxicity study of tazobactam/piperacillin and tazobactam in rats. J Toxicol Sci. 1994b;19 Suppl 2:155-76.
3. Zosyn [package insert]. Philadelphia, PA: Wyeth Corporation; 2009.
4. Sato T, Lochry EA, Hoberman AM, Christian MS. Reproductive and developmental toxicity studies of tazobactam/piperacillin or tazobactam(1)—Fertility and general reproduction study in rats with intraperitoneal administration. J Toxicol Sci. 1994a;19(suppl 2):199-24.
5. Sato T, Lochry EA, Hoberman AM, Christian MS. Reproductive and developmental toxicity studies of tazobactam/piperacillin or tazobactam (3): perinatal and postnatal study in rats with intraperitoneal administration. J Toxicol Sci. 1994c;19(suppl 2):233-47.
6. U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products, November 1998.