Official Protocol Title:	A Phase 1, open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam (MK-7625A) in pediatric participants with nosocomial pneumonia
NCT number:	NCT04223752
Document Date:	12-Dec-2022

TITLE PAGE

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Protocol Title: A Phase 1, open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam (MK-7625A) in pediatric participants with nosocomial pneumonia

Protocol Number: 036-02

Compound Number: MK-7625A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT04223752
EU CT	2022-501110-56-00
EudraCT	2018-004704-19
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	104,490

Approval Date: 12 December 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	12-DEC-2022	The end-of-study definition was changed from LPLV to LDA to allow for the data collection and evaluation needed to fulfill regulatory requirements.
Amendment 1	05-MAY-2020	Guidance regarding contraceptive use was updated to remove the option of "acceptable contraceptive methods" in order to align protocol language with recommendations outlined by Clinical Trial Facilitation Group (CTFG) guidance for contraception and pregnancy testing in clinical trials in which the investigational product has the designation of possible risk of human teratogenicity/fetotoxicity in early pregnancy. The definition of overdose was updated to align with the definition of overdose across the ceftolozane/tazobactam program.
Original Protocol	02-APR-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

The end-of-study definition was changed from LPLV to LDA to allow for the data collection and evaluation needed to fulfill regulatory requirements.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
4.4 Beginning and End-of-Study Definition 1.1 Synopsis	Text defining the end of the study as the LPLV or contact was updated to clarify that this corresponds to when the last data are available to the Sponsor.	This change was made to address strategy. The rationale is further supported by the fact that data related to the primary and secondary endpoint, PK, and/or laboratory data may not be available to the Sponsor until after the date of the LPLV or contact.
Section Number and Name	**Description of Change**	**Brief Rationale**
Other Changes in Amendment		
Title Page 10.1.1 Code of Conduct for Interventional Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Section Number and Name	Description of Change	Brief Rationale
Title Page	Updated NCT and EU CT identifying numbers.	To update new regulatory agency identifying numbers.
1.1 Synopsis	Revised estimated duration of study from 40 months to 70 months in overall design table.	To update study timelines to reflect delays in study completion caused by the Sponsor's voluntary global recall of ZERBAXA® following a sterility manufacturing issue, loss of study sites due to the conflict in Ukraine and Russia, and the ongoing COVID-19 public health emergency.
2.1 Study Rationale 2.2.2 Preclinical and Clinical Studies	Updated background information for the completed pediatric clinical studies for cUTI and cIAI.	To reflect new safety and efficacy information for completed clinical studies in the ZERBAXA® clinical development program.
5 Study Population	Updated text for specific populations as applicable to the study.	To clarify the collection, use, and confidentiality of demographic data provided by the participants.
6 Study Intervention 6.1 Study Intervention(s) Administered 8.1.8 Study Intervention Administration	Updated text to clarify that ceftolozane/tazobactam will be provided centrally or sourced locally.	To clarify the allowance of locally sourced ceftolozane/tazobactam in markets where ZERBAXA® is authorized and commercially marketed.
6.1 Study Intervention(s) Administered	Updated column headers and abbreviations in Table 3.	To align with the EU CTR.
8.1.6 Assignment of Screening Number	Screening logs will have identifying information removed before being reviewed by Sponsor.	To allow collection of participant screening logs.

Section Number and Name	Description of Change	Brief Rationale
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added that investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Clarified that collection is related to SUSARs and the collection of SAEs only.	To align with the EU CTR.
8.4.7 Events of Clinical Interest	Clarified definition of potential DILI.	To improve clarity and consistency.
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 10.3.2 Definition of AE	Updated "sponsor product" to "study intervention" to be consistent with the rest of the protocol (ie, Study Intervention Table).	To improve consistency.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added definitions of medication error, misuse, and abuse.	To align with the EU CTR.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1, open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam (MK-7625A) in pediatric participants with nosocomial pneumonia

Short Title: Safety and pharmacokinetics of ceftolozane/tazobactam in pediatric participants with nosocomial pneumonia

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses to be tested in this study.

The following objectives and endpoints will be evaluated in hospitalized male and female pediatric participants from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with nosocomial pneumonia (NP).

Primary Objective	**Primary Endpoint**
• To evaluate the safety and tolerability of ceftolozane/tazobactam for all participants	• Adverse events (AEs), including any AEs, any serious AEs, any drug-related AEs and any serious drug-related AEs • AEs leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetics (PK) of multiple doses of ceftolozane/tazobactam for each age group and/or dose level	• Plasma concentrations at each time point for ceftolozane and tazobactam • Steady state plasma area under the concentration-time curve of an 8-hour dosing interval, maximum observed concentration during a dosage interval (Cmax), elimination half-life (t1/2), volume of distribution (Vd), and clearance (CL) for ceftolozane and tazobactam

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment

Indication	Nosocomial infection, Pneumonia
Population	Pediatric participants from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 70 months from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact. For this study, the overall study ends when the last data are available to the Sponsor.

Number of Participants:

Approximately 40 participants will be enrolled.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/	Use
Group 1 (12 to <18 years of age [n=>6])	Ceftolozane/ tazobactam	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 2 g and tazobactam 1 g	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product
Group 2 (7 to <12 years of age [n=>6])	Ceftolozane/ tazobactam	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product
Group 3 (2 to <7 years of age [n=>6])	Ceftolozane/ tazobactam	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product
Group 4 (3 months to <2 years of age [n=>6])	Ceftolozane/ tazobactam	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product
Group 5 (birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months of age [n=>6])	Ceftolozane/ tazobactam	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product

IV=intravenous; NP=nosocomial pneumonia; q8h=every 8 hours. The proposed initial doses may be modified based on interim data as described in Section 6.6. Single IV doses for all cohorts will not exceed the adult maximum dose of 3 g (2 g ceftolozane and 1 g tazobactam) for NP.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: ZERBAXA®, MK-7625A, CXA-201, CXA-101/tazobactam.

Total Number of Intervention Groups/Arms	1 intervention with different doses across 5 age groups.
Duration of Participation	Each participant will participate in the study for approximately 30 days from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 2 days, each participant will receive assigned intervention for approximately 8 to 14 days. After the end of treatment, each participant will be followed for 14 days.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Steering Committee	No

There are no governance committees in this study.

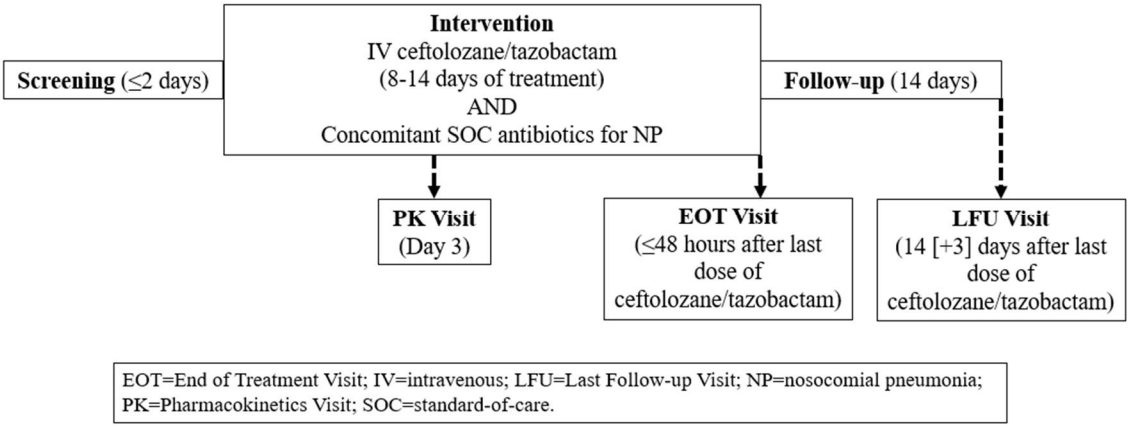
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



EOT=End of Treatment Visit; IV=intravenous; LFU=Last Follow-up Visit; NP=nosocomial pneumonia; PK=Pharmacokinetics Visit; SOC=standard-of-care.

1.3 Schedule of Activities

Study Period	Screening	Intervention					Follow-up	Notes
Visit Number/Title	1 Screening	2 Allocation	3	4 PK Visit	5-15	16 EOT Visit	17 LFU Visit	Visits 1 and 2 can be on the same day. Visit 17 can be by telephone; in-person visit required for AE or abnormal laboratory follow-up.
Scheduled Day:	≤48 hours prior to first dose of ceftolozane/ tazobactam	Day 1	Day 2	Day 3	Day 4-14	≤48 hours after last dose of ceftolozane/ tazobactam	14 days after last dose of ceftolozane/ tazobactam	
Scheduled Window:	--	--	--	+2 days	--	--	+3 days	
Administrative Procedures								
Informed Consent/Assent	X							
Inclusion/Exclusion Criteria	X							
Participant Identification Card	X	X						
Medical History	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	
Study Intervention Allocation		X						Ceftolozane/tazobactam should be initiated as soon as possible and within 24 hours of allocation.
Administration of Ceftolozane/tazobactam IV q8h		X	X	X	X			Each participant is anticipated to receive ceftolozane/tazobactam for 8-14 days.
Administration of Concomitant Standard-of-Care Antibiotics for NP	X	X	X	X	X	X		Standard-of-care antibiotic administration as applicable (may or may not be ongoing at screening and/or after stopping ceftolozane/ tazobactam).

Study Period	Screening	Intervention					Follow-up	Notes
Visit Number/Title	1 Screening	2 Allocation	3	4 PK Visit	5-15	16 EOT Visit	17 LFU Visit	Visits 1 and 2 can be on the same day. Visit 17 can be by telephone; in-person visit required for AE or abnormal laboratory follow-up.
Scheduled Day:	≤48 hours prior to first dose of ceftolozane/ tazobactam	Day 1	Day 2	Day 3	Day 4-14	≤48 hours after last dose of ceftolozane/ tazobactam	14 days after last dose of ceftolozane/ tazobactam	
Scheduled Window:	--	--	--	+2 days	--	--	+3 days	
Safety Procedures								
Full Physical Examination	X							
Height	X							
Weight	X							
Directed Physical Examination		X	X	X	X	X		Can also be performed whenever medically necessary.
Vital Signs	X	X	X	X	X	X		Heart rate, blood pressure, respiratory rate, and temperature. If Visit 1 and 2 occur on the same day, does not need to be performed twice.
Urine or Serum Pregnancy Test (WOCBP only)	X					X		Collect per local guidance.
Blood for Hematology and Chemistry Safety Evaluations	X	X	X	X	X	X	X	Required for Visits 1, 4, and 16. Only collect if clinically indicated at Visits 2, 3, 5-15, and 17.

Study Period	Screening	Intervention					Follow-up	Notes
Visit Number/Title	1 Screening	2 Allocation	3	4 PK Visit	5-15	16 EOT Visit	17 LFU Visit	Visits 1 and 2 can be on the same day. Visit 17 can be by telephone; in-person visit required for AE or abnormal laboratory follow-up.
Scheduled Day:	≤48 hours prior to first dose of ceftolozane/ tazobactam	Day 1	Day 2	Day 3	Day 4-14	≤48 hours after last dose of ceftolozane/ tazobactam	14 days after last dose of ceftolozane/ tazobactam	
Scheduled Window:	--	--	--	+2 days	--	--	+3 days	
Assessment of CrCL	X	X	X	X	X	X	X	Required for Visit 1 and only if clinically indicated at all other visits. See Section 8.3.3.1.
AE/SAE Monitoring		X	X	X	X	X	X	
Pharmacokinetics								
Plasma PK Sampling				X				Number of samples and timing is described in Section 8.6.1.

AE=adverse event; CrCL=creatinine clearance; EOT=end of treatment; IV=intravenous; LFU=last follow-up; NP=nosocomial pneumonia; PK=pharmacokinetics; q8h=every 8 hours; SAE=serious adverse event; WOCBP=woman/women of childbearing potential.

2 INTRODUCTION

Ceftolozane/tazobactam (ZERBAXA®, MK-7625A) is a fixed-dose combination of the antipseudomonal cephalosporin, ceftolozane, and the BLI, tazobactam, being evaluated for treatment of gram-negative infections, including NP in pediatric participants.

2.1 Study Rationale

The treatment of gram-negative infections is complicated by growing rates of antibiotic resistance [Nicasio, A. M., et al 2008] [Talbot, G. H. 2008]. Of the more than 2 million nosocomial infections occurring annually in the US, 50% to 60% are caused by antibiotic resistant strains. Multidrug resistance is increasing among common gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. New antibiotics with improved activity against these organisms are needed.

Ceftolozane/tazobactam is approved for use in adults and pediatric patients with cUTI, including pyelonephritis, and cIAI (in combination with metronidazole) [U.S. Prescribing Information 2022] in adults with NP.

The prevalence of antibiotic resistant gram-negative infections among children is increasing, particularly involving *P. aeruginosa* and Enterobacteriaceae [Medernach, R. L. 2018], which are frequent causes of NP [Lake, J. G., et al 2018] [Carvalhaes, C. G., et al 2018]. Patients with NP caused by antibiotic resistant organisms have prolonged hospitalizations and worse outcomes, particularly among vulnerable pediatric patients with immature immune systems [Lake, J. G., et al 2018] [Gallagher, J. C., et al 2018]. Thus, an unmet medical need exists for treatment of resistant, gram-negative infections in children with NP.

This study is being conducted to evaluate the safety and tolerability and the PK of ceftolozane and tazobactam after administration of ceftolozane/tazobactam in pediatric participants with NP.

2.2 Background

Refer to the IB/approved labeling for detailed background information on ceftolozane/tazobactam.

2.2.1 Pharmaceutical and Therapeutic Background

Ceftolozane/Tazobactam

Ceftolozane is a member of the cephalosporin class of antibiotics, which is well characterized in terms of safety, efficacy, and general antimicrobial profile. Ceftolozane is structurally similar to ceftazidime, but is less affected by common bacterial resistance mechanisms (ie, porin loss, hydrolysis by AmpC β-lactamases) [Duin, D. V. 2016]. While ceftolozane alone represents an important therapeutic option for the treatment of infections caused by *P. aeruginosa*, the efficacy of ceftolozane for the treatment of suspected gram-negative infections could be compromised by the spread of ESBL-producing bacteria. The addition of tazobactam improves the coverage of ceftolozane against select ESBL-producing

Enterobacteriaceae [Duin, D. V. 2016]. Combining ceftolozane with a BLI such as tazobactam broadens its in vitro spectrum of activity to include many drug-resistant Enterobacteriaceae and is, thereby, likely to improve its clinical utility as a therapy for serious bacterial infections caused by resistant gram-negative bacteria.

Nosocomial Pneumonia

Nosocomial pneumonia, including HABP and VABP, is one of the most frequent complications of hospital care and is associated with high cost, morbidity, and mortality [Kalil, A. C., et al 2016]. The US FDA guidance defines HABP as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalized for >48 hours or developing within 7 days after discharge from a hospital [Center for Drug Evaluation and Research 2014]. Similarly, VABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient receiving mechanical ventilation via an endotracheal or nasotracheal tube for >48 hours [Center for Drug Evaluation and Research 2014].

In comparison, the diagnostic criteria and clinical manifestations of NP in neonates, infants, and children varies considerably due to multiple factors such as distinctive underlying comorbidities, microbiology, risk factors, and outcomes of NP among different pediatric age groups and adults [Bradley, J. S. 2010]. However, the resource expenditure and associated adverse outcomes with pediatric NP remain high, particularly among those children with VABP, who are almost 3 times more likely to die in comparison to mechanically ventilated children without VABP [Bradley, J. S. 2010] [Gupta, S., et al 2015].

Aside from *Staphylococcus aureus*, the most common pathogens responsible for pediatric NP are *P. aeruginosa* and Enterobacteriaceae [Lake, J. G., et al 2018]. Antibacterial resistance among these organisms is becoming increasingly common in children, and results in serious consequences such as prolonged length of hospital stay and higher morbidity/mortality [Medernach, R. L. 2018] [Logan, L. K., et al 2017] [Kehl, S. C. 2015] [Lake, J. G., et al 2018]. Therefore, there is an unmet medical need for treatment of antibacterial-resistant gram-negative infections in children with NP.

2.2.2 Preclinical and Clinical Studies

The safety and efficacy of ceftolozane/tazobactam was demonstrated in adult Phase 3 and cUTI, cIAI, and NP studies. In addition, the safety and efficacy of ceftolozane/tazobactam has also been demonstrated in pediatric studies of cUTI and cIAI, where ceftolozane/tazobactam was well tolerated with a safety profile consistent with the known safety profile of ceftolozane/tazobactam in adults.

The safety and efficacy of ceftolozane/tazobactam for use in adults with NP (including VABP and HABP) are derived from a large, multinational, multicenter, randomized, double-

blind, active comparator-controlled Phase 3 study (MK-7625A-008) (ClinicalTrials.gov Identifier: NCT02070757). Ceftolozane/tazobactam 3 g (2 g ceftolozane and 1 g tazobactam), which is 2 times the dose used for cUTI or cIAI, administered q8h as an IV infusion (60 ±10 minutes) for up to 14 days demonstrated noninferiority versus meropenem based on the treatment difference in Day 28 all-cause mortality rate and clinical cure rate at the test-of-cure visit. Ceftolozane/tazobactam was generally well tolerated in this critically ill population with no notable or unexpected safety signals that would preclude its general use in adults with NP. The doses for the present study were selected to match adult exposures in NP and do not exceed the adult dose.

The toxicological profile of ceftolozane, both alone and in combination with tazobactam, has been well characterized in a comprehensive series of nonclinical studies (both in vitro and in vivo safety and efficacy studies) and supports the continued clinical investigation of NP in the pediatric population.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

This study will include hospitalized pediatric participants who require antibiotic therapy for NP due to either gram-positive or gram-negative pathogens. Participants will receive an antibiotic regimen that is active against gram-negative pathogens frequently isolated from pediatric patients with NP and that has proven to be effective in a large-scale clinical study for the treatment of NP in adults (Section 2.2). While no obvious benefit may be derived from participation in the study, those participants receiving narrow-spectrum antibiotics may potentially benefit from additional broad-spectrum gram-negative coverage.

Although study procedures may potentially occur more frequently than the standard-of-care, the planned study procedures are generally typical procedures performed for this patient population. Study procedures, including the number of blood draws for PK sampling, are limited to minimize risk. Additional burden may be incurred due to visits after release from the hospital; however, the procedures performed at these visits will not likely lead to significant harm (eg, blood draws, physical examinations, and vital signs) and are necessary to support a robust evaluation of the safety of the study intervention

In vitro synergy studies with ceftolozane/tazobactam demonstrated no antagonism with a variety of other classes of antibiotics; thus, ceftolozane/tazobactam is not expected to interfere with the PK or safety of other standard-of-care antibiotics.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the IB and informed consent/assent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no hypotheses to be tested in this study.

The following objectives and endpoints will be evaluated in hospitalized male and female pediatric participants from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with nosocomial pneumonia (NP).

Primary Objective	**Primary Endpoint**
• To evaluate the safety and tolerability of ceftolozane/tazobactam for all participants	• Adverse events (AEs), including any AEs, any serious AEs, any drug-related AEs and any serious drug-related AEs • AEs leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetics (PK) of multiple doses of ceftolozane/tazobactam for each age group and/or dose level	• Plasma concentrations at each time point for ceftolozane and tazobactam • Steady state plasma area under the concentration-time curve of an 8-hour dosing interval, maximum observed concentration during a dosage interval (Cmax), elimination half-life (t1/2), volume of distribution (Vd), and clearance (CL) for ceftolozane and tazobactam

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1, open-label, non-comparative, multicenter clinical study of ceftolozane/tazobactam in hospitalized pediatric participants (ages from birth to <18 years) receiving concomitant standard-of-care antibiotics for NP (including VABP and HABP).

Approximately 40 participants will be enrolled into 5 age groups (12 to <18 years, 7 to <12 years, 2 to <7 years, 3 months to <2 years, and birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months). Enrollment to all groups will open in parallel (see Section 4.2). After a minimum enrollment target of 6 participants for each age group is met, at least 10 additional participants will be enrolled across any of the 5 age groups. No more than 4 additional participants (for a total of 10 participants in any given age group) will be enrolled in any given age group. Proposed initial doses of ceftolozane/tazobactam for each age group were selected based on PK modeling and simulation analyses (see Section 4.3.1).

After the first 3 participants are enrolled into a given age group, enrollment will be paused in that age group for an interim PK analysis to confirm or modify the proposed pediatric dose for the remaining participants in that group and/or other age groups. Enrollment will continue in the other age groups during each interim PK analysis. The proposed initial pediatric doses may be modified based on whether the dose evaluated in the interim PK analysis demonstrates an acceptable safety profile in the exposed age group and is suitable based on adequate PK plasma exposures (see Section 9.7). PK samples will be collected in all pediatric participants according to the sampling scheme in Section 8.6.1. After the first 3 participants have been enrolled into a given age group, at least 3 additional participants will be enrolled in that age group after the interim PK analysis.

Each participant will participate in the study for approximately 30 days from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 2 days, each participant will receive ceftolozane/tazobactam administered as a 60-minute IV infusion (±10 minutes) q8h as add-on therapy in addition to a concomitant standard-of-care antibiotic regimen. The diagnosis of NP does not require a pathogen to be isolated from a diagnostic test and will be based on the judgment of the investigator.

The duration of ceftolozane/tazobactam administration will be a minimum of 8 days and up to a maximum of 14 days to match the treatment duration in the adult NP study (MK-7625A 008) (see Section 4.3.4). Participants who discontinue or complete concomitant standard-of-care antibiotic therapy in less than 8 days may also discontinue ceftolozane/tazobactam before the minimum duration of 8 days at the investigator's discretion. However, participants are strongly encouraged to receive a minimum of 8 days of ceftolozane/tazobactam. Participants must remain in the hospital for the duration of the intervention period; outpatient therapy is not permitted. After the end-of-study treatment, each participant will be followed for 14 days.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This study is designed to assess the safety and PK of ceftolozane/tazobactam in pediatric participants with NP. The PK of a drug in the pediatric population usually cannot be precisely predicted from that in adults, and safety must also be evaluated. Therefore, safety and PK studies are needed to identify safe and appropriate pediatric doses.

The proposed initial pediatric doses of ceftolozane/tazobactam were chosen based on a pediatric population PK approach leveraging Phase 1 pediatric PK data and PK models in adults. As ceftolozane/tazobactam is primarily renally eliminated, the proposed initial doses for each age group were based on renal function and body weight. Participants will be enrolled into 1 of 5 age groups, which were chosen to ensure that adequate safety and PK data would be available for participants at each stage of pediatric development and for consistency with the pediatric cUTI and cIAI studies of ceftolozane/tazobactam. The age groups in the present study are based on the age groups assessed in MK-7625A-010.

Parallel enrollment of all age groups is considered appropriate as ceftolozane/tazobactam was well tolerated in the Phase 1 single-dose PK and safety study of pediatric participants with proven or suspected gram-negative infection (MK-7625A-010). As ceftolozane/tazobactam, much like other β-lactam antibiotics, has a well-defined safety profile with robust PK modeling, the simultaneous enrollment of all age groups will help to mitigate delays often encountered when stepwise enrollment (ie, older children first, then younger children) is implemented.

No efficacy endpoints are evaluated in this study, as efficacy will be extrapolated from adults to the pediatric population using population PK modeling.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The safety and tolerability of ceftolozane/tazobactam in pediatric participants will be assessed by a clinical evaluation of AEs (any AEs, any SAEs, any drug-related AEs, any serious and drug-related AEs, and AEs leading to discontinuation of study intervention) and inspection of other study parameters including clinical laboratory tests and vital signs measurements at appropriate time points as specified in the SoA. AEs are assessed and recorded according to Section 10.3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

4.2.1.2 Pharmacokinetic Endpoints

Whole blood samples will be collected at the time points specified in Section 8.6.1 for determination of plasma concentrations of ceftolozane and tazobactam. Plasma concentrations of ceftolozane and tazobactam at each time point will be summarized. In

addition, plasma concentrations of ceftolozane and tazobactam will be used to update pediatric population PK models on completion of this study using the existing pediatric PK models as a starting point. The updated pediatric population PK models will be used to characterize plasma PK of both drugs. Primary plasma PK parameters for ceftolozane and tazobactam, such as steady state plasma AUC0-8, Cmax, t1/2, Vd, and CL, will be estimated through population PK modeling and provided in a separate population PK modeling report. Additional steady state plasma PK parameters may also be estimated, as appropriate, through modeling and provided in the same population PK modeling report.

4.2.2 Rationale for Sample Size

The cumulative sample size of 40 participants for this study is based on obtaining sufficient data to evaluate the safety and PK of ceftolozane/tazobactam in pediatric participants, in addition to feasibility considerations. This study is not powered to test formal hypotheses. See Section 9.9 for additional details.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The recommended dosing regimen for adult patients with NP is 3 g ceftolozane/tazobactam (2 g ceftolozane and 1 g tazobactam or adjusted based on renal function) administered as a 60-minute (±10 minutes) IV infusion q8h. This dose is 2 times the dose recommended for adult patients with cUTI or cIAI. The NP dose of 3 g was chosen, in part, based on the lung penetration data obtained in healthy adult subjects receiving a 1.5 g dose administered as a 60-minute IV infusion q8h, which showed approximately 50% to 60% penetration into lung relative to plasma exposure for both ceftolozane and tazobactam, suggesting that doubling the dose would result in lung exposures needed to achieve ceftolozane and tazobactam PK/PD targets at the site of infection [Xiao, A. J., et al 2016]. The 3 g dose was tested in a large Phase 3 study in adult participants with NP (MK-7625A-008) and is supported by the favorable efficacy and safety profiles in NP participants, as well as attainment of >90% PTA in lung, the site of action, using Monte Carlo simulations.

The proposed ceftolozane/tazobactam pediatric doses for participants with NP were projected using a similar modeling approach as described above. Pediatric population PK models for ceftolozane and tazobactam were developed using PK data from the Phase 1 PK study in pediatric participants (MK-7625A-010) informed by the adult NP models, including the effect of NP on ceftolozane and tazobactam PK. As in adults, renal function was a covariate on CL and body weight was a covariate on Vc and Vp for ceftolozane and tazobactam. Model fit for both drugs was improved by inclusion of allometric scaling on CL.

The final PK models for ceftolozane and tazobactam were used to simulate plasma and lung ELF concentration-time profiles in pediatric subjects with NP. To provide a benchmark for evaluating the safety of ceftolozane and tazobactam in simulated pediatric subjects, steady state plasma AUC0-8 and Cmax were simulated. For ensuring efficacy of the doses, PTA simulations were conducted. The PK targets for the selected pediatric doses were assumed to be the same as those for adults, which are 30% fT>MIC of 4 μg/mL for ceftolozane and 20%

fT>Ct of 1 µg/mL for tazobactam because the pathogenesis and microbiology of NP are similar in adult and pediatric populations. Using these PK/PD targets, steady state plasma and lung PTA for adult subjects with NP and 5 pediatric age groups was evaluated for ceftolozane and tazobactam.

The criteria for evaluating the appropriateness of the proposed initial doses included the following:

- Projected distributions of pediatric plasma exposures of ceftolozane and tazobactam (ie, steady state plasma AUC0-8 and Cmax) comparable to the corresponding projected distributions of exposures in adult patients with NP.
- Steady state ceftolozane lung PTA >90% at the tazobactam-potentiated ceftolozane MIC of 4 µg/mL and steady state tazobactam lung PTA >90% at the threshold concentration of 1 µg/mL.

Based on plasma exposure and PTA criteria described above, simulations in pediatric subjects indicated that the following doses are appropriate for evaluation in the current study:

- 12 to <18 years of age: ceftolozane 2 g with tazobactam 1 g via a 60-minute (±10 minutes) IV infusion q8h
- <12 years of age: ceftolozane 40 mg/kg with tazobactam 20 mg/kg via a 60-minute (±10 minutes) IV infusion q8h (not to exceed a dose of ceftolozane 2 g and tazobactam 1 g)

Like the adult NP 3 g dose, these doses for pediatric subjects with NP are 2 times the doses that were evaluated in pediatric participants with cUTI and cIAI in the MK-7625A-034 and MK-7625A-035 studies. Per age group plasma ceftolozane and tazobactam exposures and lung ELF PTA for adult and pediatric subjects are summarized in Table 1 and Table 2, respectively. As shown in these tables, the selected doses provide exposures for the age groups that are constrained within the corresponding adult steady state AUC0-8 and Cmax ranges and achieve PTAs >90%.

Table 1 Ceftolozane Exposure and Target Attainment Summary for Simulated Adult and Pediatric Subjects with NP

		Adult NP Subjects (n=1000)	Pediatric Age Group[a,b]				
			1 (n=1000)	2 (n=1000)	3 (n=1000)	4 (n=1000)	5 (n=1200)
Dose		2 g q8h	2 g q8h	40 mg/kg q8h	40 mg/kg q8h	40 mg/kg q8h	40 mg/kg q8h
Ceftolozane Exposure							
Steady state AUC0-8 (µg×h/mL)	5th, 95th	165, 787	173, 661	172, 713	163, 570	154, 565	204, 827
Steady state Cmax (µg /mL)	5th, 95th	51.2, 202	65.3, 187	78.7, 180	74.6, 162	71.7, 145	77.4, 164
ELF Target attainment	N (%)	995 (99.5)	1000 (100.0)	999 (99.9)	1000 (100.0)	999 (99.9)	1200 (100.0)

5th, 95th=5th, 95th percentiles; AUC0-8=steady state plasma area under the concentration-time curve of an 8-hour dosing interval; Cmax=maximum observed concentration during a dosage interval; eGFR=estimated glomerular filtration rate; ELF= epithelial lining fluid; h=hours; N=number of subjects achieving target attainment; n=number of subjects; NP=nosocomial pneumonia; q8h=every 8 hours.
[a] Age Group 1, 12 years ≤ age <18 years; Age Group 2, 7 years ≤ age < 12 years; Age Group 3, 2 years ≤ age <7 years; Age Group 4, 3 months ≤ age <2 years; Age Group 5, >32 gestational week age, 7 days postnatal ≤ age <3 months.
[b] eGFR ≥ 20 mL/min/1.73 m^2

Table 2 Tazobactam Exposure and Target Attainment Summary for Simulated Adult and Pediatric Subjects with NP

		Adult NP Subjects (n=1000)	Pediatric Age Group[a,b]				
			1 (n=1000)	2 (n=1000)	3 (n=1000)	4 (n=1000)	5 (n=1200)
Dose		1 g q8h	1 g q8h	20 mg/kg q8h	20 mg/kg q8h	20 mg/kg q8h	20 mg/kg q8h
Tazobactam Exposure							
Steady state AUC0-8 (µg×h/mL)	5th, 95th	21.9, 172	23.3, 111	25.7, 123	24.8, 107	24.3, 116	35.7, 175
Steady state Cmax (µg /mL)	5th, 95th	12.9, 47.0	14.7, 51.9	21.2, 53.4	20.4, 50.8	19.5, 46.7	21.5, 47.4
ELF Target attainment	N (%)	995 (99.5)	982 (98.2)	987 (98.7)	981 (98.1)	983 (98.3)	1197 (99.8)

5th, 95th=5th, 95th percentiles; AUC0-8=steady state plasma area under the concentration-time curve of an 8-hour dosing interval; Cmax=maximum observed concentration during a dosage interval; eGFR=estimated glomerular filtration rate; ELF= epithelial lining fluid; h=hours; N=number of subjects achieving target attainment; n=number of subjects; NP=nosocomial pneumonia; q8h=every 8 hours.
[a] Age Group 1, 12 years ≤ age <18 years; Age Group 2, 7 years ≤ age < 12 years; Age Group 3, 2 years ≤ age <7 years; Age Group 4, 3 months ≤ age <2 years; Age Group 5, >32 gestational week age, 7 days postnatal ≤ age <3 months.
[b] eGFR ≥ 20 mL/min/1.73 m^2

4.3.2 Maximum Dose Exposure for This Study

The maximum dose for this study will be 3 g ceftolozane/tazobactam administered as a 60-minute ±10 minutes IV infusion q8h for up to 14 days, which was the dose and duration that was evaluated in adults with NP (MK-7625A-008).

4.3.3 Rationale for Dose Interval and Study Design

A dosing interval of q8h was chosen to be consistent with the proposed 8-hour dosing interval for pediatric participants with cUTI and cIAI and is supported by model-projected exposures of ceftolozane and tazobactam that meet their respective PK targets during the proposed dosing interval.

4.3.4 Rationale for Treatment Duration

For all participants, the duration of ceftolozane/tazobactam administration will be a minimum of 8 days and up to a maximum of 14 days. The standard treatment duration for NP is variable, with no clear consensus; treatment durations ranging from 8 to 15 days have been evaluated with similar mortality rates, although shorter durations are often recommended [Kalil, A. C., et al 2016] [Foglia, E., et al 2007]. Therefore, the ceftolozane/tazobactam treatment duration of 8 to 14 days is consistent with the standard-of-care for treatment of pediatric NP and was selected to evaluate safety at the duration used to treat this patient population. In addition, this treatment duration is consistent with the adult NP study (MK-7625A-008).

Likewise, participants are anticipated to receive a minimum of 8 days of concomitant standard-of-care antibiotic therapy; however, concomitant standard-of-care antibiotics may be stopped before the 8-day minimum at the discretion of the investigator. Participants who discontinue or complete concomitant standard-of-care antibiotic therapy in less than 8 days may also discontinue ceftolozane/tazobactam prior to the minimum duration of 8 days at the investigator's discretion. However, participants are strongly encouraged to receive a minimum of 8 days of ceftolozane/tazobactam.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent/assent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last. For this study, this corresponds to when the last data are available to the Sponsor.

For studies conducted in the European Economic Area (EEA), the local start of the study is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male and female pediatric participants from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with NP will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has a diagnosis of proven or suspected NP (including HABP or VABP), as determined by the investigator.

   Note: The diagnosis of NP does not require a pathogen to be isolated from a diagnostic test.

2. Is hospitalized and anticipated to receive a minimum of 8 days of concomitant standard of-care antibiotic therapy for proven or suspected NP. The concomitant standard-of-care antibiotic therapy can have coverage for either gram-positive and/or gram-negative respiratory pathogen(s).

   Note: Concomitant standard-of-care antibiotics may be stopped before the 8-day minimum at the discretion of the investigator. Participants who discontinue or complete concomitant standard-of-care antibiotic therapy in less than 8 days may also discontinue ceftolozane/tazobactam prior to the minimum duration of 8 days at the investigator's discretion. However, participants are strongly encouraged to receive a minimum of 8 days of ceftolozane/tazobactam.

Demographics

3. Is male or female (not pregnant or nursing) from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age inclusive, at the time of providing informed consent/assent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 30 days after the last dose of study intervention:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  OR
- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause) (Appendix 5) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a WOCBP
    OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 48 hours before the first dose of study intervention.
  - Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent/Assent

4. The participant (or legally acceptable representative(s), if applicable) provides documented informed consent/assent for the study.

Additional Categories

5. Is able to comply with all study procedures and restrictions for the duration of the study.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a documented history of any moderate or severe hypersensitivity (or allergic) reaction to any β-lactam antibacterial.

   Note: A history of a rash while on a β-lactam antibiotic does not automatically exclude a participant (eg, a participant with history of a mild rash followed by uneventful re-exposure may be considered for enrollment).

2. For Groups 1 through 4, has moderate to severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the revised Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration.

   For Group 5, has CrCL <20 mL/min/1.73 m^2 based on the revised Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration.

Prior/Concomitant Therapy

3. Is receiving or is anticipated to receive piperacillin/tazobactam while receiving ceftolozane/tazobactam or has received piperacillin/tazobactam within 24 hours prior to the first dose of ceftolozane/tazobactam.

Prior/Concurrent Clinical Study Experience

4. Participation in any clinical study of a therapeutic investigational product within 30 days prior to the first dose of ceftolozane/tazobactam.
5. Previous participation in any study of ceftolozane or ceftolozane/tazobactam.

Diagnostic Assessments

Not applicable.

Other Exclusions

6. Has one or more of the following laboratory abnormalities in a specimen obtained at screening:
   - ANC <1000/mm^3
   - AST or ALT ≥3 × the ULN
   - Total bilirubin ≥2 × the ULN (if 7 to ≤28 days of age and breastfeeding, total bilirubin >10 mg/dL OR ≥2 × ULN).
7. Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the participant or the quality of study data.
8. Has any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure or septic shock.
9. Has active immunosuppression, including any of the following:
   - HIV infection, with a known CD4 percentage of <15% in pediatric participants ≤5 years of age, or CD4 count of <200 cells/mm^3 in pediatric participants >5 years of age
   - active hematological malignancy
   - recipient of solid organ or bone marrow transplants
   - currently on immunosuppressive therapy, including cancer chemotherapy
   - currently on medications for prevention of transplant rejection
   - chronic administration of systemic corticosteroids (defined as the systemic equivalent of ≥2 mg/kg total daily dose of prednisone for participants ≤20 kg, or >40 mg of prednisone per day for participants >20 kg, administered continuously for more than 14 days in the 30 days prior to the first dose of ceftolozane/tazobactam).
10. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility

criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

Replacement participants will be assigned a unique allocation number. The participant replacement strategy is as follows:

- If a participant withdraws from the study prior to receiving any study treatment (ie, participant enrolled, not treated), a replacement participant will be enrolled.
- If a participant discontinues from ceftolozane/tazobactam OR withdraws from the study prior to the PK collection, a replacement participant may be enrolled if deemed appropriate by the Sponsor based on the number of other participants in that age group meeting the PK and safety interim analysis criteria (see Section 9.7).
- If a participant discontinues from ceftolozane/tazobactam OR withdraws from the study after PK collection after having received 6 doses of ceftolozane/tazobactam, a replacement participant may be enrolled if deemed appropriate by the Sponsor based on the average treatment duration of ceftolozane/tazobactam among all participants enrolled in the study.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies of ceftolozane/tazobactam will either be provided centrally by the Sponsor or sourced locally. When provided centrally by the Sponsor, clinical supplies will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Ceftolozane/tazobactam will be distributed using an IVRS. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Clinical supplies sourced locally will be distributed and labeled in accordance with local regulatory requirements.

6.1 Study Intervention(s) Administered

The ceftolozane/tazobactam to be used in this study is outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Test Product/ Comparator	IMP or NIMP/ AxMP	Sourcing
Group 1 (12 to <18 years of age [n=>6])	Experimental	Ceftolozane/ tazobactam	Drug	Powder	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 2 g and tazobactam 1 g	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product	IMP	Centrally or locally
Group 2 (7 to <12 years of age [n=>6])	Experimental	Ceftolozane/ tazobactam	Drug	Powder	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product	IMP	Centrally or locally
Group 3 (2 to <7 years of age [n=>6])	Experimental	Ceftolozane/ tazobactam	Drug	Powder	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product	IMP	Centrally or locally
Group 4 (3 months to <2 years of age [n=>6])	Experimental	Ceftolozane/ tazobactam	Drug	Powder	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product	IMP	Centrally or locally
Group 5 (birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months of age [n=>6])	Experimental	Ceftolozane/ tazobactam	Drug	Powder	Ceftolozane 2 g and tazobactam 1 g	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg	IV Infusion	60-minute IV infusion (±10 minutes) q8h for 8-14 days	Test Product	IMP	Centrally or locally

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; NP=nosocomial pneumonia; q8h=every 8 hours.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
The proposed initial doses may be modified based on interim data as described in Section 6.6 and Section 9.7. Single IV doses for all cohorts will not exceed the adult maximum dose of 3 g (2 g ceftolozane and 1 g tazobactam) for NP.

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

The same formulation and concentration of ceftolozane/tazobactam as is used for adults will be used in pediatric participants, whereby the dose will be determined by the volume of product administered rather than reformulating the product at a decreased dose.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

The design of this study is a single arm intervention with age cohorts. A stratification will be applied prior to allocation to a dose level based on the age cohort. Study intervention allocation will be distributed across 5 age groups as defined in Section 4.1. After the minimum enrollment target of 6 participants for each age group are met, at least 10 additional participants will be enrolled across any of the 5 age groups. No more than 4 additional participants (for a total of 10 participants in any given age group) will be enrolled in any given age group.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the study intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination:

a. Piperacillin/tazobactam

b. Probenecid

c. Immunosuppressive agents

Note: Short-term treatment with systemic (IV or oral) steroids of <1 week duration (eg, treatment for an acute asthma exacerbation or acute skin condition) is allowed. Topical steroids for the treatment of skin conditions are also allowed.

All other concomitant medications necessary for the health and well-being of the participant are permitted.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

After the first 3 participants are enrolled into a given age group, enrollment will be paused in that age group for an interim PK analysis to confirm or modify the proposed pediatric dose for the remaining participants in that group and/or other age groups. The proposed initial pediatric doses may be modified based on whether the dose evaluated in the interim PK analysis demonstrates an acceptable safety profile in the exposed age group and is suitable based on adequate PK plasma exposures (see Section 9.7).

Dose modifications, if required, will be communicated to investigators and sites via Protocol Clarification Letters.

No dose adjustment for renal insufficiency is allowed in this study (see Section 7.1).

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.7 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- For Groups 1 through 4, the participant develops moderate to severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the revised Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration. For Group 5, the participant develops CrCL <20 mL/min/1.73 m^2 based on the revised Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration.

Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.10.6. Participants are anticipated to receive a minimum of 8 days of concomitant standard-of-care antibiotic therapy; however, concomitant standard-of-care antibiotics may be stopped before the 8-day minimum at the discretion of the investigator. Participants who discontinue or complete concomitant standard-of-care antibiotic therapy in less than 8 days may also discontinue ceftolozane/tazobactam prior to the minimum duration of 8 days at the investigator's discretion. However, participants are strongly encouraged to receive a minimum of 8 days of ceftolozane/tazobactam.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent/assent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 18 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent/assent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent/assent form.

Informed consent/assent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

Participants unable to provide assent at enrollment due to incapacitation will be assented per local regulations/requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

The participant's medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

At Screening, the investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 7 days before the first dose of study intervention (or within 14 days before the first dose of study intervention for all antibacterial agents, and within 30 days before the first dose of study intervention for any other investigational drug). For participants who are breastfeeding, prior medication use by the participant's mother will be recorded similarly.

Any blood or blood product transfusions in the previous 48 hours before first dose of study intervention will be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study (from the first dose of study medication to the last study evaluation). For participants who are breastfeeding, concomitant medication use by the participant's mother will be recorded similarly.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1. Pretrial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

The ceftolozane/tazobactam to be used in this study is outlined in Table 3.

Ceftolozane/tazobactam should begin as soon as possible after allocation and at the latest within 24 hours of allocation. There should be no medically inappropriate delay in allocation and subsequent treatment with ceftolozane/tazobactam. All supplies indicated in Table 3 will either be provided centrally by the Sponsor or sourced locally.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of ceftolozane/tazobactam in accordance with the protocol and any applicable laws and regulations.

8.1.8.1 Timing of Dose Administration

Ceftolozane/tazobactam will be dosed q8h (±1 hour) after the previous infusion. The second IV dose has a ±4-hour window for dosing to facilitate adjustment of the dosing schedule (once q8h) to be carried out throughout the IV dosing period.

If the first administration of ceftolozane/tazobactam occurs later on Day 1 (Visit 2) such that the second or third dose is not given on Day 1 (Visit 2), the final day of study treatment may extend to Day 15 to allow for up to 14 consecutive 24-hour periods of ceftolozane/tazobactam treatment.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.7.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

There are no efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A full physical examination will be conducted at Screening (Visit 1) by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height (cm) and weight (kg) will also be measured and recorded. Body weight will be measured without shoes, jacket, or diaper (in participants using diapers). The full physical examination will include examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system).

The investigator or qualified designee will also perform a directed physical examination at other times at the investigator's discretion, if an AE or abnormality is suspected. A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. The directed physical examination should be based on the participant's condition and circumstances, at the investigator's discretion. The directed physical examination should note any changes in the participant's condition (body systems) since the last examination and does not preclude examination of any of the body systems as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Changes in physical examination findings (abnormalities) that the investigator considers clinically significant will be recorded on the medical history eCRF page if observed prior to administration of the first dose of ceftolozane/tazobactam. Changes in physical examination findings (abnormalities) that the investigator considers clinically significant must be recorded as AEs if observed after the start of the first dose of ceftolozane/tazobactam.

8.3.2 Vital Signs

The investigator or qualified designee will record vital signs (heart rate, blood pressure, respiratory rate, and temperature [oral, tympanic, rectal, axillary, or temporal]). Systolic and diastolic blood pressure will be measured on the same arm. Heart rate and blood pressure will be measured simultaneously. If Screening (Visit 1) and Allocation (Visit 2) occur on the same day, vital signs do not need to be performed twice.

8.3.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.3.1 Assessment of Creatinine Clearance

Blood samples for serum creatinine will be obtained as indicated in the SoA and evaluated by the local laboratory. The participant's CrCL will be estimated using the serum creatinine value, height, and the revised Schwartz equation [Schwartz, G. J., et al 2009], as follows:

GFR (mL/min per 1.73 m^2) = 0.413 * H/SCr, where

- GFR = mL/min per 1.73 m^2
- H = cm
- SCr = mg/dL

For participants with unstable renal function (CrCL is close to 50 mL/min/1.73 m^2) while receiving ceftolozane/tazobactam, obtain serum creatinine value and monitor CrCL at least daily. For Groups 1 through 4, a participant who develops moderate to severe impairment of renal function, defined as an estimated CrCL <50 mL/min/1.73 m^2 based on the revised Schwartz equation, or requires peritoneal dialysis, hemodialysis, or hemofiltration, must be discontinued from ceftolozane/tazobactam. For Group 5, a participant who develops CrCL <20 mL/min/1.73 m^2 based on the revised Schwartz equation or requires peritoneal dialysis, hemodialysis, or hemofiltration, must be discontinued from ceftolozane/tazobactam.

8.3.4 Pregnancy Testing (WOCBP only)

Pregnancy testing will be performed by the local laboratory on female participants of childbearing potential. Prior to allocation, the investigator will ensure serum pregnancy tests are negative in female participants of childbearing potential. A urine pregnancy test instead of a serum pregnancy test may be performed by the local laboratory, if deemed clinically appropriate by the investigator. An additional pregnancy test will be performed on female participants of childbearing potential at the EOT Visit at the end of relevant systemic exposure.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation through 14 days after cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 4 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).
2. An overdose of the Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory result.

8.5 Treatment of Overdose

For this study, an overdose of ceftolozane/tazobactam is considered to be any dose that is greater than 1.5 times higher than the protocol-specified dose for the participant's age group. Any overdose must be reported to the Sponsor as described in Appendix 3.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma Concentrations of Ceftolozane/Tazobactam

Blood samples for ceftolozane and tazobactam concentration assays and plasma PK parameters will be collected from all participants over one 8-hour dosing period on Day 3 (Visit 4) of the treatment period after administration of at least 6 doses of ceftolozane/tazobactam. These blood samples will be collected at the following times: at the end of infusion (1 hour after start of infusion of ceftolozane/tazobactam, collect within 10 minutes after the end of total dose administration); between 4 and 5 hours after start of infusion; and between 7 and 8 hours after start of infusion, but prior to the start of the next dose of ceftolozane/tazobactam.

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

Approximately 0.25 mL blood for assay of ceftolozane/tazobactam in plasma will be collected for each PK timepoint over the 8-hour dosing interval. Approximately 0.75 mL of blood will be drawn from each participant for PK analyses. The actual time of collection of each PK sample should be documented.

Plasma will be separated from blood and sent to the central laboratory for PK testing. Details of the procedures for collection, processing, storage, and shipment of PK samples from blood (plasma) will be provided separately in a laboratory manual. Actual whole blood sample collection dates and times must be recorded on the appropriate eCRF.

The method of sampling for PK blood draws is at the discretion of the Investigator (eg, 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 intervention infusion must occur in the same limb, the blood must be drawn more distally in the vein (approximately 3 to 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 study intervention administration and sample collection at the required time points. Prior to obtaining PK samples, the line must be flushed per site standard-of-care to ensure the total dose is administered.

8.7 Pharmacodynamics

PD parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.9 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening (Visit 1)

Screening assessments are performed within 48 hours prior to the start of administration of the first dose of ceftolozane/tazobactam. Potential participants are evaluated at the Screening Visit to determine if they fulfill the entry requirements in Section 5. All Screening results must be available prior to allocation. Screening, allocation, and first dose of ceftolozane/tazobactam may all occur on the same day.

8.10.2 Allocation Visit (Visit 2; Day 1)

The Allocation Visit is the date participants are allocated to treatment and may then receive the first dose of ceftolozane/tazobactam. Screening, allocation, and first dose of ceftolozane/tazobactam may all occur on the same day.

8.10.3 Treatment Period Visits

8.10.4 Intervention Period Visits (Visits 3 through 15; Days 2 through 14)

Intervention Period Visits on ceftolozane/tazobactam occur daily beginning on Day 2 (Visit 3) and continuing through the last dose of ceftolozane/tazobactam. Assessments at these visits (concomitant medication review, directed physical examinations, vital signs, and AE/SAE monitoring) should be performed at a consistent time each day (eg, every morning), as much as possible. Safety laboratory tests should be completed on Day 3 (Visit 4) and only if clinically indicated at the other visits while receiving ceftolozane/tazobactam.

Blood is collected for PK analyses on Day 3 (Visit 4) (after ≥6 doses of ceftolozane/tazobactam). PK sample collection may occur on Day 4 (Visit 5) if the last dosing period of Day 3 (Visit 4) is selected for PK sample collection. Additionally, if

sampling on Day 3 (Visit 4) is logistically difficult, sampling may be performed at comparable time points after Day 3 (Visit 4) in subjects who are continuing to receive ceftolozane/tazobactam.

8.10.5 EOT Visit (Visit 16)

The EOT Visit will occur within 48 hours after the last dose of ceftolozane/tazobactam. Concomitant medication review, administration of concomitant standard-of-care antibiotics for NP, directed physical examinations, vital signs, safety laboratory tests, pregnancy testing for WOCBP, and AE/SAE monitoring will be performed at this visit.

8.10.6 LFU Visit (Visit 17)

The LFU Visit occurs in all participants 14 days (+3 days) after the last dose of ceftolozane/tazobactam. The LFU Visit will be conducted by telephone; however, if the participant has abnormal laboratory values or AEs that require follow-up, an in-person visit is required.

8.10.7 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue from ceftolozane/tazobactam prior to completion of the study treatment regimen will continue to be monitored in the study according to the SoA.

For participants who prematurely withdraw from the study, see Section 7.2 and Section 7.3.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to the objectives, or the statistical methods related to the objectives, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

9.1 Statistical Analysis Plan Summary

Study Design Overview	A Phase 1, open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam (MK-7625A) in pediatric participants with nosocomial pneumonia.
Treatment Assignment	All enrolled participants are to receive ceftolozane/tazobactam treatment.
Analysis Populations	Safety: ASaT Population PK: PK Population
Primary Endpoints	The primary safety parameters will include the following safety evaluations: • Any AEs • Any SAEs • Any drug-related AEs • Any serious and drug-related AEs • AEs leading to discontinuation of study intervention
Secondary Endpoints	The secondary PK parameters will include the following ceftolozane and tazobactam PK parameters: • Plasma concentrations at each time point • Steady state plasma AUC0-8, Cmax, t1/2, Vd, and CL
Statistical Methods for Key Efficacy Analyses	There are no efficacy analyses planned for this study.
Statistical Methods for Key Safety Analyses	The primary safety parameters will be evaluated by the number and percentage of all participants reporting these events with 95% CIs based on the Clopper and Pearson method. Primary safety parameters will also be evaluated separately using the same methods for participants with treatment exposure from 1 to <8 days versus treatment exposure for ≥8 days. The number and percentage of all participants reporting specific AEs will be provided for all AEs by system organ class and PT. Summary statistics of clinical laboratory tests for baseline and all post-baseline evaluations including means, mean changes from baseline, standard deviations, minimum and maximum values over time will be provided. Summary statistics for vital signs will also be provided.

Interim Analyses	Interim PK analyses will be conducted after enrollment of the first 3 participants into a given age group.
Multiplicity	There are no multiplicity adjustments planned for this study.
Sample Size and Power	In this study, approximately 40 participants will be enrolled and treated. With this sample size, there will be at least 64% probability to observe any AEs that have an underlying true incidence rate of 2.5% or more, and there will be at least 87% probability to observe any AEs that have an underlying true incidence rate of 5% or more. If no AEs are observed, the upper bound of the 2-sided 95% CI for the 0% AE incidence rate will be 8.8%, based on the Clopper and Pearson method.

9.2 Responsibility for Analyses/In-house Blinding

There is no blinding required for this single arm study. The analysis of the safety data obtained from this study will be the responsibility of the Sponsor's Clinical Biostatistics department.

The official, final database will not be locked until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The plasma concentrations at each time point and the primary PK parameters for ceftolozane and tazobactam will be summarized by the Sponsor's Quantitative Pharmacology and Pharmacometrics department and the Early Clinical Development Statistics department.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. There are no hypotheses to be tested in this study.

9.4 Analysis Endpoints

9.4.1 Safety Endpoints

Safety endpoints include AEs (any AEs, any SAEs, any drug-related AEs, any serious and drug-related AEs, and AEs leading to discontinuation of study intervention), clinical laboratory tests, and vital sign measurements.

The rationale for safety endpoints is provided in Section 4.2.1.1, and ECIs are defined in Section 8.4.7. The proportion of subjects who experience AEs of elevated laboratory values that are reported as ECIs during the study treatment period will be estimated.

9.4.2 PK Endpoints

Plasma concentrations for ceftolozane and tazobactam at each time point will be determined and summarized in the CSR. Plasma concentration data will be used to update the existing ceftolozane and tazobactam pediatric population PK models. Due to the sparse PK sampling, the other PK endpoints, including steady state Cmax, AUC0-8, t1/2, Vd, and CL will be

characterized using a population PK modeling approach. These parameters will be summarized in a separate population PK modeling report.

9.5 Analysis Populations

9.5.1 Safety Population

The safety population will include participants who receive any dose (including partial doses) of ceftolozane/tazobactam (ASaT).

9.5.2 PK Population

The PK population will include participants who receive at least 6 doses of ceftolozane/tazobactam and have at least 1 quantifiable plasma concentration of ceftolozane or tazobactam.

9.6 Statistical Methods

9.6.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of relevant parameters for all participants overall (ASaT), including AEs, clinical laboratory parameters, and vital sign measurements.

The broad AE categories consisting of the percentage of participants with any AEs, any serious AEs, any drug-related AEs, any serious and drug-related AEs, and AEs leading to discontinuation of study intervention will be summarized for the ASaT population using point estimates with 95% CIs (Table 5). The calculation of 95% CIs is based on the exact binomial method proposed by Clopper and Pearson. These summaries will also be performed separately for participants with treatment exposure from 1 to <8 days versus treatment exposure for ≥8 days.

For continuous measurements, such as changes from baseline in laboratory parameters and vital signs, summary statistics (including mean, mean change from baseline, standard deviation, minimum and maximum values over time) for baseline, on-treatment, and change from baseline values will be provided in table format.

Table 5 Analysis Strategy for Safety Parameters

Safety Endpoint	Within Group 95% CI	Descriptive Statistics
Any AE	X	X
Any Serious AE	X	X
Any Drug-related AE	X	X
Any Serious and Drug-related AE	X	X
Discontinuation due to AE	X	X
Specific AEs, System Organ Classes, or PTs		X
Change from Baseline Results (Laboratory results, Vital Signs)		X

AE= adverse event; CI=confidence interval; PT=Preferred term.
Note: 95% CIs will be calculated using the Clopper Pearson method.
X=results will be provided

9.6.2 Statistical Methods for PK Analyses

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

The primary PK parameters for ceftolozane and tazobactam (steady state plasma AUC0-8, Cmax, t1/2, Vd, and CL) will be characterized for each age group and/or dose level, as appropriate. Data will be presented in tables and listings. Listings may include but are not limited to: participant ID number, dose administered, body weight, plasma drug concentrations, time points, and individual derived PK parameters. Summary tables may include but are not limited to: the number of participants, arithmetic means, SD, %CV, minimum, median, and maximum values, and geometric mean for individual parameters.

Based on PK data obtained within this study and previous ceftolozane/tazobactam studies in adults, a separate pediatric population PK analysis will be performed for ceftolozane and tazobactam. The results of this analysis will be reported separately in a population PK modeling report.

9.7 Interim Analyses

After the first 3 participants are enrolled into a given age group, enrollment will be paused in that age group for an interim PK analysis to confirm or modify the proposed pediatric dose for the remaining participants in that group and/or other age groups. Enrollment will continue in the other age groups during each interim PK analysis. The proposed initial pediatric doses may be modified based on whether the dose evaluated in the interim PK analysis demonstrates an acceptable safety profile in the exposed age group and is suitable based on adequate PK plasma exposures.

All observed PK data will be entered into a population PK dataset on a rolling basis. Proposed initial doses will be considered suitable if the observed ceftolozane and tazobactam plasma exposures are similar to corresponding plasma exposures in adult participants with NP that have proved safe and efficacious. The criteria for demonstrating adequate PK plasma exposures and an acceptable safety profile of the proposed doses include the following:

- Population PK model predicted pediatric plasma exposures of ceftolozane and tazobactam (ie, steady state plasma AUC0-8 and/or Cmax) within the ranges of the 5th and 95th percentile of the corresponding model-projected exposures in adult participants with NP.
- Absence of a safety signal (eg, no SAEs related to study intervention).

  Note: If a safety signal is detected, additional analyses involving plasma PK exposure data will be evaluated to determine the appropriate course of action.

After the first 3 participants have been enrolled into a given age group, at least 3 additional participants will be enrolled in that age group following the interim PK analysis. At least 3 additional participants per age group, for a total of 6 participants per age group, is expected to provide sufficient data to inform pediatric population PK model development and for

determining the appropriate dose for a given age group. Dose modifications, if required, will be communicated to investigators and sites via Protocol Clarification Letters.

9.8 Multiplicity

There are no multiplicity adjustments planned for this study.

9.9 Sample Size and Power Calculations

The cumulative sample size of 40 participants for this study is based on obtaining sufficient data to evaluate the safety and PK of ceftolozane/tazobactam in pediatric participants, in addition to feasibility considerations. This study is not powered to test formal hypotheses.

With approximately 40 participants enrolled and treated, there will be at least 64% probability to observe any AEs that have an underlying true incidence rate of 2.5% or more, and there will be at least 87% probability to observe any AEs that have an underlying true incidence rate of 5% or more. If no AEs are observed, the upper bound of the 2-sided 95% CI for the 0% AE incidence rate will be 8.8%, based on Clopper and Pearson method.

In addition, the sample size of 40 will provide for at least 6 participants per age group for the PK analysis, which is considered appropriate for the planned pediatric population PK analysis. The Phase 1 single-dose PK study (MK-7625A-010) had a similar PK sample size and enrolled approximately 6 participants per age group. Pediatric population PK models using MK-7625A-010 PK data adequately described the observed plasma concentration-time profiles of ceftolozane and tazobactam in all age groups, enabling PK target calculation and PTA simulation to support pediatric dose determination from the Phase 2 cUTI/cIAI studies [Modeling and Simulation Report: Population... 2017].

9.10 Subgroup Analyses

No subgroup analysis will be performed for PK or safety; plasma concentrations of ceftolozane and tazobactam will be summarized by time point and by cohort, but this is not considered to be a subgroup analysis.

9.11 Compliance (Medication Adherence)

Each participant will be scheduled to receive ceftolozane/tazobactam q8h (3 times daily) for approximately 8 to 14 days (maximum of fourteen 24-hour periods). Treatment compliance will be documented in the eCRF by recording the date, time, and length of infusion for each dose of ceftolozane/tazobactam. Study intervention adherence will be summarized as treatment exposure (number of days on study therapy and number of doses of study therapy received). As the study will only enroll hospitalized participants receiving IV therapy, high study intervention adherence among all participants is anticipated.

9.12 Extent of Exposure

The extent of exposure to ceftolozane/tazobactam will be summarized as both continuous and categorical variables alongside counts and percentages for the “Number of Days on Therapy” in the ASaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate

an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will

be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will

review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by the local laboratory.

The timing for the collection of blood and urine samples for safety monitoring is provided in the SoA.

- Pregnancy Testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count Hemoglobin Hematocrit			WBC count with Differential: Neutrophils Band Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Pregnancy Testing	• Serum or urine β hCG pregnancy test (as needed for WOCBP)			
ALT=alanine aminotransferase; AST=aspartate aminotransferase; β hCG=human chorionic gonadotropin; BUN=blood urea nitrogen; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WBC=white blood cell.				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
    - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
    - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.
f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?

- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based on the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- Time Course: Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- Dechallenge: Was the study intervention discontinued or dose/exposure/frequency reduced?

- If yes, did the AE resolve or improve?

- If yes, this is a positive dechallenge.

- If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)

- Rechallenge: Was the participant re-exposed to the study intervention in this study?

- If yes, did the AE recur or worsen?

- If yes, this is a positive rechallenge.

- If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).

- Yes, there is a reasonable possibility of study intervention relationship:

- There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

- No, there is not a reasonable possibility of study intervention relationship:

- Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c, d] • IUS[c, e] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen- containing) hormonal contraception[c, d]
  • Oral
  • Intravaginal
  • Transdermal
  • Injectable

• Progestogen-only hormonal contraception[c, d]
  • Oral
  • Injectable

Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. [f] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. • Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-8	Steady state plasma area under the concentration-time curve of an 8-hour dosing interval
BLI	β-lactamase inhibitor
CD4	cluster of differentiation 4
CI	confidence interval
cIAI	complicated intraabdominal infection
Cmax	maximum observed concentration during a dosage interval
CL	clearance
CONSORT	Consolidated Standards of Reporting Trial
CrCL	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
cUTI	complicated urinary tract infection
CV	coefficient of variation
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
ELF	epithelial lining fluid
EMA	European Medicines Agency

Abbreviation	Expanded Term
EOT	end of treatment
ESBL	extended spectrum β-lactamase
EU	European Union
EU CT	EU Clinical Trial
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
ft>Ct	time that free plasma concentration exceeds the threshold concentration
fT>MIC	time that free plasma concentration exceeds the minimum inhibitory concentration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H	height
HABP	hospital-acquired bacterial pneumonia
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous

Abbreviation	Expanded Term
IVRS	interactive voice response system
JAPIC-CT	Japan Project-Industry Council for Clinical Trials
LAM	lactational amenorrhoea method
LDA	last data available
LFU	last follow-up
LPLV	last participant last visit
MIC	minimum inhibitory concentration
NCT	National Clinical Trial
NP	nosocomial pneumonia
PD	pharmacodynamic
PICC	peripherally inserted central catheter
PK	pharmacokinetic
PT	Preferred Term
PTA	probability of target attainment
q	every
q8h	every 8 hours
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SLAB	supplemental laboratory test(s)
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
t1/2	elimination half-life
ULN	upper limit of normal
US(A)	United States (of America)
VABP	ventilator-associated bacterial pneumonia
Vc	central volume of distribution
Vd	volume of distribution
Vp	peripheral compartment
WHO	World Health Organization

Abbreviation	Expanded Term
WOCBP	woman/women of childbearing potential
UTN	Universal Trial Number

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