Official Protocol Title:	A Prospective, Randomized, Double-Blind, Multicenter, Phase 3 Study To Assess The Safety And Efficacy Of Intravenous Ceftolozane/Tazobactam Compared With Meropenem In Adult Patients With Ventilated Nosocomial Pneumonia
NCT number:	NCT02070757
Document Date:	28-Jun-2018

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PHASE 3 STUDY TO ASSESS THE SAFETY AND EFFICACY OF INTRAVENOUS CEFTOLOZANE/TAZOBACTAM COMPARED WITH MEROPENEM IN ADULT PATIENTS WITH VENTILATED NOSOCOMIAL PNEUMONIA

IND Number:	104,490
EudraCT Number:	2012-002862-11
Protocol Number:	CXA-NP-11-04 (MK-7625A PN008)
Phase:	3
Investigational Drug:	Ceftolozane/tazobactam
Investigational Site(s):	Multicenter
Dose Forms:	Intravenous
Sponsor:	Cubist Pharmaceuticals, LLC (formerly known as Cubist Pharmaceuticals, Inc.), an indirect wholly-owned subsidiary of Merck & Co., Inc. and with a principal place of business address of: Weystrasse 20 6000 Lucerne 6 Switzerland
Sponsor Medical Director:	PPD
Version:	7.0 – SS2 JAPAN
Date:	28-Jun-2018
Supersedes:	Version 7.0 – SS1 JAPAN; 19 September 2017 Version 6.0 – SS1 JAPAN; 15 March 2016 Version 5.0; 22 October 2014 Version 4.0; 14 March 2014 Version 3.0; 27 November 2013 Version 2.0; 06 February 2013 Version 1.0; 11 May 2012

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

STATEMENT OF CONFIDENTIALITY

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

PROTOCOL APPROVAL

Protocol Title:	A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia
Protocol Number	CXA-NP-11-04
Version:	7.0 – SS2 JAPAN

28-JUN-2018

PPD

Date

Merck & Co., Inc.

INVESTIGATOR'S AGREEMENT

I have read the foregoing protocol (CXA-NP-11-04) Version 7.0 – SS2 JAPAN and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by the Sponsor or their designee and the Ethics Committee (EC) or Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB or EC responsible for this study.

I further agree that the Sponsor or their designee shall have access to any source documents from which case report form information may have been generated.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SUMMARY OF CHANGES

1.1. Primary Reasons for this Amendment

Section Number(s) and Title(s)	Description of Change	Rationale for Change
2 Synopsis 6 Trial Objectives and Purpose	Added text explaining that the efficacy and safety of ceftolozane/tazobactam in the population of patients with sepsis will be evaluated under a Japan-specific amendment.	To evaluate the efficacy and safety of ceftolozane/tazobactam in population of patients with sepsis.
Appendix F.	Added the assessment plan of sepsis.	To clarify the assessment plan of sepsis.

2. SYNOPSIS

Name of Sponsor/Company: Cubist Pharmaceuticals, LLC	
Name of Investigational Product: Ceftolozane/tazobactam	
Name of Active Ingredient: Ceftolozane/tazobactam	
Title of Study: A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia	
Study center(s): Global multi-center	
Study Duration: 38 to 50 months	**Phase of development:** 3

Objectives: To accommodate the unique requirements of different regulatory jurisdictions, the study objectives have been separated out in this section. In addition, the efficacy and safety of ceftolozane/tazobactam in the population of patients with sepsis will be evaluated under a Japan-specific amendment. Further details are provided in Appendix F.

Study Objectives per the United States (US) Food and Drug Administration (FDA):

Primary objective:

- To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with ventilated nosocomial pneumonia (VNP) based on the difference in Day 28 all-cause mortality rates in the Intent-to-treat (ITT) population using a non-inferiority margin of 10%.

Key Secondary objective:

- To compare the clinical response rates of ceftolozane/tazobactam versus meropenem in adult subjects with VNP in the ITT population at the Test-of-cure (TOC) visit (7 to 14 days after the End-of-therapy [EOT] visit).

Other Secondary objectives:

- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the microbiological ITT (mITT) population
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* isolated from the baseline lower respiratory tract (LRT) culture
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the TOC visit
- To compare the per-pathogen microbiological response rates at the TOC visit (ceftolozane/tazobactam versus meropenem)
- To compare the Day 14 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit for ceftolozane/tazobactam versus meropenem
- To compare the clinical response rates at the Late Follow-up (LFU) visit for ceftolozane/tazobactam versus meropenem
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the EOT visit

- To compare the per-pathogen clinical response at TOC by baseline minimum inhibitory concentration (MIC) for ceftolozane/tazobactam versus meropenem
- To evaluate the safety and tolerability of ceftolozane/tazobactam

Exploratory objectives:

- To compare the time to all-cause mortality in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture
- To compare the per-pathogen microbiological response at TOC by baseline minimum inhibitory concentration (MIC) for ceftolozane/tazobactam versus meropenem
- To compare the superinfection and new infection rate for ceftolozane/tazobactam versus meropenem
- To compare the emergence of nonsusceptibility to study drug for ceftolozane/tazobactam versus meropenem
- To compare the time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen
- To compare the incidence of 4-fold increases in MIC (ceftolozane/tazobactam versus meropenem) for subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 μg/mL)
- To evaluate the pharmacokinetics of ceftolozane/tazobactam
- To compare the health economics outcomes, including total number of days in hospital, proportion of patients discharged from the acute care hospital, number of days in intensive care unit (ICU), and number of days on a ventilator, of ceftolozane/tazobactam and meropenem in adults subjects with VNP within 28 days of randomization
- To evaluate the change in procalcitonin from baseline to Day 3 and to EOT

Study Objectives per European Medicines Agency (EMA):

Primary objective:

- To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with VNP based on the difference in clinical response rates in the ITT population at the TOC visit (7 to 14 days after the EOT visit), using a non-inferiority margin of 12.5%

Key Secondary objective:

- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the ITT population

Other Secondary objectives:

- To compare the clinical response rates of ceftolozane/tazobactam versus meropenem in adult subjects with VNP at the TOC visit in the CE population
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the TOC visit
- To compare the per-pathogen microbiological response rates at the TOC visit (ceftolozane/tazobactam versus meropenem)

- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the mITT population
- To compare the Day 14 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit for ceftolozane/tazobactam versus meropenem
- To compare the clinical response rates at the LFU visit for ceftolozane/tazobactam versus meropenem
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the EOT visit
- To compare the per-pathogen clinical response at TOC by baseline MIC for ceftolozane/tazobactam versus meropenem
- To evaluate the safety and tolerability of ceftolozane/tazobactam

Exploratory objectives:

- To compare the time to all-cause mortality in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture
- To compare the per-pathogen microbiological response at TOC by baseline MIC for ceftolozane/tazobactam versus meropenem
- To compare the superinfection and new infection rate for ceftolozane/tazobactam versus meropenem
- To compare the emergence of nonsusceptibility to study drug for ceftolozane/tazobactam versus meropenem
- To compare the time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen
- To compare the incidence of 4-fold increases in MIC (ceftolozane/tazobactam versus meropenem) for subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 μg/mL)
- To evaluate the pharmacokinetics of ceftolozane/tazobactam
- To compare the health economics outcomes, including total number of days in hospital, proportion of patients discharged from the acute care hospital, number of days in ICU, and number of days on a ventilator, of ceftolozane/tazobactam and meropenem in adults subjects with VNP within 28 days of randomization
- To evaluate the change in procalcitonin from baseline to Day 3 and to EOT

Methodology: This is a prospective, randomized, double-blind, multicenter Phase 3 study to assess the safety and efficacy of ceftolozane/tazobactam 3000 mg (comprising 2000 mg ceftolozane and 1000 mg tazobactam) every 8 hours (q8h) administered as an intravenous (IV) infusion in the treatment of adult subjects with VNP (including ventilator-associated bacterial pneumonia [VABP] and ventilated hospital-acquired bacterial pneumonia [HABP] subjects), compared with meropenem 1000 mg q8h administered as an IV infusion. Subjects will be enrolled and randomized (1:1) to receive either ceftolozane/tazobactam or meropenem. Randomization will be stratified by diagnosis (VABP or ventilated HABP) and by age (≥65 or <65 years) to facilitate balanced distribution of high-risk subjects between the 2 treatment arms. The number of subjects enrolled with VABP will be at least 50% of the randomized population.
Patient participation will require a minimum commitment of 36 days and a maximum of 51 days.

Number of patients (planned): Approximately 726 subjects will be randomized.

Diagnosis and main criteria for inclusion:

To be eligible for enrollment, a subject must satisfy all of the following entry criteria before they will be allowed to participate in the study and prior to any study related procedures:

1. Provide written informed consent prior to any study-related procedure not part of normal medical care. If the subject is unable to do so, local country laws and institution-specific guidelines and requirements in place for obtaining informed consent should be met. A legally acceptable representative may provide consent, provided this is approved by local country and institution-specific guidelines. If a subject comes to consciousness while still in the study and per the Investigator's judgment the subject is able to read, assess, understand, and make his/her own decision to participate in the trial, the subject can agree to continue study participation and the subject may be re-consented, if required by local country and institution-specific guidelines;
2. Be males or females aged 18 years or older;
   If female, subject must not be pregnant or nursing, and is either:
   - Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or
   - Of childbearing potential and meets at least 1 of the following:
     - Is practicing an effective method of contraception (eg, oral/parenteral contraceptives plus barrier method), or
     - Has a vasectomized partner, or
     - Is currently abstinent from sexual intercourse.

     Subjects must be willing to practice the chosen contraceptive method or remain abstinent during the conduct of the study and for at least 35 days after last dose of study medication. Non-vasectomized males are required to practice effective birth control methods (eg, abstinence, use of condom, or use of other barrier device) during the treatment period and for at least 75 days after last dose of study medication;
3. Intubated (via endotracheal tube, including tracheostomy patients) and on mechanical ventilation at the time of randomization:

   For ventilated HABP:

   - At least 1 of the following signs and/or symptoms must be present within the 24 hours **prior** to intubation OR within the 48 hours **after** intubation in a patient who has been either hospitalized for ≥48 hours or who has been discharged from a hospital within the prior 7 days (includes patients institutionalized in skilled nursing or other long-term care facility):
     - A new onset of cough (or worsening of baseline cough)
     - Dyspnea, tachypnea, or respiratory rate greater than 30 per minute, particularly if any or all of these signs or symptoms are progressive in nature
     - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air, OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air, OR worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2).

   For VABP:

   - Receiving mechanical ventilation ≥48 hours and at least one of the following:
     - Acute changes made in the ventilator support system to enhance oxygenation, as determined by worsening partial pressure of oxygen on arterial blood gas, or worsening PaO2/FiO2.
     - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air (or FiO2 equivalent), OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air (or FiO2 equivalent), OR worsening PaO2/FiO2.

4. Chest radiograph obtained within the 24 hours prior to the first dose of study drug shows the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia (based on Investigator evaluation or report from a qualified medical professional who is not the investigator). A computed tomography (CT) scan may be used in place of a chest X-ray;
5. Have the following clinical criteria within the 24 hours prior to the first dose of study drug:
   - Purulent tracheal secretions
   - And at least 1 of the following:
     - Documented fever (body temperature $\geq$38°C [100.4°F])
     - Hypothermia (body temperature $\leq$35°C [95.2°F])
     - White blood cell (WBC) count $\geq$10,000 cells/mm^3
     - WBC count $\leq$4,500 cells/mm^3
     - $\geq$15% immature neutrophils.
6. Have a baseline lower respiratory tract specimen obtained for Gram stain and quantitative culture within 36 hours prior to the first dose of study drug. This specimen can be obtained by a bronchoalveolar lavage (BAL), nonbronchoscopic BAL (mini-BAL), protected brush specimen (PBS), or an endotracheal aspirate (ETA);

   Note: ETA specimens with an average of $\geq$10 squamous epithelial cells or $\leq$25 polymorphonuclear cells per low power field will be considered inadequate, and a repeat specimen that is adequate will need to be obtained for Gram stain and subsequent quantitative culture.

   Note: If BAL, mini-BAL, or PBS is available at the site, these modalities are strongly recommended rather than an ETA for obtaining the baseline LRT specimen.
7. Willing and able to comply with all study procedures and restrictions.

Investigational product, dosage and mode of administration:
Ceftolozane/tazobactam 3000 mg q8h, IV infusion.

Duration of treatment: The duration of study drug administration will be a minimum of 8 days (24 doses) and up to a maximum of 14 days (42 doses). The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of dummy infusions. In subjects with *P. aeruginosa* isolated from the baseline LRT culture, a treatment duration of 14 days is strongly recommended for study drug administration.

Reference therapy, dosage and mode of administration:
Meropenem 1000 mg q8h, IV infusion.

Study Endpoints per the US FDA:

Primary Endpoint:

- Day 28 all-cause mortality in the ITT population

Key Secondary Endpoint:

- Clinical response at the TOC visit in the ITT population

Secondary Endpoints:

- Day 28 all-cause mortality in the mITT population
- Clinical response at the TOC visit in the CE population
- Clinical response for subjects at the TOC visit in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the mITT population
- Clinical response for subjects at the TOC visit in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the mITT population

- Per-subject microbiological response at TOC in the Microbiologically Evaluable (ME) population
- Per-pathogen microbiological response for *P. aeruginosa* at TOC in the ME population
- Per-pathogen microbiological response for Enterobacteriaceae at TOC in the ME population
- Per-pathogen microbiological response at TOC in the ME population
- Day 14 all-cause mortality in the ITT population
- Clinical response at EOT in the ITT and CE populations
- Clinical response at the LFU visit in the CE population
- Per-subject microbiological response at EOT in the ME population
- Per-pathogen microbiological response at EOT in the ME population
- Per-pathogen clinical response at TOC by baseline MIC in the mITT and ME populations

Exploratory Endpoints:

- Time to all-cause mortality in the ITT population
- Clinical response for subjects at TOC in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the ME population
- Clinical response for subjects at TOC in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the ME population
- Per-subject microbiological response at TOC in the mITT population
- Per-pathogen microbiological response at TOC in the mITT population
- Per-subject microbiological response at EOT in the mITT population
- Per-pathogen microbiological response at EOT in the mITT population
- Per-pathogen microbiological response by baseline MIC in the mITT and ME populations
- Superinfection and new infection rates in the mITT population
- Emergence of nonsusceptibility to study drug in the mITT population
- Time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen in the mITT and ME populations
- Emergence of a 4-fold increase in MIC to study drug for treated subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 µg/mL) in the mITT population
- Pharmacokinetics
- Total number of days in hospital within 28 days after randomization for the ITT population
- Proportion of patients discharged from the acute care hospital within 28 days after randomization for the ITT population
- Number of days in ICU through 28 days after randomization for the ITT population
- Number of days on a ventilator through 28 days after randomization for the ITT population
- Change in procalcitonin from baseline to Day 3 and to EOT in the ITT population.

Safety: Safety will be evaluated in the Safety population through review of summaries of deaths, serious adverse events (SAEs), adverse events (AEs), laboratory evaluations, vital signs, and physical examinations.

Study Endpoints per the EMA:

Primary Endpoint:

- Clinical response at the TOC visit in the ITT population

Key Secondary Endpoint:

- Day 28 all-cause mortality in the ITT population

Secondary Endpoints:

- Clinical response at the TOC visit in the CE population
- Clinical response for subjects at the TOC visit in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the mITT population
- Clinical response for subjects at the TOC visit in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the mITT population
- Per-subject microbiological response at TOC in the ME population
- Per-pathogen microbiological response for *P. aeruginosa* at TOC in the ME population
- Per-pathogen microbiological response for Enterobacteriaceae at TOC in the ME population
- Per-pathogen microbiological response at TOC in the ME population
- Day 28 all-cause mortality in the mITT population
- Day 14 all-cause mortality in the ITT population
- Clinical response at EOT in the ITT and CE populations
- Clinical response at the LFU visit in the CE population
- Per-subject microbiological response at EOT in ME population
- Per-pathogen microbiological response at EOT in the ME population
- Per-pathogen clinical response at TOC by baseline MIC in the mITT and ME populations

Exploratory Endpoints:

- Time to all-cause mortality in the ITT population
- Clinical response for subjects at TOC in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the ME population
- Clinical response for subjects at TOC in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the ME population
- Per-subject microbiological response at TOC in the mITT population
- Per-pathogen microbiological response at TOC in the mITT population
- Per-subject microbiological response at EOT in mITT population
- Per-pathogen microbiological response at EOT in the mITT population
- Per-pathogen microbiological response by baseline MIC in the mITT and ME populations
- Superinfection and new infection rates in the mITT population
- Emergence of nonsusceptibility to study drug in the mITT population
- Time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen in the mITT and ME populations
- Emergence of a 4-fold increase in MIC to study drug for treated subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 µg/mL) in the mITT population
- Pharmacokinetics
- Total number of days in hospital within 28 days after randomization for the ITT population
- Proportion of patients discharged from the acute care hospital within 28 days after randomization for the ITT population
- Number of days in ICU through 28 days after randomization for the ITT population
- Number of days on a ventilator through 28 days after randomization for the ITT population
- To evaluate the change in procalcitonin from baseline to Day 3 and to EOT visit in the ITT population

Safety: Safety will be evaluated in the Safety population through review of summaries of deaths, SAEs, AEs, laboratory evaluations, vital signs, and physical examinations.

Statistical methods:

Primary Efficacy Analysis per US FDA:

For analyses of dichotomous endpoints, 2-sided 95% confidence intervals (CI) for the difference in proportions between ceftolozane/tazobactam and meropenem will be calculated, with adjustment for the study stratification factors (diagnosis [VABP or ventilated HABP] and by age [≥65 or <65 years]). The estimated overall proportion will be calculated as a weighted average across all strata, constructed using Mehrotra-Railkar continuity-corrected minimum-risk [MRc] stratum weights [22]. The 2-sided 95% confidence interval (CI) for the treatment group proportions and the treatment difference will be calculated as stratified Newcombe CIs, constructed using the MRc weights with the methods presented by Yan and Su [23].

Primary Efficacy Analysis per EMA:

Similar general methodologies detailed in the preceding US FDA Analysis section will be employed; however, a 2-sided 97.5% CI will be constructed instead of 95% CIs.

Sample Size and Power Considerations for the US FDA Analysis:

To demonstrate the non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in Day 28 all-cause mortality rates, using a non-inferiority margin of 10%, a sample size of 726 subjects (363 per arm) in the ITT population will have 90% power at a 1-sided significance level of 0.025, assuming a Day 28 all-cause mortality rate of 20% in both ceftolozane/tazobactam and meropenem arms.

Sample Size and Power Considerations per the EMA Analysis:

To demonstrate the non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in clinical cure rates of VNP at the TOC visit in the ITT population, using a non-inferiority margin of 12.5%, at a 1-sided significance level of 0.0125, a sample size of 726 subjects (363 per arm) will have 85.3% power assuming a cure rate of 58.4% in both ceftolozane/tazobactam and meropenem arms.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
APACHE	Acute Physiology and Chronic Health Evaluation
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BLI	β-lactamase inhibitor
BUN	Blood urea nitrogen
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CFU	Colony forming unit
CI	Confidence interval
cIAI	Complicated intra-abdominal infections
CL_{CR}	Creatinine clearance
COPD	Chronic obstructive pulmonary disease
CPIS	Clinical Pulmonary Infection Score
CRP	C-reactive protein
CT	Computed tomography
cUTI	Complicated urinary tract infections
CYP450	Cytochrome P450
D	Day
DAO	Data-as-Observed
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
ELF	Epithelial lining fluid

Abbreviation	Definition
EMA	European Medicines Agency
EOT	End of therapy
ESBL	Extended spectrum β-lactamase
ETA	Endotracheal aspirate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HABP	Hospital-acquired bacterial pneumonia
HIV	Human immunodeficiency virus
h	Hour
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	Interactive Response Technologies
ITT	Intent-to-Treat
Kg	Kilogram
IV	Intravenous
L	Liter
LAR	Legally-authorized representative
LFU	Late follow-up
LRT	Lower respiratory tract
M1	Tazobactam metabolite
MAOI	Monoamine oxidase inhibitor (MAOI)
MDR	Multidrug resistant
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram
MIC	Minimum inhibitory concentration
min	Minute
mini-BAL	nonbronchoscopic bronchoalveolar lavage
mITT	Microbiological Intent-to-Treat

Abbreviation	Definition
mL	Milliliter
MRc	Continuity-corrected minimum risk
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NYHA	New York Heart Association
PaO_2/FiO_2	Partial pressure of oxygen to the fraction of inspired oxygen
PBP	Penicillin-binding protein
PBS	Protected brush specimen
PD	Pharmacodynamic
PK	Pharmacokinetic
PTA	Probability of target attainment
q8h	Every eight hours
q12h	Every twelve hours
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOFA	Sepsis Organ Failure Assessment
$t_{½}$	Terminal half-life
%T>MIC	Time above the minimum inhibitory concentration
TEAE	Treatment-emergent adverse event
TFA	Treatment Failure Approach
TOC	Test-of-cure
US	United States
ULN	Upper limit of normal
VABP	Ventilator-associated bacterial pneumonia
VNP	Ventilated nosocomial pneumonia
V_{ss}	Volume of distribution at steady state
WBC	White blood cell

5. INTRODUCTION

5.1. Nosocomial Pneumonia

Nosocomial pneumonia is a prevalent hospital-acquired infection associated with increased morbidity, mortality, and prolongation of hospital stay [1]. As much as 50% of all deaths associated with nosocomial infection are due to nosocomial pneumonia. A diagnosis of nosocomial pneumonia has been linked to prolongation of hospital stay by an excess of 4 days at an additional cost of $40,000 or more per patient [2,3].

The term nosocomial pneumonia encompasses hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and healthcare-associated pneumonia. According to the 2005 American Thoracic Society/Infectious Diseases Society of America guidelines, HABP is defined as pneumonia occurring 48 hours or more after hospital admission, which was not incubating at the time of admission [4]. It is typically characterized by the presence of new or progressive infiltrates on chest radiography associated with clinical symptoms suggestive of pneumonia (eg, fever, leukocytosis, and production of purulent sputum) [4]. Ventilator-associated bacterial pneumonia is a subset of HABP, and develops in mechanically ventilated patients 48 to 72 hours after endotracheal intubation [4]. Healthcare-associated pneumonia includes any patient with recent health-care exposure, including those hospitalized in an acute care hospital, nursing home, long-term care, or skilled nursing facility [4].

Gram-negative bacilli account for greater than 50% of commonly isolated pathogens in nosocomial pneumonia. Notable among these are *Pseudomonas aeruginosa*, *Enterobacter* spp., *Klebsiella pneumoniae*, and *Acinetobacter* spp. [4,5,6]. Other commonly isolated lower respiratory tract (LRT) pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Staphylococcus aureus*, and *Serratia marcescens*. Recent trends show an increase in the prevalence of nosocomial pneumonia caused by multidrug resistant (MDR) bacteria, most commonly *P. aeruginosa* with documented resistance to β-lactams, carbapenems, aminoglycosides, and fluoroquinolones [6,7]. The therapeutic effectiveness of current therapies for nosocomial pneumonia (especially ventilated nosocomial pneumonia [VNP]) are limited by the increasing prevalence of pathogens that express extended spectrum β-lactamases (ESBLs), AmpC β-lactamases, or methicillin resistance, emphasizing the need for development of new and effective antimicrobials [8].

Initial empiric antibiotic treatment may include the use of cephalosporins, aminoglycosides, fluoroquinolones, penicillins, or carbapenems alone or in combination. Antibiotic selection is typically individualized based on a given patient's risk factors for MDR pathogens (eg, prior hospitalization, admission from a long term care or skilled nursing facility, recent antibiotic exposure) and local susceptibility patterns [4,8]. Prompt and adequate antimicrobial therapy has been shown to reduce mortality and improve morbidity associated with nosocomial pneumonia [9].

5.2. Ceftolozane/tazobactam for Injection

Ceftolozane/tazobactam, an antibacterial consisting of ceftolozane, a novel antipseudomonal cephalosporin, with tazobactam, a well-established β-lactamase inhibitor (BLI), is being developed for the treatment of serious bacterial infections. Ceftolozane/tazobactam is currently approved for use in adult patients with complicated urinary tract infections (cUTI) and complicated intraabdominal infections (cIAI) at a dose of 1500 milligrams (mg; compromising 1000 mg ceftolozane and 500 mg tazobactam) every 8 hours (q8h).

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

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

Ceftolozane is a potent PBP3 inhibitor, and shows affinities at least 2-fold higher than those of ceftazidime for all the essential PBPs (1b, 1c, and 3) in *P. aeruginosa*. Like most cephalosporins, ceftolozane alone does not have activity against ESBL-producing Enterobacteriaceae and gram-negative anaerobes.

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

In summary, ceftolozane is a novel cephalosporin antibiotic which, in combination with the potent BLI, tazobactam, has broad-spectrum antibacterial coverage against β-lactam-resistant Enterobacteriaceae and MDR *P. aeruginosa*. Both *in vitro* and *in vivo* efficacy data support its clinical development in nosocomial pneumonia as a potential human therapeutic agent for the treatment of severe bacterial infections caused by susceptible organisms, including Enterobacteriaceae and *P. aeruginosa*.

5.3. Nonclinical Experience

When tested individually or in combination, ceftolozane and tazobactam (from historical data in combination with piperacillin) each displays an acceptable safety profile in animals. In studies of ceftolozane alone, the no-observed-adverse-effect level for both rats and dogs was 300 mg/kilogram (kg)/day. Intravenous toxicity studies of up to 6 months duration have been performed with tazobactam alone and in combination with piperacillin in rats and dogs. Tazobactam appears to be very well tolerated, with no drug-related mortalities or serious clinical abnormalities. The potential target organs identified in these studies were the hematological, hepatic, and gastrointestinal systems; however, only relatively minor changes were observed in each of these organ systems.

The combination of ceftolozane and tazobactam did not increase the toxicity of the individual compounds in rats after 4 weeks of repeated dosing, and did not significantly alter the pharmacokinetic (PK) profile of the individual compounds in a dog study. The combination of ceftolozane and tazobactam had similar PK characteristics, including a short plasma half-life ($t_{½}$), renal elimination, rapid distribution into the extracellular fluid compartment, and low plasma protein binding. Because both of these compounds are primarily excreted by the kidney via glomerular filtration, the potential for drug-drug interactions is likely limited to drugs excreted by tubular secretion (eg, probenecid), as this is an alternate mechanism of tazobactam excretion.

The efficacy of ceftolozane has been demonstrated in various animal models, including sepsis, pneumonia, urinary tract infection, burn wound, and thigh infection models. In general, the *in vivo* efficacy of ceftolozane against *P. aeruginosa*, including MDR isolates, was better than, or comparable to that of ceftazidime, imipenem, and ciprofloxacin. Specifically, in a neutropenic mouse pneumonia model, ceftolozane demonstrated potent activity against *K. pneumoniae* and drug-resistant *P. aeruginosa*.

In conclusion, ceftolozane/tazobactam has broad-spectrum antibacterial activity that includes cephalosporin- and carbapenem-resistant *P. aeruginosa*. *In vitro* and *in vivo* efficacy, safety, and PK data support its clinical development as a potential human therapeutic agent for the treatment of severe bacterial infections.

Refer to the Investigator's Brochure/approved label for additional information on the nonclinical experience with ceftolozane/tazobactam.

5.4. Clinical Experience

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

Doses as high as 9000 mg of ceftolozane/tazobactam per day (3000 mg q8h intravenously [IV]) have been given, and have generally been well tolerated by all subjects.

Refer to the Investigator's Brochure/approved label for additional information on the clinical experience with ceftolozane/tazobactam.

5.4.1. Pharmacokinetics

The results from the adult Phase 1 and Phase 2 studies demonstrated ceftolozane/tazobactam PK characteristics are generally consistent with those of other renally-excreted β-lactam antibiotics. Ceftolozane/tazobactam had linear PK across a wide range of doses (250 to 3000 mg for ceftolozane and 100 to 1500 mg for tazobactam); and its volume of distribution at steady state (V_{ss}), approximately 11 to 18 liters (L), was roughly equivalent to the extracellular fluid volume. The plasma protein binding was low; approximately 16 to 21% and 30% for ceftolozane and tazobactam, respectively. The $t_{½}$ for ceftolozane and tazobactam was 2 to 3 hours and approximately 1 hour, respectively, independent of dose and with little or no accumulation after multiple dosing q8h or every 12 hours (q12h). Ceftolozane/tazobactam was primarily cleared from the systemic circulation into the urine by glomerular filtration, but tazobactam was also partly cleared by tubular secretion. About 20% of the tazobactam dose is converted to a single inactive metabolite (M1) via hydrolysis of the β-lactam ring while >95% for ceftolozane was eliminated as unchanged parent drug, suggesting minimal potential for cytochrome P450 (CYP450) mediated metabolism. Co-administration of ceftolozane/tazobactam given as 1-hour IV infusions in a fixed 2:1 ratio of ceftolozane to tazobactam did not change the PK profiles of either drug, nor of the tazobactam M1 metabolite.

Systemic clearance was linearly related to creatinine clearance (CL_{CR}), but no other significant intrinsic factors affecting the PK of ceftolozane/tazobactam were identified. An ethno-bridging study that was conducted suggested that the PK of ceftolozane/tazobactam is dose-independent and comparable between Japanese, Chinese and Caucasian healthy subjects. In addition, a drug-drug interaction study suggested a low potential for any CYP450 or transporter-mediated PK interaction, and there is a low potential for PK interaction with other drugs eliminated primarily by glomerular filtration, such as tobramycin and vancomycin.

5.4.2. Safety

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

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

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

In the integrated Phase 3 studies of ceftolozane/tazobactam for cUTI and cIAI (CXA-cUTI-10-04, CXA-cUTI-10-05, CXA-cIAI-10-08, and CXA-cIAI-10-09), 1015 adult patients received treatment with ceftolozane/tazobactam. The most common AEs from these trials were nausea, headache, diarrhea, pyrexia, constipation, hypertension, insomnia, and, vomiting. Overall SAE rates were 5.3% and 5.2% in the ceftolozane/tazobactam and comparator arms, respectively. Drug discontinuation rates due to AEs were similar, with 2% of patients who discontinued ceftolozane/tazobactam and 1.9% of patients who discontinued comparator drug. Drug-related SAEs with ceftolozane/tazobactam were limited to only three cases (two cases of *Clostridium difficile* colitis and one of pseudomembranous colitis) compared to one drug-related SAE with comparator drug. In cUTI, there was one death in the ceftolozane/tazobactam treatment arm and none in the comparator arm. In cIAI, there were 11 deaths in the ceftolozane/tazobactam arm and eight deaths in the comparator arm. All of the deaths reported in these Phase 3 studies were deemed unrelated to study therapy by the Investigator. Collectively, two subjects in Phase 3 experienced a shift from negative direct Coombs' test at baseline to positive at the end of therapy visit, but none were associated with a report of hemolytic anemia.

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

5.5. Summary of Risks and Benefits

5.5.1. Ceftolozane/tazobactam

The potential human toxicity of ceftolozane/tazobactam should be evaluated in the context of the human experience in clinical studies. Ceftolozane and tazobactam have been studied in humans, both individually and as a combination. The clinical experience for the combination product is described in Section 5.4. To date, no clinically important or unexpected safety signal has been observed. In general, ceftolozane/tazobactam appears safe and well tolerated in the populations studied, and its safety profile consistent with the cephalosporin class of antibiotics.

As both ceftolozane and tazobactam are primarily excreted by the kidney via glomerular filtration, the potential for drug-drug interactions is likely limited to drugs excreted by tubular secretion (eg, probenecid), as this is an alternate mechanism of tazobactam excretion. In addition, a drug-drug interaction study (Section 5.4) suggested a low potential for any CYP450 or transporter-mediated PK interaction, and there is a low potential for PK interaction with other drugs eliminated primarily by glomerular filtration, such as tobramycin and vancomycin.

For more detailed information regarding the risks and benefits associated with ceftolozane/tazobactam, please refer to the Investigator's Brochure/approved label.

5.5.2. Meropenem

Meropenem is widely used for the treatment of a variety of serious bacterial infections, including nosocomial pneumonia. Clinical practice and published treatment guidelines [4] for nosocomial pneumonia recommend a dosing regimen of 1000 mg q8h administered by IV infusion for meropenem.

Meropenem is approved in the European Union and several other countries for treatment of nosocomial pneumonia and is widely used in the United States (US) for nosocomial infections. It is generally considered one of the best available antibiotics for this indication, and appears in evidence-based guidelines as a first-line treatment option for nosocomial pneumonia [4,10]. Meropenem is highly potent, has a broad spectrum of activity against a range of bacterial organisms including most of the expected pathogens for this indication, and is stable to various bacterial resistance mechanisms [11].

The recommended dose in this indication, which will be used in this study, is 1000 mg q8h administered by IV infusion. To facilitate blinding, meropenem will be administered in this study as a 1-hour infusion (versus over 30 minutes [min]) to match the duration of infusion of ceftolozane/tazobactam. The efficacy of meropenem is not affected by administration in this way, as it is a β-lactam antibiotic that's efficacy is dependent on the percent of time the drug concentration exceeds the minimum-inhibitory concentration (%T>MIC) of the pathogens being treated. Improved efficacy of β-lactam antibiotics often requires either prolonged duration of infusion or more frequent dosing [4]. Prolonged infusions of meropenem, of longer than 1-hour, have been administered to nosocomial pneumonia patients with excellent results and without additional safety or tolerability risks [12,13]. In addition, meropenem, at

a dose of 1000 mg every 8 hours, has also been administrated as a 1-hour infusion in the completed Phase 3 cIAI study (Study CXA-cIAI-10-08/09) versus ceftolozane/tazobactam.

The clinical safety of meropenem is well described in the clinical studies used to support its marketing authorization by the US Food and Drug Administration (FDA) [14]. In clinical studies of 2904 immunocompetent subjects treated with meropenem, the most frequently reported AEs were (>1% incidence): diarrhea (4.8%), nausea/vomiting (3.6%), inflammation at the injection site (2.4%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%). Premature discontinuation of meropenem due to AE was reported in 1.2% of subjects in these trials. Other rare, but important AEs reported with meropenem include: hypersensitivity reactions, seizures, and *C. difficile*-associated diarrhea. Case reports have shown that co-administration of carbapenems, including meropenem, to patients receiving divalproex or valproic acid, may result in a reduction in valproic acid concentrations, increasing the risk for breakthrough seizures [14]. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with carbapenem agents should be avoided.

5.6. Rationale

5.6.1. Study Rationale

Nosocomial pneumonia is often associated with high morbidity and mortality. Current literature suggests that the pathogens in patients with nosocomial pneumonia often include MDR gram-negative pathogens as well as *S. aureus* [15,16]. Prompt therapy with effective antibiotics has been shown to significantly improve survival for subjects with nosocomial pneumonia. There are limited clinical data correlating epithelial lining fluid (ELF) concentrations and clinical outcome; hence, the clinical significance of differences in pulmonary penetration of antibiotics is unknown. However, adequate antibiotic concentrations at the site of bacterial infection are required for efficacy and there are some data that demonstrate that ELF concentrations predict effective concentrations in pneumonia.

The intrapulmonary penetration of the 1500 mg q8h dose of ceftolozane/tazobactam was studied in a comparative ELF healthy volunteer study, using piperacillin/tazobactam as a comparator. The results showed that the ceftolozane component of ceftolozane/tazobactam had an ELF/Plasma area under the curve (AUC) ratio of 0.48, compared to 0.26 for the piperacillin component of piperacillin/tazobactam. In addition, the concentration of ceftolozane in the ELF exceeded 8 µg/mL for more than 60% of its 8-hour dosing interval. These results confirm that ceftolozane penetrates well into the ELF and that its penetration was comparable to piperacillin/tazobactam (a β-lactam approved for treatment of lower respiratory infections), supporting ceftolozane's potential utility as an effective therapeutic agent in nosocomial pneumonia. Ceftolozane/tazobactam is well suited for study as a potential therapeutic agent in VNP because of its good intrapulmonary penetration and broad spectrum activity against gram-negative pathogens, including MDR *P. aeruginosa* and most ESBL-producing Enterobacteriaceae.

This study is designed to assess the safety and efficacy of ceftolozane/tazobactam in subjects with VNP, comprising VABP and ventilated HABP compared with meropenem, a

well-characterized β-lactam antibiotic widely used for the treatment of nosocomial pneumonia.

5.6.2. Dose Rationale

Ceftolozane/tazobactam was studied in Phase 3 trials of adult subjects with either cUTI or cIAI at a dose of 1500 mg (ie, 1000 mg of ceftolozane with 500 mg tazobactam). The 1500-mg dose selected for the cUTI and cIAI indications was supported by the safety and efficacy results of 2 successful randomized, controlled Phase 2 studies (CXA-101-03 and CXA-IAI-10-01). However, due to the increased variability in PK seen in subjects with nosocomial pneumonia and the increasing prevalence of MDR bacteria in this subject population, a higher (3000 mg) dose was selected for this study. This is consistent with current clinical practice as other β-lactam antibiotics, such as meropenem, have been used at higher doses for more serious and difficult-to-treat infections, such as VNP.

The infusion duration selected for the 3000 mg dose is 1 hour. The 1-hour infusion duration was based on the pharmacokinetic/pharmacodynamics (PK/PD) driver for ceftolozane/tazobactam. Similar to other β-lactam antibiotics (including the cephalosporins) efficacy is dependent on the %T>MIC of the pathogens being treated. Therefore, the 1-hour infusion was selected to ensure optimum activity based on the %T>MIC parameter.

A robust and comprehensive dose evaluation process was used to select the dose for the treatment of subjects with nosocomial pneumonia caused by gram-negative pathogens. A summary of this dose selection approach is as follows:

<u>PK/PD analyses of nonclinical data:</u>

- Dose-fractionation studies in animal models of infection determined that the potency of ceftolozane was dependent on the %T>MIC for the infecting pathogen.
- Data from the mouse neutropenic thigh infection model demonstrated that for ceftolozane the %T>MIC required for *in vivo* stasis is 21.4 to 28.5 and for 1-log kill is 26.7 to 35.3. The ceftolozane %T>MIC required for bactericidal activity were similar for both Enterobacteriaceae and *P. aeruginosa*.
- Once the PD parameter correlating with efficacy was identified, PK/PD analyses of observed human PK data from Phase 1 and 2 studies were used to select the dose.

<u>PK/PD analyses of clinical data:</u>

- A stable, reliable, and interpretable population PK model was developed. This population PK model characterized observed clinical PK data and allowed a calculation of %T>MIC for individual PK profiles. To better understand the distribution and inherent increased variability in PK profiles that might result from a much larger sample size in the Phase 3 clinical trials, 1000 replicate Monte Carlo simulations were performed to derive the probability of target attainment (PTA; the probability of achieving the target of 40% or 50% time above minimum inhibitory concentration [MIC] values of pathogens). PK/PD analysis was also performed to determine the PTA against various pathogens based on the MIC distributions of ceftolozane/tazobactam from a 2008 surveillance study.

Population PK combined with Monte Carlo simulations of observed clinical data is a well-established PK/PD approach in antibiotic clinical development that ensures a thorough exposure-response evaluation necessary for selecting the most optimal dose of antibiotics [17]. Based on the PTA from PK/PD analysis, and demonstrated safety/tolerability, a dose of 3000 mg q8h ceftolozane/tazobactam administered by IV infusion was selected for the treatment of subjects with nosocomial pneumonia caused by gram-negative pathogens. Table 2 shows the PTA for 2 different doses of ceftolozane/tazobactam across a range of %T>MIC thresholds between 30 to 60%.

Table 2: Probability of Target Attainment for Dosing Regimen, MIC, and %T>MIC (Utilizing a Population PK Model) for Enterobacteriaceae and *P. aeruginosa* Strains

Ceftolozane/tazobactam	MIC (µg/mL)	%T>MIC					
		30%	35%	40%	45%	50%	60%
1500 mg q8h 60-min infusion	4	100	100	100	100	99.7	95.5
	8	100	99.7	98.2	96.1	89.8	74.6
	16	96.1	85.0	74.9	57.8	44.9	24.6
3000 mg q8h 60-min infusion	4	100	100	100	100	100	100
	8	100	100	100	100	99.4	97.0
	16	100	99.7	98.8	95.8	90.7	75.1

Abbreviations: MIC= minimum inhibitory concentration; %T>MIC= time above the minimum inhibitory concentration; q8h = every 8 hours; min = minute; PK = pharmacokinetic; µg/mL = microgram/milliliter.
Source: Data on File.

As expected, for both doses of ceftolozane/tazobactam, as the %T>MIC and MIC values increase, the PTA decreases. However, the 3000 mg q8h dose of ceftolozane/tazobactam retains excellent PTA for pathogens with MIC values ≤8 microgram/milliliter (µg/mL) up to a %T>MIC threshold of 60. Conversely, with the 1500 mg q8h dose of ceftolozane/tazobactam, the PTA for pathogens with MIC values ≤8 µg/mL declines to below 90% at a %T>MIC threshold of 50 and above. In addition to achieving desirable PTA, it is very important during dose selection to account for the physiological changes frequently seen in subjects with nosocomial pneumonia. Renal impairment is a well-recognized problem in critically ill subjects. Renal hyperclearance is also an important concern, especially in hospitalized younger subjects (< 55 years of age) without co-morbidities upon admission to hospital. Renal hyperclearance, defined as the increased renal elimination of solute, has been reported in certain subjects in the intensive care unit (ICU) particularly younger age groups and may compromise the activity of renally excreted antibiotics [18]. Consideration of both renal impairment and renal hyperclearance is important when selecting an appropriate dosage regimen for a primarily renally excreted antibacterial agent for treatment of infections in the critically ill. An analysis of CL_{CR} from subjects enrolled in clinical trials of HABP (20.5 to 241.0 mL/min) and VABP (26.8 to 283.6 mL/min) confirms the wide variation in renal function in this subject population. In this study, approximately 15% of subjects with VABP and 10% of subjects with HABP subjects had a CL_{CR} ≥150 mL/min [19].

In order to assess the impact of hyperclearance on the PK/PD of ceftolozane/tazobactam, a distribution of CL_{CR} from critically ill subjects obtained from medical literature was incorporated in the population PK model to estimate antibacterial PTA in the critically ill. This initial PK/PD analysis was based on data collected in two Phase 1 studies (subjects with normal and impaired renal function) and one Phase 2 study of ceftolozane in subjects with cUTI. This PK/PD analysis was used to predict the PTA with ceftolozane using thresholds of 40% and 50% T>MIC. The results are presented in Table 3.

Table 3: Probability of Target Attainment for 2 Doses of Ceftolozane/tazobactam (q8h, 1-hour infusion) by MIC and %T>MIC Stratified by Creatinine Clearance

CL_{CR} (mL/min)	MIC (µg/mL)	1500 mg ceftolozane/tazobactam		3000 mg ceftolozane/tazobactam	
		40% T>MIC	50% T>MIC	40% T>MIC	50% T>MIC
180	4	100	96	100	100
	8	93	64	100	99
	16	40	11	97	81
200	4	100	93	100	99
	8	88	52	99	93
	16	27	6	88	66
220	4	99	87	100	99
	8	80	42	99	88
	16	20	4	81	42
250	4	97	79	100	97
	8	71	32	98	81
	16	12	2	73	30

Abbreviations: CL_{CR}=creatinine clearance; MIC=minimum inhibitory concentration; %T>MIC=percent time above the minimum inhibitory concentration; q8h=every 8 hours.
Source: Data on File.

As shown in Table 3, by increasing the dose of ceftolozane/tazobactam to 3000 mg, the PTA was improved in subjects with renal hyperclearance for pathogens with an MIC up to 8 µg/mL.

When PK data from a Phase 2 study in subjects with cIAI became available, the population PK analysis was again conducted including this data. Estimates of clearance and volume of distribution along with the associated inter-individual variability were obtained from these analyses. To further account for the concentration at the site of action for a comprehensive exposure-response assessment, this analysis also incorporated mean ELF penetration data (ie, ELF/plasma AUC ratio of 0.48 (range: 0.25-0.65) from a completed ceftolozane ELF study (CXA-ELF-10-03). Using the foregoing, the analysis estimated plasma and ELF concentrations versus time profiles in 1000 simulated subjects with nosocomial pneumonia. This analysis evaluated the PTA of the 3000 mg every 8 hours dose of

ceftolozane/tazobactam against 3 key pathogens frequently seen in nosocomial pneumonia (namely, *P. aeruginosa*, *E. coli*, and *K. pneumoniae)*. The MIC distribution for these pathogens was imputed from the 2008 United States surveillance data. The PTA was defined as the achievement of an ELF or plasma concentration of ceftolozane higher than the MIC(s) of the lower respiratory pathogen(s) for a given subject (using a threshold %T>MIC of 50) on Day 7 of treatment. Plasma and ELF concentrations were estimated at 15 time-points post administration on Day 7 when dosed q8h. The results of these simulations are shown in Table 4.

Table 4: Probability of Target Attainment Versus Key Pathogens in Nosocomial Pneumonia Using the Simulated 3000-mg Dose of Ceftolozane/tazobactam

Organism	Dosing Regimen	50% T>MIC in Plasma	50% T>MIC in ELF
P. aeruginosa	3000 mg q8h	99.4	98.5
E. coli	3000 mg q8h	98.8	95.5
K. pneumoniae	3000 mg q8h	92.6	89.3

Abbreviations: ELF= epithelial lining fluid; T>MIC = Time above minimum inhibitory concentration; q8h=every 8 hours; mg = milligram.
Source: Data on File.

These results suggest that the 3000 mg dose of ceftolozane/tazobactam administered q8h is likely to provide adequate concentrations for treatment of the vast majority of lower respiratory infections caused by these pathogens.

This clinical trial simulation was then repeated to predict concentration-time profiles in subjects with varying degree of renal impairment. Creatinine clearance was previously identified as a covariate in a population PK model, which suggested increased plasma exposure (AUC) to ceftolozane/tazobactam in subjects with severe and moderate renal impairment. Based on these simulations, the results showed that no dose adjustment is required in subjects with mild renal impairment (CL_{CR} >50 to 89 mL/min) compared with that in subjects with normal renal function (CL_{CR} ≥90 mL/min). The dose in subjects with severe renal impairment (CL_{CR} 15 to 30 mL/min) and moderate renal impairment (CL_{CR} >30 to 49 mL/min) should be reduced by 4-fold (ie, 750 mg ceftolozane/tazobactam every 8 hours) and 2-fold (1500 mg ceftolozane/tazobactam every 8 hours), respectively.

Since the PTA was optimized for a 3000 mg dose of ceftolozane/tazobactam, it was important to ascertain safety and tolerability of this dose. In healthy volunteers, the safety and tolerability of a 10-day course of ceftolozane/tazobactam 3000 mg every 8 hours by IV infusion over 60 minutes was evaluated. In this study (CXA-MD-11-07), subjects were randomized to receive either 3000 mg ceftolozane/tazobactam (n=8) or 1500 mg ceftolozane/tazobactam (n=4), or placebo (n=4) for 10 days. The study results showed that ceftolozane/tazobactam was generally well tolerated in this study (Table 5).

Fifteen of 16 randomized subjects completed the study as planned; one subject randomized to the 3000 mg ceftolozane/tazobactam arm prematurely discontinued treatment after the second dose due to a drug-related AE of vomiting. Other drug-related AEs reported by this

subject included nausea, flushing, and bilateral leg aches. There were no SAEs or deaths reported during the study. The type, incidence, and distribution of AEs were generally similar in subjects randomized to either the 3000 mg or 1500 mg dose of ceftolozane and consistent with the side effect profile expected for β-lactams. The most frequently reported group of AEs were non-treatment-limiting injection site reactions. Remarkably, no AEs were reported during or after study drug therapy in subjects randomized to placebo. Two subjects in the 3000 mg ceftolozane/tazobactam arm had a negative direct Coombs' test at baseline with sero-conversion to a weekly positive test at follow-up. None of these subjects had symptoms or laboratory values suggestive of hemolytic anemia or any AE suggestive of anemia. When dosed at 3000 mg, the plasma concentrations of ceftolozane and tazobactam showed a dose-proportional increase compared to the 1500 mg dose, indicating that the PK of ceftolozane and tazobactam was linear. No accumulation of either ceftolozane or tazobactam was observed following repeated dosing for 10 days.

Table 5: Treatment-emergent Adverse Events Reported in Study CXA-MD-11-07 (Safety Population)

System Organ Class/Preferred Term	Ceftolozane/tazobactam 3000 mg (n=8) n (%)	Ceftolozane/tazobactam 1500 mg (n=4) n (%)	Placebo (n=4)
Subjects with at least 1 TEAE	*4 (50.0)*	*3 (75.0)*	*0*
Infusion site irritation	2 (25.0)	1 (25.0)	0
Nausea	1 (12.5)	0	0
Vomiting	1 (12.5)	0	0
Infusion site extravasation	1 (12.5)	0	0
Infusion site inflammation	1 (12.5)	0	0
Pain in extremity	1 (12.5)	0	0
Flushing	1 (12.5)	0	0
Sensation of heaviness	0	1 (25.0)	0
Headache	0	1 (25.0)	0

TEAE=Treatment emergent adverse event; mg = milligram.
Source: CSR CXA-MD-11-07.

Overall, these results demonstrate that the 3000 mg q8h IV dose of ceftolozane/tazobactam was well tolerated in this healthy volunteer population without any safety signals. The data supports its use in this Phase 3 VNP clinical trial.

In conclusion, a comprehensive exposure-response approach with high probability of target attainment, the favorable ELF data demonstrating good lung penetration, and the demonstrated safety and tolerability of the higher dose of ceftolozane/tazobactam in the Phase 1 study CXA-MD-11-07, support a dose of 3000 mg every 8 hours by IV infusion over 60 minutes of ceftolozane/tazobactam for the treatment of subjects with VNP caused by gram-negative pathogens.

6. TRIAL OBJECTIVES AND PURPOSE

To accommodate the unique requirements of different regulatory jurisdictions, the study objectives have been separated out in this section. In addition, the efficacy and safety of ceftolozane/tazobactam in the population of patients with sepsis will be evaluated under a Japan-specific amendment. Further details are provided in Appendix F.

6.1. Study Objectives per the US FDA

Primary objective:

- To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with VNP based on the difference in Day 28 all-cause mortality rates in the Intent-to-treat (ITT) population using a non-inferiority margin of 10%

Key Secondary objective:

- To compare the clinical response rates in the ITT population of ceftolozane/tazobactam versus meropenem in adult subjects with VNP at the TOC visit (7 to 14 days after the End-of-therapy [EOT] visit)

Other Secondary objectives:

- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the microbiological ITT (mITT) population
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the TOC visit
- To compare the per-pathogen microbiological response rates at the TOC visit (ceftolozane/tazobactam versus meropenem)
- To compare the Day 14 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit for ceftolozane/tazobactam versus meropenem
- To compare the clinical response rates at the Late Follow-up (LFU) visit for ceftolozane/tazobactam versus meropenem
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the EOT visit

- To compare the per-pathogen clinical response at TOC by baseline MIC for ceftolozane/tazobactam versus meropenem
- To evaluate the safety and tolerability of ceftolozane/tazobactam

Exploratory objectives:

- To compare the time to all-cause mortality in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture
- To compare the per-pathogen microbiological response at TOC by baseline MIC for ceftolozane/tazobactam versus meropenem
- To compare the superinfection and new infection rate for ceftolozane/tazobactam versus meropenem
- To compare the emergence of nonsusceptibility to study drug for ceftolozane/tazobactam versus meropenem
- To compare the time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen
- To compare the incidence of 4-fold increases in MIC (ceftolozane/tazobactam versus meropenem) for subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 µg/mL)
- To evaluate the pharmacokinetics of ceftolozane/tazobactam
- To compare the health economics outcomes, including total number of days in hospital, proportion of patients discharged from the acute care hospital, number of days in ICU, and number of days on a ventilator, of ceftolozane/tazobactam and meropenem in adults subjects with VNP within 28 days after randomization
- To evaluate the change in procalcitonin from baseline to Day 3 and to EOT

6.2. Study Objectives per the European Medicines Agency (EMA)

Primary objective:

- To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with VNP based on the difference in clinical response rates in the ITT population at the TOC visit (7 to 14 days after the EOT visit), using a non-inferiority margin of 12.5%

Key Secondary objective:

- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the ITT population

Other Secondary objectives:

- To compare the clinical response rates of ceftolozane/tazobactam versus meropenem in adult subjects with VNP at the TOC visit in the CE population
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture
- To compare the clinical response rates at the TOC visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the TOC visit
- To compare the per-pathogen microbiological response rates at the TOC visit (ceftolozane/tazobactam versus meropenem)
- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the mITT population
- To compare the Day 14 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit for ceftolozane/tazobactam versus meropenem
- To compare the clinical response rates at the LFU visit for ceftolozane/tazobactam versus meropenem
- To compare the microbiological response rates of ceftolozane/tazobactam versus meropenem at the EOT visit
- To compare the per-pathogen clinical response at TOC by baseline MIC for ceftolozane/tazobactam versus meropenem
- To evaluate the safety and tolerability of ceftolozane/tazobactam

Exploratory objectives:

- To compare the time to all-cause mortality in the ceftolozane/tazobactam versus meropenem arms
- To compare the clinical response rates at the EOT visit (ceftolozane/tazobactam versus meropenem) in the subset of subjects who had *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture
- To compare the per-pathogen microbiological response at TOC by baseline MIC for ceftolozane/tazobactam versus meropenem
- To compare the superinfection and new infection rate for ceftolozane/tazobactam versus meropenem

- To compare the emergence of nonsusceptibility to study drug for ceftolozane/tazobactam versus meropenem
- To compare the time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen
- To compare the incidence of 4-fold increases in MIC (ceftolozane/tazobactam versus meropenem) for subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 μg/mL)
- To evaluate the pharmacokinetics of ceftolozane/tazobactam
- To compare the health economics outcomes, including total number of days in hospital, proportion of patients discharged from the acute care hospital, number of days in ICU, and number of days on a ventilator, of ceftolozane/tazobactam and meropenem in adults subjects with VNP within 28 days after randomization
- To evaluate the change in procalcitonin from baseline to Day 3 and to EOT

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a prospective, randomized, double-blind, multicenter, Phase 3 study to assess the safety and efficacy of ceftolozane/tazobactam 3000 mg (comprising 2000 mg ceftolozane and 1000 mg tazobactam) q8h administered as an IV infusion in the treatment of adult subjects with VNP (including VABP and ventilated HABP subjects), compared with meropenem 1000 mg q8h administered as an IV infusion.

Approximately 726 subjects will be enrolled and randomized 1:1 to receive either ceftolozane/tazobactam or meropenem. Randomization will be stratified by diagnosis (VABP or ventilated HABP) and by age (≥65 or <65 years) to facilitate balanced distribution of high-risk subjects between the 2 treatment arms. The number of subjects enrolled with VABP will be at least 50% of the randomized population.

Figure 1 presents a schematic of the study design. Subject participation will require a minimum commitment of 36 days and a maximum of 51 days. All screening assessments for study eligibility must occur within 24 hours before administration of the first dose of study drug. However, baseline LRT specimens for quantitative culture, LRT specimens for Gram stain, and serum procalcitonin levels may be obtained up to 36 hours before receipt of first dose of study drug.

The duration of study drug administration will be a minimum of 8 days (24 doses) and up to a maximum of 14 days (42 doses) [20]. The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of dummy infusions. In subjects with *P. aeruginosa* isolated from the baseline LRT culture, a treatment duration of 14 days is strongly recommended for study drug administration. Subjects must remain hospitalized throughout the treatment period and complete all study treatment intravenously. No oral switch is permitted in this study.

Table 6 presents a Schedule of Assessments.

Figure 1: Study Design

Screening	Treatment	EOT	D 14[a]	TOC	D 28[a]	LFU
Day -1 to 1	Days 1 to 14	Within 24 hours after last dose of study drug	Day 14	7-14 days after the EOT	Day 28	28 to 35 days after the EOT
Assess eligibility Collect LRT specimen Randomize to treatment	Infuse blinded IV study therapy (ceftolozane/tazobactam 3000 mg q8h or meropenem 1000 mg q8h) Total duration of study drug administration is a minimum of 8 days (24 doses) and a maximum of 14 days (42 doses)[b]	Evaluation for assessment of microbiological response, clinical response, and safety	Assess for All-cause mortality	Subjects return to study center for primary assessment of microbiological response, clinical response, and safety	Assess for All-cause mortality	Evaluation for final assessment of clinical response and safety

EOT = end-of-therapy visit; IV=intravenous; LFU = Late Follow-up visit; LRT= lower respiratory tract; q8h=every 8 hours; TOC = Test-of-cure visit; D = day; mg = milligram.

[a] If TOC visit and LFU visit are not on Day 14 and Day 28, respectively, an assessment of all-cause mortality must be conducted independently.

[b] The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of dummy infusions.

Table 6: Schedule of Assessments

	Screening	Treatment Period						Post Treatment Period				
	D-1 to 1[a]	D1	D2	D3	D4-7	D8	D9-14[b]	EOT/ Early Term	Day 14	TOC (7-14 days after EOT)	Day 28	LFU (28-35 days after EOT)[c]
General Procedures/Assessments												
Informed consent[d]	x											
Assess Inclusion/Exclusion Criteria	x											
Randomization	x											
Ceftolozane/tazobactam or meropenem administration		x	x	x	x	x	x					
Clinical Procedures/Assessments												
Medical history (including height and weight and demographics) [e]	x											
Calculate APACHE II score [f]	x											
Assess need for adjunctive gram-negative coverage	x											
Empiric baseline linezolid administration [g]		x	x	x	x[i]	x[i]	x[i]					
Discontinue empiric gram-negative adjunctive therapy (if started at baseline) [h]				x								
Capture clinical presentation of the subject in eCRF (ie, responding or not responding to treatment)				x								
Complete physical examination	x											
Focused pulmonary examination	x	x	x	x	x	x	x	x		x		x[i]

	Screening	Treatment Period						Post Treatment Period				
	D-1 to 1[a]	D1	D2	D3	D4-7	D8	D9-14[b]	EOT/ Early Term	Day 14	TOC (7-14 days after EOT)	Day 28	LFU (28-35 days after EOT)[c]
Assessment of clinical symptoms of pneumonia	x	x	x	x	x	x	x	x		x		x
Assessment of severity of lung injury (PaO_2/FiO_2)	x	x[q]	x[q]	x[q]	x[q]	x[q]	x[q]	x[q]		x[q]		x[i,q]
Temperature and vital signs	x	x	x	x	x	x	x	x		x		x[i]
Assess for prior/concomitant medications	x	x	x	x	x	x	x	x		x		x
Assess for concomitant pulmonary procedures		x	x	x	x	x	x	x				
Assess for adverse events		x	x	x	x	x	x	x		x		x
Radiology Procedures/Assessments												
Chest X-ray/CT scan	x		x[i]	x[i]	x[i]	x[i]		x[i]				
Microbiology Procedures/Assessments												
Blood sample for aerobic blood cultures	x		x[i]	x[i]	x[i]	x[i]	x[i]	x[i]				
Respiratory sample Gram stain	x[j,r]											
Obtain quantitative LRT culture[k]	x[j]	x[l]	x[l]	x[l]		x[l]		x[i,l]		x[i,l]		
Laboratory Procedures/Assessments												
Blood samples for serum hematology and chemistry evaluations	x			x		x		x		x		x[i]
Serum creatinine and calculated CL_{CR}[m]	x											
Serum procalcitonin	x[j]	x	x	x		x		x		x		
C-reactive protein	x	x	x	x		x		x		x		
Direct Coombs' test	x							x				
Serum pregnancy test	x											

	Screening	Treatment Period						Post Treatment Period				
	D-1 to 1[a]	D1	D2	D3	D4-7	D8	D9-14[b]	EOT/ Early Term	Day 14	TOC (7-14 days after EOT)	Day 28	LFU (28-35 days after EOT)[c]
Blood samples for WBC count (with differential)	x[n]	x	x	x	x	x	x	x		x		x[i,]
Pharmacokinetic Sampling					x[o]							
Assess components of the CPIS	x											
Assess Components of the SOFA Score	x											
Efficacy Procedures/Assessments												
Assess clinical response								x		x		x
Assess for all-cause mortality[p]									X		x	

APACHE=Acute Physiology and Chronic Health Evaluation; BAL=Bronchoalveolar lavage; CL_{CR} = Creatinine clearance; CPIS=Clinical Pulmonary Infection Score; CT=computed tomography; eCRF=Electronic case report form; EOT=End-of-therapy; ETA=Endotracheal aspirate; D=Day; LFU=Late Follow-up; LRT=Lower respiratory tract; PBS=Protected brush specimen; SOFA=Sepsis Organ Failure Assessment; TOC=Test-of-cure; WBC=white blood cell; $PaO_2/FiO2$ = partial pressure of oxygen to the fraction of inspired oxygen.

[a] Prior to study drug administration. Note, there is no Study Day 0.
[b] Applies to subjects receiving greater than 8 days of study treatment.
[c] LFU visit may be conducted by telephone if the subject does not have any known adverse events or laboratory abnormalities that require an in-person follow-up assessment.
[d] Informed Consent Form may be signed up to 72 hours before receipt of first dose of study drug.
[e] The medical history will also include reviews of the subject's significant baseline comorbidities.
[f] Modified APACHE II score can be used. See Section 11.1.3.
[g] Alternatives to linezolid may be permitted following prior documented approval by the medical monitor.
[h] Assess when results of the baseline LRT culture are available (within 72 hours of starting study drug).
[i] If applicable and clinically indicated.
[j] May be obtained up to 36 hours before receipt of first dose of study drug.
[k] BAL (or mini-BAL) or PBS are strongly recommended for obtaining the LRT specimen, when these modalities are available at the site. If ETA is used, refer to Section 11.3.2. Sputum specimens may be used for post baseline LRT specimens only in extubated subjects.
[l] Only required in intubated subjects.
[m] Serum CL_{CR} may be performed locally as frequently as clinically indicated to guide appropriate drug therapy in subjects with renal impairment.
[n] Blood sample for WBC count with differential must include a band count, for determining the CPIS.
[o] If blood samples cannot be collected on Day 4, samples can be collected after Day 4 and within the treatment period, but preferably between Day 4 and Day 6.
[p] If the TOC visit and the LFU visit are on Day 14 and Day 28, respectively, the assessment of all-cause mortality should be done at these visits.
[q] O_2 saturation may be substituted for PaO_2 in subjects who do not have an arterial line or in whom drawing an arterial blood gas would not be considered standard of care. See Appendix E.
[r] Results of the baseline Gram stain are not required if the subject has a lower respiratory tract culture obtained within 72 hours prior to the first dose of study drug confirming the presence of a gram-negative pathogen. For LRT samples collected by ETA, the adequacy of the sample (based on polymorphonuclear and squamous cell count) must still be assessed.

7.2. Study Visits

7.2.1. Screening (Baseline)

Baseline (screening) assessments are to be performed within 24 hours before the start of administration of the first dose of study drug. However, baseline LRT specimen for quantitative culture and Gram stain, and baseline serum procalcitonin levels may be obtained up to 36 hours before receipt of the first dose of study drug. The Informed Consent Form may be signed up to 72 hours before receipt of first dose of study drug.

All results of baseline study assessments required to fulfill the eligibility criteria (with the exception of the baseline LRT culture result) must be available before randomization and administration of the first dose of study drug. For a complete list of assessments refer to the Schedule of Assessments (Table 6).

NOTE: Local (ie, site) or regional laboratory results will be used to determine subject eligibility for study enrollment as well as for the ongoing management of the subject during the treatment period.

7.2.2. Treatment Period

The duration of study drug administration will be a minimum of 8 days (24 doses) and up to a maximum of 14 days (42 doses). The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of dummy infusions. In subjects with *P. aeruginosa* isolated from the baseline LRT culture, a treatment duration of 14 days is strongly recommended for study drug administration.

For study days occurring during the treatment period, all study assessments are to be performed when applicable. For study assessments that are to be performed daily, the assessments are to be performed preferably at a consistent time, for each calendar day.

For a complete list of assessments, refer to the Schedule of Assessments (Table 6).

7.2.3. End-of-therapy Visit

The EOT visit must occur within the 24 hours following the completion of the last dose of study drug.

For a complete list of assessments, refer to the Schedule of Assessments (Table 6).

7.2.4. Test-of-cure Visit

The TOC visit should occur within 7 to 14 days after the EOT visit.

For a complete list of assessments, refer to the Schedule of Assessments (Table 6).

7.2.5. Late Follow-up Visit

The LFU visit should occur within 28 to 35 days after the EOT visit. The LFU visit may be conducted by telephone to assess the subject's wellbeing if the subject does not have any known AEs or laboratory abnormalities that require an in-person follow-up assessment. If subjects have symptoms suggestive of respiratory infection during the telephone interview, an in-person visit must be scheduled. Subjects who are still hospitalized at the time of the LFU evaluation will have an in-person visit.

For a complete list of assessments, refer to the Schedule of Assessments (Table 6).

7.3. Number of Subjects

Approximately 726 subjects will be randomized.

7.4. Treatment Assignment

Subjects will be randomized 1:1 to receive either ceftolozane/tazobactam 3000 mg every 8 hours by IV infusion or meropenem 1000 mg every 8 hours by IV infusion. All IV infusions will be administered as a 60 (±10)-minute infusion, with a (±) 2-hour dosing window.

Randomization will be stratified by diagnosis (VABP or ventilated HABP) and age (≥65 or <65 years) to facilitate balanced distribution of high-risk subjects between the 2 treatment arms. The number of subjects enrolled with VABP will be at least 50% of the randomized population.

7.5. Dose Adjustment Criteria

Dose adjustments will be made based on subject CL_{CR} levels as shown in Table 7 and Table 8.

A dummy infusion is not required in cases where dosing every 8 hours is used for both ceftolozane/tazobactam and meropenem.

Conversely, to maintain blinding of the dosing regimens when meropenem is required to be dosed q12h, the treatment schedule must be adjusted to four infusions per day by adding dummy infusion(s). These four infusions (active plus dummy) are to accommodate the three q8h infusions for ceftolozane/tazobactam and the two q12h infusions for meropenem. Note: The first study drug infusion subjects receive following randomization must always be active study drug (ie, either ceftolozane/tazobactam or meropenem) and NOT a dummy infusion; see Table 9.

Dose adjustments for renal insufficiency will be performed by the unblinded pharmacist following notification from the Investigator, including the subject's CL_{CR} value.

Refer to the pharmacy manual for specific instructions regarding preparation of doses following adjustments.

Table 7: Dose Adjustments for Subjects Randomized to Ceftolozane/tazobactam Intravenous 60-minute Infusions

Renal Function	Dose	Infusion Frequency
CL_{CR} >50 mL/min	3000 mg IV (comprising 2000 mg ceftolozane and 1000 mg tazobactam)	q8(±2)h
CL_{CR} 30 - 50 mL/min	1500 mg IV (comprising 1000 mg ceftolozane and 500 mg tazobactam)	q8(±2)h
CL_{CR} 26 - 29 mL/min	750 mg IV (comprising 500 mg ceftolozane and 250 mg tazobactam)	q8(±2)h
CL_{CR} 15 - 25 mL/min	750 mg IV (comprising 500 mg ceftolozane and 250 mg tazobactam)	q8(±2)h
CL_{CR} <15 mL/min	Discontinue study drug	

CL_{CR}=creatinine clearance; IV=intravenous; q8h=every 8 hours.

Table 8: Dose Adjustments for Subjects Randomized to Meropenem Intravenous 60-minute Infusions

Renal Function	Dose	Infusion Frequency
CL_{CR} >50 mL/min	1000 mg IV	q8(±2)h
CL_{CR} 30 - 50 mL/min	1000 mg IV	q12(±2)h
CL_{CR} 26 - 29 mL/min	1000 mg IV	q12(±2)h
CL_{CR} 15 - 25 mL/min	500 mg IV	q12(±2)h
CL_{CR} <15 mL/min	Discontinue study drug	

CL_{CR}=creatinine clearance; IV=intravenous; q8h=every 8 hours; q12h=every 12 hours.

Subjects with CL_{CR} ≤50 mL/min, based on the treatment randomized, should be dosed as shown in Table 9. The first study drug infusion subjects receive following randomization must always be active study drug (ie, either ceftolozane/tazobactam or meropenem) and not a dummy (saline) infusion.

Table 9: Dosing Schedule for Subjects with CL_{CR} ≤50 mL/min

Elapsed Time (h)	Randomized to ceftolozane/tazobactam	Randomized to meropenem
First dose*	Active ceftolozane/tazobactam	Active meropenem infusion
01:00		
02:00		
03:00		
04:00		
05:00		
06:00		
07:00		
08:00	Active ceftolozane/tazobactam	Dummy (saline) infusion
09:00		
10:00		
11:00		
12:00	Dummy (saline) infusion	Active meropenem infusion
13:00		
14:00		
15:00		
16:00	Active ceftolozane/tazobactam	Dummy (saline) infusion
17:00		
18:00		
19:00		
20:00		
21:00		
22:00		
23:00		

CL_{CR} = creatinine clearance; h = hours

*The first study drug infusion subjects receive following randomization must always be active study drug (ie, either ceftolozane/tazobactam or meropenem) and not a dummy (saline) infusion

Subjects who develop a CL_{CR} <15 mL/minute or who are placed on dialysis or hemofiltration must be withdrawn from study drug because dose recommendations of ceftolozane/tazobactam for such subjects have not yet been determined. These subjects will continue to be followed through the LFU visit. For additional subject withdrawal criteria, please refer to Section 8.3.

7.6. Criteria for Study Termination

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

To be eligible for enrollment, a subject must satisfy all of the following entry criteria before they will be allowed to participate in the study and prior to any study related procedures:

1. Provide written informed consent prior to any study-related procedure not part of normal medical care. If the subject is unable to do so, local country laws and institution-specific guidelines and requirements in place for obtaining informed consent should be met. A legally acceptable representative may provide consent, provided this is approved by local country and institution-specific guidelines. If a subject comes to consciousness while still in the study and per the Investigator's judgment the subject is able to read, assess, understand, and make his/her own decision to participate in the trial, the subject can agree to continue study participation and the subject may be re-consented, if required by local country and institution-specific guidelines;
2. Be males or females aged 18 years or older;
   If female, subject must not be pregnant or nursing, and is either:
   - Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or
   - Of childbearing potential and meets at least 1 of the following:
     - Is practicing an effective method of contraception (eg, oral/parenteral contraceptives plus barrier method), or
     - Has a vasectomized partner, or
     - Is currently abstinent from sexual intercourse.

   Subjects must be willing to practice the chosen contraceptive method or remain abstinent during the conduct of the study and for at least 35 days after last dose of study medication.
   Non-vasectomized males are required to practice effective birth control methods (eg, abstinence, use of condom, or use of other barrier device) during the treatment period and for at least 75 days after last dose of study medication;
3. Intubated (via endotracheal tube, including tracheostomy patients) and on mechanical ventilation at the time of randomization:

   <u>For ventilated HABP:</u>

   - At least 1 of the following signs and/or symptoms must be present within the 24 hours **prior** to intubation OR within the 48 hours **after** intubation in a patient who has been either hospitalized for ≥48 hours or who has been discharged from a hospital within the prior 7 days (includes patients institutionalized in skilled nursing or other long-term care facility):
     - A new onset of cough (or worsening of baseline cough)

- Dyspnea, tachypnea, or respiratory rate greater than 30 per minute, particularly if any or all of these signs or symptoms are progressive in nature
- Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air, OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air, OR worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2)

For VABP:

- Receiving mechanical ventilation ≥48 hours and at least one of the following:
  - Acute changes made in the ventilator support system to enhance oxygenation, as determined by worsening partial pressure of oxygen on arterial blood gas, or worsening PaO_2/FiO_2
  - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air (or FiO_2 equivalent), OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air (or FiO_2 equivalent), OR worsening PaO_2/FiO_2.

4. Chest radiograph obtained within the 24 hours prior to the first dose of study drug shows the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia (based on Investigator evaluation or report from a qualified medical professional who is not the Investigator). A computed tomography (CT) scan may be used in place of a chest X-ray.
5. Have the following clinical criteria within the 24 hours prior to the first dose of study drug:

- Purulent tracheal secretions
- And at least 1 of the following:
  - Documented fever (body temperature ≥38°C [100.4°F])
  - Hypothermia (body temperature ≤35°C [95.2°F])
  - White blood cell (WBC) count ≥10,000 cells/mm^3
  - WBC count ≤4,500 cells/mm^3
  - ≥15% immature neutrophils.

6. Have a baseline lower respiratory tract specimen obtained for Gram stain and quantitative culture within 36 hours prior to the first dose of study drug. This specimen can be obtained by a bronchoalveolar lavage (BAL), nonbronchoscopic BAL (mini-BAL), protected brush specimen (PBS), or an endotracheal aspirate (ETA);

   Note: ETA specimens with an average of ≥10 squamous epithelial cells or ≤25 polymorphonuclear cells per low power field will be considered

inadequate, and a repeat specimen that is adequate will need to be obtained for Gram stain and subsequent quantitative culture.

Note: If BAL, mini-BAL, or PBS is available at the site, these modalities are strongly recommended rather than an ETA for obtaining the baseline LRT specimen.

7. Willing and able to comply with all study procedures and restrictions.

8.2. Subject Exclusion Criteria

A subject will not be enrolled if the subject meets any of the following criteria:

1. Any of the following diagnoses or conditions that interfere with the assessment or interpretation of outcome:
   - Atypical, viral, or fungal (including *Pneumocystis jiroveci*), known or suspected community-acquired bacterial pneumonia
   - Tracheobronchitis (without documented pneumonia), chemical pneumonitis, or postobstructive pneumonia
   - Active primary or metastatic lung cancer
   - Pleural effusions (or empyema) requiring therapeutic drainage, lung abscess, or bronchiectasis
   - Cystic fibrosis, acute exacerbation of chronic bronchitis, or active pulmonary tuberculosis
   - New York Heart Association (NYHA) Stage IV Congestive Heart Failure or Cirrhotic Liver Disease
   - Full thickness burns (greater than 15% of total body surface area)
   - Severe confounding respiratory condition due to penetrating chest trauma (ie, chest trauma with paradoxical respiration)
2. 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 subject (eg, a subject with history of a mild rash followed by uneventful re-exposure may be considered for enrollment)
3. Received systemic or inhaled antibiotic therapy effective against gram-negative pathogens that cause VNP, for >24 hours (ie, >1 dose of a once daily antibiotic, >2 doses of a twice daily antibiotic, etc.) in the 72 hours prior to the first dose of study drug. Drugs with only gram-positive activity [eg, daptomycin, vancomycin, linezolid] are allowed.

   Exceptions:
   - Persistent/worsening signs and/or symptoms of VNP are still present despite ≥48 hours of antibiotic therapy for the treatment of the current VNP, and (a) a LRT culture obtained while the subject is on the failing antibiotic therapy for this episode of VNP showed growth of a gram-negative pathogen and (b) the isolated pathogen is not known to be resistant to one of the study drugs.

- Signs and/or symptoms of VNP develop after receiving ≥48 hours of antibacterial therapy for treatment of an infection other than the current VNP. NOTE: Subjects on ≥48 hours of antibiotics for infection prophylaxis (rather than treatment of a documented or suspected infection) are not eligible for enrollment under this exception.
- Treatment with a non-absorbed antibiotic used for gut decontamination (eg, low-dose erythromycin) or to eradicate *C. difficile*.

4. Baseline Gram stain shows the presence of only gram-positive bacteria.

   Exception: If the subject has a lower respiratory tract culture growing a gram-negative pathogen obtained within 72 hours prior to the first dose of study drug, these results will supersede baseline Gram stain results of only gram-positive bacteria.

5. Active immunosuppression, including human immunodeficiency virus (HIV) with a known CD_4 count of <200 cells/mm^3, active hematological malignancy, recipients of solid organ or bone marrow transplants, subjects currently on immunosuppressive therapy including cancer chemotherapy, medications for prevention of transplant rejection, or chronic administration of corticosteroids (defined as >40 mg of prednisone per day administered continuously for more than 14 days prior to the first dose of study drug);
6. Receipt of >24 hours of a carbapenem within 7 days prior to the first dose of study drug;
7. Growth of a meropenem-resistant or ceftolozane/tazobactam-resistant, gram-negative pathogen from a respiratory or blood culture, within 15 days prior to the first dose of study drug;
8. Development of end-stage renal disease defined as a CL_{CR} <15 mL/min, OR requirement for peritoneal or hemo-dialysis or hemofiltration, OR a urine output <20 mL/hour over a 24-hour period;
9. The presence of any of the following:
   - Alanine aminotransferase **(**ALT) or aspartate aminotransferase **(**AST) >3 × upper limit of normal (ULN)
   - Total bilirubin >2 × ULN
   - Alkaline phosphatase >4 × ULN.

   Note: Subjects with an alkaline phosphatase value >4 × ULN and <5× ULN are eligible if this value is historically stable.
10. Hematocrit <21% or hemoglobin <7 gm/dL;
11. Neutropenia with absolute neutrophil count <500/mm^3;
12. Platelet count <50,000/mm^3;
13. Expected survival <72 hours;
14. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of study data;

15. Participation in any clinical study of a therapeutic investigational product within 30 days prior to the first dose of study drug;
16. Previous participation in any study of ceftolozane or ceftolozane/tazobactam;
17. Employees of the Investigator or study center, directly involved in the study or other studies conducted by the Investigator or study center, as well as family members of the employees or the Investigator.
18. Anticipated concomitant use of any of the following medications during the course of study therapy (through the EOT visit): valproic acid or divalproex sodium. For subjects who will receive linezolid as gram-positive adjunctive therapy, anticipated concomitant use of serotonin re-uptake inhibitors, tricyclic antidepressants, or serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone during the course of linezolid treatment.
19. For subjects who will receive linezolid as gram-positive adjunctive therapy, receipt of a monoamine oxidase inhibitor within 14 days prior to the first dose of study drug or anticipated concomitant use during linezolid therapy.

8.3. Subject Withdrawal Criteria

8.3.1. Early Termination

Subjects will be informed that they have the right to discontinue study participation at any time without prejudicing their medical care and are not obliged to state their reasons. Subjects that discontinue for any reason should be asked to provide the reason(s) for discontinuation and assessments should be performed as outlined in the Schedule of Assessments (Table 6). Any discontinuations must be fully documented in the electronic case report form (eCRF).

8.3.2. Criteria for Premature Discontinuation of Study Drug or Subject Withdrawal from Study

Subjects should be encouraged to complete all study assessments. However, subjects retain the right to withdraw consent to participate in this study at any time without penalty or loss of benefits to which they are otherwise entitled. For all subjects who prematurely withdraw consent from participation in the study, the subject will be queried to investigate the root cause for withdrawal of participation.

Subjects may be prematurely discontinued from study medication, at the discretion of the Investigator, should any untoward effect occur (including an AE or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug administration).

In addition, subjects may be prematurely discontinued from study medication, at the discretion of the Investigator, for insufficient therapeutic effect. An insufficient therapeutic effect may be determined any time before the scheduled completion of therapy. This determination will require an overall assessment of clinical status based on signs and symptoms and available laboratory data.

The following reasons require premature discontinuation from study drug administration per protocol:

- Subjects in whom **all** baseline gram-negative LRT pathogens are resistant to both study drugs.
- Investigator decides to continue (or add) gram-negative adjunctive therapy beyond 72 hours of treatment or if the Investigator decides to add to or change the study treatment post baseline.
- Development of end stage renal disease defined as a CL_{CR} less than 15 mL/min or oliguria (less than 20 mL/h urine output over 24 hours), or if dialysis or hemofiltration is required while the subject is receiving study drug therapy.
- Suspected or confirmed pregnancy or nursing during the study drug administration period. Female subjects whose pregnancy test becomes positive during study therapy must stop study drug immediately and be followed through the immediate postnatal period or until termination of the pregnancy.

All subjects who prematurely discontinue study drug, regardless of the reason, should be followed for safety through the LFU visit.

8.3.3. Procedures for Premature Discontinuation of Study Drug

Discontinuations must be fully documented in the subject's medical record and in the eCRF. All efforts must be made to complete and report the required observations as thoroughly as possible.

Each subject who discontinues early from study drug therapy is to undergo EOT evaluations on the day of discontinuation. In this case, only the assessments required for the EOT visit must be performed and recorded in the eCRF. The subject should return 7 to 14 days after EOT for a TOC evaluation, and should return to the study site or be contacted a minimum of 28 days and a maximum of 35 days after EOT for a LFU assessment. See Table 6 for a complete list of assessments to be performed.

8.3.4. Replacement Policy

Randomized subjects will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

9.1.1. Investigational Product: Ceftolozane/tazobactam

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

Product Name:	Ceftolozane/tazobactam
Dosage Form:	IV infusion over 60 (±10) minutes
Unit Dose:	3000 mg (2000 mg ceftolozane and 1000 mg tazobactam) q8h
Route of Administration:	Intravenous

9.1.2. Active Comparator: Meropenem

Product Name:	Meropenem
Dosage Form:	IV infusion over 60 (±10) minutes
Unit Dose:	1000 mg q8h
Route of Administration:	Intravenous

9.2. Prior, Concomitant, and Adjunctive Medications and Procedures

All **nonantibiotic** medications given within 7 days prior to the first dose of study drug through the EOT visit must be recorded in the appropriate section of the eCRF. After the EOT visit through the LFU visit, only nonantibiotic medications given for the treatment of pneumonia or sepsis should be recorded in the eCRF.

All **nonstudy antibiotics** given up to 14 days prior to the first dose of study drug through the LFU visit should be recorded in the eCRF.

All concomitant diagnostic and therapeutic pulmonary procedures after the administration of the first dose of study drug through the LFU visit should be collected in the eCRF.

9.2.1. Prohibited Medications

Concomitant use of valproic acid or divalproex sodium during the course of study therapy is prohibited.

For subjects who will receive linezolid as gram-positive adjunctive therapy, the following are prohibited:

- Prior use of a monoamine oxidase inhibitor within 14 days of the first dose of linezolid.
- Concomitant use of any of the following medications during linezolid therapy:
    - serotonin re-uptake inhibitors,

- tricyclic antidepressants,
- serotonin 5-HT1 receptor agonists (triptans),
- meperidine,
- buspirone, or
- monoamine oxidase inhibitors.

9.2.2. Nonstudy Antibiotic Use

In the 72 hours preceding the first dose of study drug for treatment of the current VNP, subjects may not receive ***more than 24 hours*** (ie, >1 dose of a once daily antibiotic, >2 doses of a twice daily antibiotic, etc.) of antibiotic therapy active against gram-negative pathogens known to cause VNP. Exceptions to this prior antibiotic rule are noted in Section 8.2 under Exclusion criteria #3.

After randomization, nonstudy antibiotics for the treatment of VNP are not permitted except in the following circumstances:

- Allowed empiric adjunctive therapy (as described in Section 9.2.3) administered at baseline for potential resistant pathogens, OR
- For treatment of documented clinical and/or microbiologic failure.

If nonstudy antibiotics for the treatment of VNP are required after randomization, the subject must be discontinued from study treatment (see Section 8.3.2).

9.2.3. Guidance on Empiric Adjunctive Therapy

9.2.3.1. Gram-positive Adjunctive Therapy

Because ceftolozane/tazobactam has limited activity against *S. aureus* and both ceftolozane/tazobactam and meropenem are inactive against methicillin-resistant *S. aureus* (MRSA), empiric therapy at baseline with linezolid 600 mg every 12 hours IV is required in all subjects pending baseline LRT culture results. In this study, linezolid is the preferred agent for gram-positive adjunctive therapy because of its proven activity against both methicillin-susceptible *S. aureus* (MSSA) and MRSA and its convenience of administration compared to vancomycin [21].

Alternatives to linezolid may be permitted if these are standard of care at the site and are an effective treatment for gram-positive pneumonia (ie, daptomycin and tigecycline are not acceptable alternatives). Approval of linezolid alternatives should be obtained from the Medical Monitor prior to first subject being enrolled at the site. At sites with a low incidence of MRSA pneumonia (eg, MRSA prevalence <5% as determined by the local antibiogram), the Investigator may request, from the Medical Monitor, substitution of linezolid with a semisynthetic, anti-staphylococcal penicillin (eg, nafcillin). Semisynthetic penicillins with gram-negative activity (ie, ampicillin) are not acceptable alternatives for linezolid. For subjects who do not tolerate linezolid, or in whom linezolid is contraindicated, alternatives are permitted. In all cases, any substitution gram-positive adjunctive therapy must not have any activity against gram-negative bacteria. Such cases should be discussed with the Medical Monitor prior to or within 24 hours following dosing.

If *S. aureus* is isolated from the baseline LRT culture, gram-positive adjunctive therapy should be continued for a ***minimum*** of 8 days. See Section 9.2.3.3 for further guidance

on the management of gram-positive adjunctive therapy following baseline LRT culture results.

9.2.3.2. Gram-negative Adjunctive Therapy

To protect subjects who may be at risk for LRT infections caused by gram-negative pathogens potentially resistant to 1 or both study therapies, empiric adjunctive gram-negative therapy with IV amikacin will be permitted at baseline, at sites where the local prevalence of meropenem-resistant *P. aeruginosa* is at least 15% (eg, as determined by the local antibiogram).

The recommended dose of IV amikacin is 15 mg/kg daily; the dose may be adjusted for creatinine clearance per standard of care at the site. Alternative aminoglycosides may be permitted if these are standard of care at the site. Approval of amikacin alternatives should be obtained from the Medical Monitor prior to first subject being enrolled at the site. For subjects who do not tolerate amikacin, or in whom amikacin is contraindicated, alternatives are permitted. Such cases should be discussed with the Medical Monitor prior to or within 24 hours following dosing.

The ***maximum*** duration of gram-negative adjunctive therapy started at baseline is 72 hours, at which time the results of the baseline LRT culture should be available. See Section 9.2.3.3 for further guidance on the management of gram-negative adjunctive therapy following baseline LRT culture results.

9.2.3.3. Guidance on Study Drug Therapy following Baseline Culture Results

Susceptibility testing to both study drugs (and adjunctive therapy, as appropriate) is required for all gram-negative pathogens isolated and will be conducted at the local microbiology laboratory. Susceptibility testing methods (eg, MIC gradient test strips) will be provided to all sites, however other standard and validated testing methods may be used if available.

Upon availability of the **baseline** LRT culture and pathogen susceptibility results:

Management of study drug and empiric gram-negative adjunctive therapy:

- If **all** gram-negative isolates are resistant to both study drugs: study drug must be discontinued, appropriate nonstudy antibiotics started, and the subject followed for safety through the LFU visit.
- If gram-negative isolate(s) with varying susceptibility results is/are present: the Investigator is strongly encouraged to base decisions regarding continuation or discontinuation of study therapy on the clinical presentation of the patient and the totality of the available clinical and laboratory data, including the baseline LRT culture susceptibility testing results. Empiric gram-negative adjunctive therapy, if started at baseline, must be discontinued after 72 hours.
- If no growth of any gram-negative organism: study drug should be continued based on the discretion of the Investigator and guided by the subject's clinical response. Empiric gram-negative adjunctive therapy, if started at baseline, must be discontinued after 72 hours.

Management of empiric gram-positive adjunctive therapy:

- If *S. aureus* (MSSA or MRSA) is present [with or without a gram-negative pathogen]: linezolid should be continued for a ***minimum*** of 8 days. If MSSA is the only LRT pathogen isolated, the Investigator may switch the gram-positive adjunctive therapy to an anti-staphylococcal semisynthetic penicillin (with gram-positive coverage only) and complete treatment with the semisynthetic penicillin.
- If *S. aureus* (MRSA or MSSA) does not grow: empiric gram-positive coverage should be discontinued, unless in the opinion of the Investigator, continuation provides expected benefit for the patient. If gram-positive adjunctive therapy is discontinued and then a subsequent, post-baseline LRT culture shows presence of *S. aureus,* the appropriate gram-positive adjunctive therapy may be reinitiated (ie, linezolid if MRSA or anti-staphylococcal semisynthetic penicillin for MSSA).

In all instances above, Investigators must capture a description of the subject's clinical condition in the eCRF at the time of availability of the results of baseline LRT culture. All subjects, regardless of discontinuation or continuation of study drug, should be followed for safety through the LFU visit.

9.3. Screening, Randomization, and Blinding

9.3.1. Screening Procedure

All subjects who are screened (including screen failures) will be assigned a screening number by each site and will be documented. This will be reviewed at monitoring visits and will be part of the study record. Subjects meeting all eligibility criteria will be enrolled into the study once informed consent has been obtained.

9.3.2. Subject Identification and Numbering

Once eligibility has been determined by the inclusion and exclusion criteria, subjects will be randomized to study drug group or comparator control group and a subject identification number will be assigned based on a centralized computer-generated randomization schedule.

9.3.3. Randomization

An interactive response technologies (IRT), stratified by baseline diagnosis (VABP or ventilated HABP) and by age (≥65 or <65 years), will be used to randomize subjects (1:1) to either the ceftolozane/tazobactam or meropenem treatment group. The number of subjects enrolled with VABP will be at least 50% of the randomized population.

After informed consent has been obtained and study eligibility has been established, the study site's unblinded pharmacist or designee will obtain, via the IRT, the subject number and the study drug assignment from a computer-generated randomization schedule. Subjects are considered randomized when the unblinded pharmacist or designee obtains the subject number and study drug assignment from the IRT.

Once a subject number and treatment have been assigned to a subject, the subject identification number cannot be reused even if the subject discontinues the study early or withdraws prior to receiving any study medication. Subjects who discontinue from the study will not be permitted to re-enroll.

9.3.4. Blinding

This is a double-blinded study. The subject, site personnel (with the exception of the unblinded pharmacist), Sponsor personnel (with the exception of the unblinded drug supply and quality assurance teams, as appropriate) and Sponsor designees (with the exception of the unblinded monitoring team) will have no knowledge of treatment assignment.

Unblinded Sponsor and designee roles and responsibilities are described in the Unblinded Team Plan.

A double dummy design will be used to maintain the study blind for certain categories of renal impairment (see Section 7.5).

9.3.5. Unblinding of Subjects

A treatment assignment should only be unblinded in a situation of urgent medical necessity when the identity of the study medication must be known in order to select appropriate continuing therapy for the disease under study or to manage an AE. The decision should be made only after consultation with the Medical Monitor unless the urgency of a case requires immediate action.

When the Investigator needs to identify the study drug used by a subject and the dosage administered in case of emergency (eg, the occurrence of serious adverse experiences), he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the Investigator, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the Investigator must enter the severity of the adverse experiences observed, the relation to study drug, the reason thereof, etc., in the source documentation.

Treatment assignments can also be obtained through a controlled IRT transaction.

If a treatment code is unblinded for any reason, the Investigator will promptly notify the Medical Monitor and document who unblinded the subject, the reason for doing so, and the date of unblinding in the eCRF.

All subjects, regardless of the reason for unblinding, should be followed for safety through the LFU visit.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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

10.2. Study Drug Packaging and Labeling

Labeling and packaging of ceftolozane/tazobactam will meet applicable regulatory requirements. All drug shipment requests for ceftolozane/tazobactam will be processed and approved by the Sponsor or designee.

10.3. Study Drug Storage

Study medication must be stored in a secure, limited access area, and may be dispensed only by specifically authorized personnel (eg, pharmacist or delegate).

10.4. Study Drug Preparation

10.4.1. Ceftolozane/tazobactam

Vials of study medication must be stored under secure conditions at ≥2°C to ≤8°C (36°F to 46°F). Please refer to the Pharmacy Manual for additional storage and handling information and preparation instructions.

10.4.2. Meropenem

Meropenem should be stored as indicated in the Package Insert. Please refer to the Pharmacy Manual and Package Insert [14] for specific instructions on preparation.

10.5. Administration

Subjects will be randomized 1:1 to either ceftolozane/tazobactam 3000 mg q8h or meropenem 1000 mg q8h. All infusions will be administered intravenously as a 60 ±10-minute infusion, with a ±2-hour dosing window.

10.6. Study Drug Accountability

Unused study medication must not be discarded nor used for any purpose other than the present study. The study monitor will collect the drug accountability forms and check all study medication prior to arranging for return or destruction of all study medication.

11. ASSESSMENT OF EFFICACY

This section describes all assessments to be performed from screening through the last study evaluation. Subjects will be monitored from the first dose of study drug through the last study evaluation.

For complete details and timing of procedures and assessments please refer to the Schedule of Assessments (Table 6).

11.1. Clinical Assessments

11.1.1. Medical/Surgical History

A recent medical/surgical history (within 5 years) will be obtained and documented. In addition, significant baseline co-morbidities will be recorded in the eCRF including diabetes, congestive heart failure, chronic obstructive pulmonary disease (COPD), empyema, and pleural effusion.

11.1.2. Physical Examination and Clinical Symptom Assessment

A complete physical examination (ie, skin, eyes, ears/nose/throat, head/neck, chest, heart/vascular, abdomen, neurological [sensory and motor], musculoskeletal and extremities) including a detailed pulmonary exam, temperature, vital signs (blood pressure and heart rate), height, and weight will be performed at baseline. Core temperatures should be taken, but if a core temperature is not feasible, other standard methods are acceptable.

A clinical symptom assessment (to evaluate the presence and severity of cough [if applicable], tachypnea [if applicable], dyspnea, rigors or shaking chills, and pleuritic chest pain), temperature, vital signs, and a focused physical examination of the pulmonary system will be performed as indicated (and if applicable) at time points specified in the Schedule of Assessments (Table 6).

Whenever possible the same person should conduct the physical examination for any given subject throughout the study.

11.1.3. APACHE II Score

Record the subjects' Acute Physiology and Chronic Health Evaluation (APACHE) II score (see Appendix B). The APACHE II score used in this study is a modified version of the APACHE II score, as many subjects in this study will be sedated, making an accurate assessment of the Glasgow Coma Scale difficult. The Glasgow Coma Scale should **not** be calculated on obtunded or otherwise sedated subjects. In these subjects if a reliable pre-sedation Glasgow Coma Scale score is available, this should be used in calculating the APACHE II score. If a reliable pre-sedation score is **not** available, a score of 15 should be given for the Glasgow Coma Scale component of the APACHE II score (resulting in 0 points on this APACHE II score component).

11.1.4. Assessment of Need for Adjunctive Gram-negative Therapy at Baseline

Assess the need for empiric gram-negative adjunctive therapy at baseline.

Empiric adjunctive therapy with amikacin to cover potential meropenem-resistance will be only permitted at baseline, at sites where the prevalence of meropenem-resistant *P. aeruginosa* (as determined by the local antibiogram) is at least 15%.

11.1.5. PaO_2/FiO_2

Record subjects' PaO_2/FiO_2 to document severity of lung injury. Post-screening, in subjects without arterial access or in whom arterial blood sampling would not be considered standard of care, measurement of O_2 saturation may be substituted for the PaO_2 measurement (Appendix E).

11.1.6. Clinical Pulmonary Infection Score

Record the components required to calculate a modified clinical pulmonary infection score (CPIS), including a qualitative examination of the tracheal secretions (Appendix C).

11.1.7. Sepsis Organ Failure Assessment Score

Record the components required to calculate a System Organ Failure Assessment (SOFA) score (Appendix D).

11.1.8. Evaluation of the Baseline Lower Respiratory Tract Culture

Results of the baseline LRT culture should be available and reviewed within 72 hours of starting study drug. Guidance on the continuation or discontinuation of study drug and adjunctive therapy is provided in Section 9.2.3.3.

11.1.9. Assessment of Clinical Response

Determine clinical outcome as described in Section 13.3.1, based on an overall assessment of clinical status based on signs and symptoms and available laboratory data.

Subjects concluded to have an insufficient therapeutic effect and who discontinue study drug therapy should be considered a "clinical failure" on the day they prematurely discontinue treatment (their effective EOT visit). These subjects do not need efficacy and clinical response assessments at the TOC or LFU visits (as a clinical failure at an earlier visit is always carried forward to subsequent visits). However, these subjects should complete all other scheduled procedures required at these visits.

11.2. Chest X-ray

Obtain a chest X-ray to document the presence of new or progressive infiltrates consistent with VNP. A CT scan may be used in place of a chest X-ray. The Investigator's (or qualified designee's at the site) interpretation of the chest X-ray will be used to make the enrollment decision.

In addition to the local reading of chest X-rays, a centralized independent second evaluation of the baseline X-ray, will be conducted on all subjects enrolled in the study.

11.3. Microbiological Assessments

11.3.1. Specimens for Quantitative Lower Respiratory Tract Culture

A quantitative LRT culture obtained at baseline is required in all subjects to establish a microbiologic diagnosis of VNP. The LRT culture specimen may be obtained by any 1 of

the following techniques: BAL, mini-BAL, PBS, or an ETA. However, at sites where BAL, mini-BAL, or PBS are available, these modalities are strongly recommended, instead of an ETA, for obtaining the baseline LRT specimen.

All baseline ETA specimens should be assessed for adequacy prior to randomization. ETA specimens with an average of ≥10 squamous epithelial cells or ≤25 polymorphonuclear cells per low power field will be considered inadequate, and a repeat specimen that is adequate will need to be obtained for Gram stain and subsequent quantitative culture.

Whenever possible, it is recommended that the same method used to obtain the baseline LRT specimen be used consistently throughout the study for obtaining post-baseline LRT specimens.

For post-baseline specimens only, sputum samples may be used for extubated subjects. Sputum specimens with an average of ≥10 squamous epithelial cell or ≤25 polymorphonuclear cells per low power field on Gram stain will be considered inadequate and a repeat specimen that is adequate should be obtained.

In addition to the local microbiology testing, all locally-identified pathogens will be sent to a central microbiology laboratory for re-identification and susceptibility testing.

11.3.2. Gram Stains

At baseline, perform a Gram stain on an acceptable baseline respiratory specimen (BAL, mini-BAL, PBS and ETA). Gram stain results for the baseline respiratory specimen must be available prior to randomization As per Exclusion Criterion #4, subjects whose baseline respiratory specimen shows only gram-positive bacteria on Gram stain are not eligible for the study unless the subject has a lower respiratory tract culture growing a gram-negative pathogen obtained within 72 hours prior to the first dose of study drug (these results will supersede baseline Gram stain results of only gram-positive bacteria, refer to Section 8.2).

All ETA baseline specimens must be assessed for adequacy of the sample, regardless of the exception to Exclusion Criterion #4 noted above. An ETA specimen with an average of ≥10 squamous epithelial cells or ≤25 polymorphonuclear cells per low power field will be considered inadequate, and a repeat ETA specimen that is adequate will need to be obtained for Gram stain and subsequent quantitative culture.

11.3.3. Specimens for Blood Culture

Obtain blood samples for blood culture (1 aerobic bottle from 2 separate sites for a total of 2 aerobic bottles).

In addition to the local microbiology testing, all locally-identified pathogens will be sent to a central microbiology laboratory for re-identification and susceptibility testing.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Laboratory Assessments

Laboratory samples should be drawn at time points specified in the Schedule of Assessments (Table 6). Laboratory samples sent to the central laboratory will be used for analysis and will not be used for the subjects' real-time clinical management.

Laboratory samples necessary for the routine clinical management of the subject should be drawn and analyzed locally, as per the site's standard of care.

> **Note:** Local (ie, site) or regional laboratory results will be used to determine subject eligibility for study enrollment.

The total volume to be drawn in the study may vary based on local/regional specific laboratory requirements. Approximately 150 – 175 mL of blood per subject will be required throughout the study period for study related assessments.

12.1.1.1. Hematology and Coagulation

Hemoglobin, hematocrit, red blood cell count, WBC count (total and differential), platelets, and prothrombin time.

12.1.1.2. Blood Chemistry

Total bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, phosphorus, calcium, glucose, total protein, albumin, sodium, potassium, bicarbonate, chloride, and magnesium.

12.1.1.3. Creatinine Clearance

Estimate the subject's CL_{CR} using the subject's serum creatinine value, body weight, and the appropriate Cockroft-Gault formula below. For body weight, actual body weight should be used; use of ideal or adjusted body weight is not permitted. If actual body weight is not available, an estimation of actual body weight should be used.

For serum creatinine reported in µmol/L:

$$\text{Males: } CL_{CR}\ (\text{mL/min}) = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{0.814 \times \text{serum creatinine (µmol/L)}}$$

$$\text{Females: } CL_{CR}\ (\text{mL/min}) = 0.85x \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{0.814 \times \text{serum creatinine (µmol/L)}}$$

For serum creatinine reported in mg/dL:

$$\text{Males: } CL_{CR}\ (\text{mL/min}) = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: } CL_{CR}\ (\text{mL/min}) = 0.85 \times \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

12.1.2. Other Blood Sampling

Obtain a sample for evaluation of the direct Coombs' test, serum procalcitonin and C-reactive protein (CRP) according to the Schedule of Assessments (Table 6).

A blood specimen for WBC count (with differential) should be obtained daily.

In addition, an arterial blood gas sample should be obtained. Post-screening, the measurement of O_2 saturation may be substituted for the PaO_2 measurement in subjects without arterial access or in whom arterial blood sampling would not be considered standard of care (see Appendix E).

12.1.2.1. Pharmacokinetic Sample Collection

All sites (except at sites where the absence of key equipment [eg, refrigerated centrifuge] does not permit the site from doing so) will collect blood samples from all patients over 1 dosing interval to evaluate the PK of ceftolozane/tazobactam in adult subjects with VNP. The blood samples for determination of plasma PK will be collected on Day 4 of the treatment period. If Day 4 is not possible, PK samples can be collected after Day 4. Timing of blood samples and study drug administration will be recorded. Blood samples will be obtained at the following times relative to 1 of the 3 daily infusions:

- Immediately (within 15 minutes) before the start of a blinded study drug administration on or after Day 4;
- At the end of blinded study drug infusion (within 10 minutes after end of infusion);
- 30 to 90 minutes after the end of blinded study drug administration;
- 2.5 to 3.5 hours after the end of blinded study drug administration;
- 5.0 to 6.0 hours after the end of blinded study drug administration.

For subjects with renal impairment requiring 4 daily doses of blinded study drug, blood samples should be obtained following the first daily infusion.

12.1.2.2. Pregnancy Screen

Serum pregnancy tests will be performed for all females of child-bearing potential and for those who are less than 1 year postmenopausal.

12.2. Adverse and Serious Adverse Events

Adverse events and SAEs will be collected from administration of the first dose of study medication through the LFU visit, whether or not they are related to the study, and must be recorded on the AE and SAE eCRFs.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- An AE may be a new event or a pre-existing condition that has become aggravated or has worsened in severity or frequency.
- An AE may be a clinically significant change from baseline in physical examination, laboratory tests, or other diagnostic investigation (eg, laboratory result, X-ray finding).

Pregnancy is not an AE; however, if a female subject or the female partner of a male subject who has received at least 1 dose of study medication becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures in Section 12.5.2. If a female subject becomes pregnant during study drug administration, study drug must be stopped immediately.

Clinical failures, including the following, are NOT AEs:

- progression, relapse, or recurrence of new symptoms or complications attributable to VNP
- lack of resolution (persistence) or insufficient improvement in signs and symptoms of VNP which were present at baseline that required new or prolonged antibiotic therapy

12.2.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death; or
- Is life-threatening.

  Note: "Life-threatening" refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe;

- Requires inpatient hospitalization or prolongation of existing hospitalization.

  Note: Adverse events requiring hospital admission that are less than 24 hours in duration do not meet this criterion. However, hospitalizations of less than 24 hours that meet any other seriousness criteria must be reported as SAEs. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion;

- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;

- Is considered to be an important medical event.

Note: Important medical events are those that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

12.2.2. Overdose

An overdose is defined as a deliberate or accidental administration of study drug at a dose that is 1.5 times higher than the protocol-specified dose for the subject's renal function, with or without associated AEs. Report signs and symptoms of an overdose, if any, as AEs as described in Section 12.5.

12.2.3. Planned Hospitalization

A hospitalization planned prior to first dose of study medication is considered a therapeutic intervention and not the results of a new AE. If the planned hospitalization or procedure is executed as planned, it should be recorded in the subject's medical history. However, if complications arise during the planned hospitalization or procedure or the subject experiences an AE during the planned hospitalization or procedure, it must be reported as an AE.

12.2.4. Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, beginning immediately after administration of the first dose of study medication. Each subject will be followed for safety monitoring until the late follow-up visit in the trial as described in the Schedule of Assessments (Table 6).

- Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator.
- An AE, actions taken as a result of the AE, and follow-up results must be recorded in the eCRF, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

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

12.2.5. Monitoring of Laboratory Assessments

The Investigator will review clinical laboratory values for significance and consideration as an AE.

12.3. Relationship to Study Drug

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

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

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

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

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

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

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

12.4. Recording Adverse Events

12.4.1. Assessment of Severity

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction). The event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as

"serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

The severity of AEs will be assessed according to the following definitions:

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

12.4.2. Reference Safety Information for the Assessment of Expectedness of AEs

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

The RSI for assessing the expectedness of an AE for comparator (meropenem) in this trial can be found in the most recent clinically packaged product for the country of use.

Known signs and symptoms of VABP and ventilated HABP and known complications of mechanical ventilation listed below are considered expected events for this protocol: pneumothorax, acute lung injury, acute respiratory distress syndrome, empyema, worsening lung function, reintubation, ongoing fever, pulmonary infiltrates, increasing PaO_2/FiO_2, ongoing positive LRT culture, or elevated WBC count.

12.5. Reporting Adverse Events

12.5.1. Reporting of Nonserious Adverse Events

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

12.5.2. Reporting of Drug Exposure During Pregnancy

If a female subject or the female partner of a male subject who has received at least 1 dose of study medication becomes pregnant during the course of study, the Investigator must report this using the Pregnancy Reporting Form within 24 hours of becoming aware of the event.

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

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

12.5.3. Reporting of Expedited Safety Observations by the Investigator

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the Investigator or qualified designee to the Sponsor:

- SAE;
- Death of a subject;
- Overdose (deliberate or accidental);
- New onset of cancer.

The Investigator is to report any Expedited Safety Observations from the list above within **24 hours** of becoming aware of the event. If the observation above that is reported is also an AE, the Investigator must record the AE in the eCRF, as well as in the subject's source documentation. If not all information on the Safety Reporting Form is available at the time of the initial report, follow-up SAE reports will be completed and submitted.

The Investigator is required to follow SAEs until resolution, stabilization, or withdrawal of consent. Resolution is defined as:

- Resolved without residual effects;
- Resolved with residual effects;
- A return to baseline for a pre-existing condition;
- Fatal; or
- The Investigator does not expect any further improvement or worsening of the event.

In the event the eCRF is not available, expedited safety observations can be reported by fax or email using hardcopy forms (Appendix A). Events reported using hardcopy forms must be entered into the eCRF once it becomes available.

12.5.4. Expedited Reporting by the Sponsor to Applicable Health Authorities

The Sponsor will monitor the data for safety and manage the expedited reporting of relevant safety information to the applicable Health Authorities in accordance with applicable laws and regulations.

12.5.5. Safety Notifications by the Sponsor to Investigators

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

12.5.6. Unblinding Treatment for a Subject During the Trial

Requirements for emergency unblinding by the Investigator are detailed in Section 9.3.5. To assess an occurrence of a safety observation, the Sponsor may unblind the treatment of any subject.

13. STATISTICS

13.1. Data Collection, Processing and Reporting

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

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

The eCRFs will be completed for all subjects randomized to study treatment. The eCRFs for subjects who are randomized but not treated will be completed with all data collected at the time of subject study discontinuation. A Clinical Monitor will review the eCRFs entered by investigational staff for completeness and accuracy.

Automatic validation programs or manual checks for data discrepancies in the eCRFs may result in electronic queries generated for resolution by the investigational site. Designated Investigative site staff is required to respond to these queries and make any necessary changes to the data. After database lock, the Investigator will receive a CD-ROM of the subject data for archiving at the investigational site.

All TEAEs (events occurring from the first dose of study medication through the last study evaluation) will be recorded. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using a standard dictionary (eg, WHODrug) and Medical History will be coded using MedDRA.

An IRT will be used to allocate the randomized treatments to subjects as they are enrolled. The randomized treatment assignments will be transferred electronically for integration with the clinical study data at the appropriate time.

13.2. Statistical Considerations

13.2.1. Analysis per the US FDA

13.2.1.1. General Methodology

For analyses of dichotomous endpoints, 2-sided 95% confidence intervals (CIs) for the difference in proportions between ceftolozane/tazobactam and meropenem will be calculated, with adjustment for the study stratification factors [diagnosis (VABP or ventilated HABP) and by age (≥65 or <65 years)]. For negative endpoints, eg, Day 28 all-cause mortality, the difference will be calculated as meropenem minus ceftolozane/tazobactam; for positive endpoints, eg, clinical response at TOC, the difference will be calculated as ceftolozane/tazobactam minus meropenem. The estimated overall proportion will be calculated as a weighted average across all strata, constructed using Mehrotra-Railkar continuity-corrected minimum-risk [MRc] stratum weights [22]. The 2-sided 95% CIs for the treatment group proportions and the treatment

difference will be calculated as stratified Newcombe CIs, constructed using the MRc weights with the methods presented by Yan and Su [23].

For analysis of other secondary and exploratory dichotomous endpoints with reduced sample sizes (eg, per-pathogen microbiological response and subgroup analyses), the 2-sided 95% CIs for the treatment difference will be calculated as unstratified Newcombe CIs.

For continuous outcomes, comparisons between treatment groups will be performed using analysis of covariance (ANCOVA) with a model that contains fixed-effect terms for treatment and strata.

For time-to-event endpoints, Kaplan-Meier curves that are stratified by diagnosis (VABP or ventilated HABP) and by age (≥65 or <65 years) will be produced, along with an overall Kaplan-Meier curve. Comparisons of the survival curves between treatment groups will be based on a stratum-adjusted log-rank test. Subjects who do not have the event outcome recorded will not be excluded from these analyses, but will be right-censored as of the subject's last available evaluation, unless otherwise specified. All tests will be 2-sided and will be conducted at the 0.05 significance level.

For categorical data, descriptive statistics will consist of frequency and percentage for each category and 95% CIs will be constructed around the percentage, when appropriate. Descriptive statistics for continuous data will consist of sample size (n), mean, standard deviation, median, minimum, and maximum. Summary tables will be presented by treatment groups.

For time-to-event endpoints, summaries will include the number of subjects, the number of subjects who achieved the event of interest, the number of subjects censored and the quartiles, ie, the 25th, 50th (median) and 75th percentiles of the distribution of the event times (in days). A 95% CI will also be provided for the median event times.

13.2.1.2. Multiple Comparisons and Multiplicity Adjustments

In order to maintain an overall 1-sided 0.025 type I error rate across the primary and key secondary efficacy endpoints in the ITT population, a sequential testing approach will be used. Testing will be performed in the following sequence:

Step 1: Non-inferiority for the primary efficacy endpoint (Day 28 all-cause mortality in the ITT population) will be evaluated. If the primary efficacy endpoint demonstrates non-inferiority of ceftolozane/tazobactam to meropenem at the 1-sided 0.025 significance level, then Step 2 will be performed.

Step 2: Non-inferiority for the key secondary endpoint (favorable clinical response at the TOC visit in the ITT population) will be tested between ceftolozane/tazobactam and meropenem at the 1-sided 0.025 significance level.

13.2.2. Analysis per the EMA

13.2.2.1. General Methodology

Similar general methodologies detailed in the preceding US FDA Analyses section will be employed (see Section 13.2.1). However, a 2-sided 97.5% CI will be constructed instead of 95% CIs, regardless of the data and safety monitoring board (DSMB) review.

13.2.2.2. Multiple Comparisons and Multiplicity Adjustments

In order to maintain a 1-sided 0.0125 overall type I error rate across the primary and key secondary efficacy endpoints in the ITT population, a sequential testing approach will be used. Testing will be performed in the following sequence:

Step 1: Non-inferiority for the primary efficacy endpoint (clinical response at TOC for the ITT population) will be evaluated. If the primary efficacy endpoint demonstrates non-inferiority of ceftolozane/tazobactam to meropenem at the 1-sided 0.0125 significance level, then Step 2 will be performed.

Step 2: Non-inferiority for the key secondary efficacy endpoint (Day 28 all-cause mortality in the ITT population) will be tested between ceftolozane/tazobactam and meropenem at the 1-sided 0.0125 significance level.

13.2.3. Handling of Missing Data

Every effort should be made to collect all data at specified times, according to the schedule of study events. For all data points other than all-cause mortality, clinical, and microbiological outcomes, missing data will be handled as follows:

- Missing values for individual data points will remain missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with data available will be included in the denominators).

For all-cause mortality, missing data will be handled as follows:

- For the analysis of Day 14 and Day 28 all-cause mortality rates, subjects whose mortality outcome is missing or unknown will be analyzed as deceased on Day 14 or Day 28.
- For the analysis of time to all-cause mortality, subjects with a missing or unknown all-cause mortality status will be analyzed as follows:

    1) Assumed to have died at the time of last study contact, and

    2) Have their time to all-cause mortality censored at the time of last contact.

For clinical response, missing data will be primarily handled with a Treatment Failure Approach (TFA) for the ITT and mITT populations and with Data-as-Observed (DAO) approach for the CE and ME populations defined as follows:

- TFA: All subjects with a missing clinical response at the EOT and TOC visits will be categorized as treatment failures in the ITT and mITT populations. For the analysis of clinical response, all subjects with clinical response of missing or indeterminate who meet the population criteria (ITT or mITT, as appropriate) will be included in the denominator.
- DAO: All subjects with missing clinical response, including indeterminate, will be excluded from the CE and ME populations. A missing clinical outcome at the TOC visit will be considered an indeterminate outcome unless the clinical outcome at EOT was failure. A clinical response of failure at EOT will be carried forward to the TOC visit.

For per-pathogen microbiological outcome, missing data will be considered presumed eradication, presumed persistence or indeterminate as defined in Table 13.

For per-subject microbiological outcome, missing data will be considered presumed cure, presumed failure or indeterminate as defined in Table 14.

Handling of missing AE data and partial and missing dates is presented in detail in the SAP.

13.2.4. Populations for Analysis

The definitions of analysis populations are outlined below. Further details are provided in the SAP.

13.2.4.1. Intent-to-treat Population

The Intent-to-treat (ITT) population will consist of all randomized subjects, regardless of whether or not they go on to receive study drug. Subjects in the ITT population will be categorized based on the treatment arm that they are randomized to.

13.2.4.2. Safety Population

The Safety population is a subset of the ITT population who receive any amount (ie, full or partial dose) of study drug. All safety analyses will be performed in this population. Subjects in the Safety population will be categorized based on the actual treatment that they receive, irrespective of the treatment arm they are randomized to.

13.2.4.3. Microbiological Intent-to-treat Population

The Microbiological Intent-to-treat (mITT) population is a subset of the ITT population who receive any amount of study drug and have at least 1 bacterial respiratory pathogen isolated from the baseline LRT culture that is susceptible to at least 1 of the study drugs. Subjects with *S. aureus* as their only baseline LRT pathogen are excluded from the mITT population.

13.2.4.4. Clinically Evaluable Population

The Clinically Evaluable (CE) population is a subset of the ITT population who have received study drug, adhere to the study protocol through the TOC visit, and have an evaluable clinical outcome (either Cure or Failure) at the TOC visit (or are classified as a clinical failure prior to the TOC visit).

13.2.4.5. Microbiologically Evaluable Population

The Microbiologically Evaluable (ME) population is a subset of mITT who adhere to the study protocol through the TOC visit, have an evaluable clinical outcome (either Cure or Failure) at the TOC visit (or are classified as clinical failure prior to the TOC visit), and have at least 1 bacterial respiratory pathogen (at the appropriate colony-forming unit (CFU)/mL threshold) isolated from the baseline LRT culture that is susceptible to at least 1 of the study drugs. To be eligible for the ME population, the following quantitative bacterial counts are required: $\geq 10^5$ CFU/mL for ETA, $\geq 10^4$ CFU/mL for BAL/mini-BAL, and $\geq 10^3$ CFU/mL for PBS.

13.2.5. Study Endpoints

Study endpoints to accommodate the unique requirements of different regulatory jurisdictions, have been outlined in Table 10.

Table 10: Study Endpoints per Different Regulatory Jurisdictions

	Per the US FDA	Per the EMA
Primary Endpoint	• Day 28 all-cause mortality in the ITT population.	• Clinical response at the TOC visit in the ITT population.
Key Secondary Endpoint	• Clinical response at the TOC visit in the ITT population	• Day 28 all-cause mortality in the ITT population
Secondary Endpoints	• Clinical response at the TOC visit in the CE population • Clinical response for subjects at the TOC visit in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the mITT population • Clinical response for subjects at the TOC visit in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the mITT population • Per-subject microbiological response at TOC in the ME population • Per-pathogen microbiological response for *P. aeruginosa* at TOC in the ME population • Per-pathogen microbiological response for Enterobacteriaceae at TOC in the ME population • Per-pathogen microbiological response at TOC in the ME population • Day 28 all-cause mortality in the mITT population • Day 14 all-cause mortality in the ITT population • Clinical response at EOT in the ITT and CE populations • Clinical response at the LFU visit in the CE population • Per-subject microbiological response at EOT in the ME population • Per-pathogen microbiological response at EOT in the ME population • Per-pathogen clinical response at TOC by baseline MIC in the mITT and ME	
Exploratory Endpoints	• Time to all-cause mortality in the ITT population • Clinical response for subjects at TOC in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the ME population • Clinical response for subjects at TOC in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the ME population • Per-subject microbiological response at TOC in the mITT population • Per-pathogen microbiological response at TOC in the mITT population • Per-subject microbiological response at EOT in the mITT population • Per-pathogen microbiological response at EOT in the mITT population • Per-pathogen microbiological response by baseline MIC in the mITT and ME populations • Superinfection and new infection rates in the mITT population	

	Per the US FDA	Per the EMA
	• Emergence of nonsusceptibility to study drug in the mITT population • Time to a ≥1-log reduction in bacterial burden of the causative gram-negative pathogen(s) identified from the baseline lower respiratory specimen in the mITT and ME populations • Emergence of a 4-fold increase in MIC to study drug for treated subjects with *P. aeruginosa* or Enterobacteriaceae isolated from the baseline LRT culture (the elevated MIC must be ≥2 µg/mL) in the mITT population • Pharmacokinetics • Total number of days in hospital within 28 days after randomization for the ITT population • Proportion of patients discharged from the acute care hospital within 28 days after randomization for the ITT population • Number of days in ICU through 28 days after randomization for the ITT population • Number of days on a ventilator through 28 days after randomization for the ITT population • Change in procalcitonin from baseline to Day 3 and to the EOT visit in the ITT population.	
Safety Endpoints	Safety will be evaluated in the Safety population through review of summaries of: • Deaths and other SAEs • Adverse events • Laboratory evaluations • Vital signs • Physical examinations.	

13.2.6. Subject Disposition

Descriptive statistics of disposition information for all randomized subjects will be presented by treatment arm. The number and percent of subjects included in the various analysis populations specified in Section 13.2.4 will be provided. The number and percent of subjects who complete treatment, discontinue study medication prematurely, or discontinue the study prematurely, will be tabulated. The primary reason for premature discontinuation of study medication and/or discontinuation from study participation will be tabulated.

13.2.7. Demographics and Baseline Data

Subject demographics and baseline characteristics will be presented by treatment group. Unless otherwise noted, baseline will be the assessment obtained closest and prior to the first dose of study drug.

13.2.8. Primary Endpoint Analysis

13.2.8.1. Primary Efficacy Analysis per the US FDA

The primary statistical goal of this study for the US FDA is to establish non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in the Day 28 all-cause mortality rates using a 10% non-inferiority margin in the ITT population [24].

The hypotheses for non-inferiority are as follows where p_1 is the proportion of deceased subjects on Day 28 treated with meropenem and p_2 is the proportion of deceased subjects on Day 28 treated with ceftolozane/tazobactam:

Null Hypothesis, H_0: $p_1 - p_2 \leq -10\%$

Alternative Hypothesis, H_1: $p_1 - p_2 > -10\%$.

A 2-sided 95% CI around the difference (meropenem minus ceftolozane/tazobactam) in the Day 28 all-cause mortality rates will be constructed, adjusting for the stratification factors (diagnosis [VABP or ventilated HABP] and age [≥65 or <65 years]). The estimated overall difference in proportions between the 2 groups will be calculated as a weighted average across all strata, constructed using Mehrotra-Railkar MRc stratum weights [22]. The 2-sided 95% CI for the difference will be calculated as a stratified Newcombe CI, constructed using MRc weights with methods presented by Yan and Su [23].

Ceftolozane/tazobactam will be considered non-inferior to meropenem if the lower limit of the 2-sided 95% CI around the difference is greater than minus 10% [25].

As sensitivity analysis, a 95% CI for the difference in Day 28 all-cause mortality rates (meropenem minus ceftolozane/tazobactam) unadjusted for the stratification factors will be constructed.

13.2.8.2. Primary Efficacy Analysis per the EMA

The primary statistical goal of this study per the EMA analysis is to establish non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in clinical cure rates at TOC using a 12.5% non-inferiority margin in the ITT population.

The hypotheses for non-inferiority are as follows, where p_1 is the proportion of subjects treated with ceftolozane/tazobactam with a clinical response of cure at the TOC visit and p_2 is the proportion of subjects treated with meropenem with a clinical response of cure at the TOC visit:

Null Hypothesis, H_0: $p_1 - p_2 \leq -12.5\%$

Alternative Hypothesis, H_1: $p_1 - p_2 > -12.5\%$.

A 2-sided, 97.5% CI around the difference (ceftolozane/tazobactam minus meropenem) in the clinical cure rates at TOC will be constructed, adjusting for the stratification factors (diagnosis [VABP or ventilated HABP] and age [≥65 or <65 years]). When calculating the clinical cure rate for each treatment group, all subjects in the ITT population in each treatment group will be included in the denominator. The estimated overall difference in proportions between the 2 groups will be calculated as a weighted average across all strata, constructed using Mehrotra-Railkar MRc stratum weights [22]. The 2-sided 97.5% CI for the difference will be calculated as a stratified Newcombe CI, constructed using MRc weights with methods presented by Yan and Su [23].

Ceftolozane/tazobactam will be considered non-inferior to meropenem if the lower limit of the 2-sided 97.5% CI around the difference is greater than minus 12.5% [25].

As sensitivity analysis, a 97.5% CI for the difference in clinical cure rates at TOC (ceftolozane/tazobactam minus meropenem) unadjusted for the stratification factors will be constructed.

13.2.9. Secondary and Exploratory Endpoint Analyses

13.2.9.1. Key Secondary Endpoints per US FDA Analyses

The key secondary efficacy endpoints listed in Table 10 will be compared between ceftolozane/tazobactam and meropenem using the methodology for dichotomous endpoints described in Section 13.2.1.1. Clinical response at the TOC visit will be compared between ceftolozane/tazobactam and meropenem for the ITT populations using a 12.5% non-inferiority margin.

13.2.9.2. Key Secondary Endpoints per EMA Analyses

All key secondary efficacy endpoints listed in Table 10, will be compared between ceftolozane/tazobactam and meropenem using the methodology for dichotomous endpoints described in Section 13.2.2.1. Day 28 all-cause mortality rates in the mITT population will be compared between ceftolozane/tazobactam and meropenem using a 10% non-inferiority margin.

13.2.9.3. Other Secondary and Exploratory Endpoints (Per the USA FDA and EMA Analyses)

The proportions of subjects achieving the outcome of interest will be provided by treatment group for other dichotomous secondary efficacy and exploratory endpoints. The 2-sided, 95% (per US FDA) or 97.5% (per EMA) of the difference in proportions will be used to compare other dichotomous secondary efficacy and exploratory endpoints between ceftolozane/tazobactam and meropenem.

Stratified Kaplan-Meier method will be used to analyze time to event endpoints, eg, time to all-cause mortality in the ITT population and time to a 1-log reduction in bacterial burden of the causative gram-negative baseline LRT pathogen(s) in the mITT and ME populations.

The proportion of patients who are discharged from the acute care hospital within 28 days after randomization will be presented by treatment group for the ITT population. Descriptive statistics will also be provided for the total number of days in hospital within 28 days after randomization, the number of days in the ICU through 28 days after randomization and the number of ventilator days through 28 days after randomization by treatment group in the ITT population. Analyses will be conducted only in those patients who did not die prior to Study Day 28.

Procalcitonin levels and change from baseline to Day 3 and to EOT will also be summarized by treatment group in the ITT population. Change from baseline will be calculated for each patient at the specified time point as the value at the specified time point minus the baseline value.

Further details of statistical methods will be described in the SAP for these other secondary and exploratory endpoints.

13.2.10. Safety Analyses

13.2.10.1. Adverse Events

The incidence (n and %) of TEAEs, SAEs, and early termination of study medication and/or study participation due to an AE will be presented for subjects in each treatment arm. Additionally, AEs will be tabulated according to severity and relatedness categories as reported by the Investigator. Adverse events will be presented in tables organized alphabetically by System Organ Class and Preferred Term. Each subject will be counted only once for each AE reporting level.

13.2.10.2. Vital Signs

Vital sign data will be tabulated for actual values and change from baseline for all scheduled time points.

13.2.10.3. PaO_2/FiO_2

PaO_2/FiO_2 data will be tabulated for actual values and change from baseline for all scheduled time points.

13.2.10.4. Clinical Pulmonary Infection Score

Modified CPIS will be calculated and tabulated for actual values at baseline.

13.2.10.5. Sepsis Organ Failure Assessment Score

The SOFA score will be calculated and tabulated for actual values at baseline.

13.2.10.6. Safety Laboratory Tests

Change in laboratory assessments from baseline will be evaluated and presented by treatment group. Baseline is defined as the closest value prior to the first dose of study drug. Shifts from baseline to post-baseline grade in selected safety laboratory parameters will also be examined.

13.2.10.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug format medication dictionary.

13.2.11. Sample Size and Power Considerations

Approximately 726 subjects will be enrolled into this study, randomized 1:1 to receive ceftolozane/tazobactam or meropenem. This study is designed to show non-inferiority in the primary outcome measure of Day 28 all-cause mortality in the ITT population for the US FDA analysis. For the analysis per the EMA, this study is designed to show non-inferiority in the primary outcome of clinical cure rate in the ITT population.

13.2.11.1. Sample Size and Power Considerations per the US FDA Analysis

To demonstrate the non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in Day 28 all-cause mortality rates, using a non-inferiority margin of 10%, a sample size of 726 subjects (363 per arm) in the ITT population will have 90% power at a 1-sided significance level of 0.025, assuming a Day 28 all-cause mortality rate of 20% in both ceftolozane/tazobactam and meropenem arms. Note that due to the

planned futility look by the DSMB when approximately 30% of patients have been enrolled and completed the study, the power of the primary endpoint analysis was decreased from 92% to 90%.

13.2.11.2. Sample Size and Power Considerations per the EMA Analysis

To demonstrate the non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in clinical cure rates of VNP at the TOC visit in the ITT population, using a non-inferiority margin of 12.5%, at a 1-sided significance level of 0.0125, a sample size of 726 subjects (363 per arm) will have 85.3% power assuming a cure rate of 58.4% in both ceftolozane/tazobactam and meropenem arms. Note that due to the planned futility look by the DSMB when approximately 30% of patients have been enrolled and completed the study, the power of the primary endpoint analysis was decreased from 88.0% to 85.3%.

The cure rate assumption is based on data from a recent pivotal trial in VNP caused by predominantly gram-negative organisms [16].

13.2.12. Statistical Analysis Plans

A separate comprehensive SAP will be prepared and finalized before database lock and analysis of the data per the US FDA and EMA. The SAPs will provide detailed descriptions of the statistical methods and expand on the details provided in this protocol.

13.2.13. Pharmacokinetics

Plasma samples will be analyzed to determine plasma concentration of ceftolozane, tazobactam, and M1-tazobactam using a validated tandem mass spectrometric assay.

Detailed instructions on collecting and processing blood PK samples are provided in Table 6 and Section 12.1.2.1.

Descriptive statistics of pharmacokinetic information for subjects will be presented by, and analyzed for, the following analytes: ceftolozane, tazobactam, and M-1-tazobactam. Noncompartmental analyses will be conducted to estimate standard PK parameters such as maximum concentration achieved (C_{max}), total exposure during one dosing interval ($AUC_{0-\tau}$), steady-state volume of distribution (V_{ss}), half-life ($t_{½}$), and clearance (CL_{ss}), as allowed by the data.

As data allow, the Sponsor may explore plasma exposure-response analyses based on noncompartmental analysis of plasma PK data. In addition, the Sponsor may characterize plasma PK using population PK to predict individual exposure values for potential exposure-response analysis to determine influence of covariates, and to evaluate the probability of target attainment (plan and results, if applicable, will be documented separately).

13.3. Evaluation Criteria

13.3.1. Clinical Response Definitions

Clinical outcome assessments will be made at the EOT, TOC, and LFU visits.

13.3.1.1. Clinical Outcomes at the EOT and TOC Visit

Clinical response at the EOT and TOC visit will be classified as cure, failure, or indeterminate (Table 11). A favorable clinical response is "clinical cure."

Table 11: Clinical Response Categories at the EOT and TOC Visit

Outcome	Definition
Cure	• Complete resolution of all or most of the clinical signs and symptoms of VNP which were present at baseline, AND • No new signs, symptoms or complications attributable to VNP, AND • No additional antibiotic therapy administered for VNP*, except for the approved adjunctive therapy, AND • Patient is alive *Subjects receiving potentially effective concomitant antibiotic therapy for an indication other than VNP may still be considered a clinical cure provided they meet all other Cure criteria.
Failure	• Progression, relapse, or recurrence of new symptoms or complications attributable to VNP, OR • Lack of resolution (persistence), insufficient improvement in signs and symptoms of VNP which were present at baseline, study drug discontinuation due to resistant LRT pathogens, or need for alternative or prolonged antibiotic therapy for treatment of VNP, OR • Patient died of VNP
Indeterminate	• Subject **prematurely discontinued** study drug due to No Growth or only *S. aureus* isolated from the baseline LRT culture, OR • Study data are not available for the evaluation of efficacy for any reason including: o Lost to follow-up o Withdrawal of consent o Subject died from cause other than VNP o Randomized not treated

13.3.1.2. Clinical Outcomes at the LFU Visit

Clinical response at the LFU visit will be classified as sustained cure, relapse, or indeterminate only in subjects deemed a clinical cure at the TOC visit (Table 12). A favorable clinical response is "sustained clinical cure."

Table 12: Clinical Response Categories at the LFU Visit

Outcome	Definition
Sustained Cure	No recurrence of signs or symptoms of pneumonia and, in addition, did not receive any antibiotics for the treatment of VNP* since the TOC visit. *Subjects receiving potentially effective concomitant antibiotic therapy for an indication other than VNP may still be considered a clinical cure provided they meet all other Cure criteria.
Relapse	Recurrence of signs or symptoms of pneumonia or new radiologic evidence of pneumonia or received antibiotic after the TOC for treatment of pneumonia.
Indeterminate	• Subject **prematurely discontinued** study drug due to No Growth or only *S. aureus* isolated from the baseline LRT culture, OR • Study data are not available for the evaluation of efficacy for any reason including: – Lost to follow-up – Withdrawal of consent – Subject died from cause other than VNP – Randomized not treated

13.3.2. Microbiological Response Definitions

Microbiological outcome assessments will be made at the EOT and TOC visits. Microbiological outcome assessments will be determined by the Sponsor, based on the results of the LRT culture from the appropriate visit.

13.3.2.1. Per-pathogen Microbiologic Outcomes at the EOT and TOC Visits

Microbiological response at the EOT and TOC visits will be classified per-pathogen as eradication, presumed eradication, persistence, presumed persistence, indeterminate, and recurrence (Table 13).

Table 13: Per-pathogen Microbiologic Outcome Categories at the EOT and TOC Visits

Outcome	Definition
Eradication	Absence defined as a ≥1- log reduction in bacterial burden of the original baseline LRT pathogen AND a per pathogen count of $\leq 10^4$ CFU/mL for ETA or sputum specimens, $\leq 10^3$ CFU/mL for a BAL specimen, and $\leq 10^2$ CFU/mL for a PBS specimen) from a follow-up LRT culture.
Presumed eradication	Absence of material to culture (eg, inability to obtain a culture in an extubated subject) in a subject deemed a clinical cure.
Persistence	Continued presence of the original causative baseline pathogen(s) from a LRT culture obtained at or after EOT. Presence is defined as <1-log reduction in bacterial burden of the baseline pathogen OR $>10^4$ CFU/mL for ETA or sputum specimens, $>10^3$ CFU/mL for a BAL specimen, and $>10^2$ CFU/mL for a PBS specimen OR baseline organism is still present, but no quantitative culture count was determined.

Outcome	Definition
Presumed persistence	Absence of material to culture in a subject deemed a clinical failure.
Indeterminate	Absence of respiratory material to culture at the EOT or TOC in a subject with Indeterminate clinical response
Recurrence (at the TOC visit)[a]	Isolation of the original causative bacterial baseline pathogen(s) at the appropriate diagnostic threshold (ie, $\geq 10^5$ CFU/mL for ETA or sputum specimens, $\geq 10^4$ CFU/mL for a BAL specimen, and $\geq 10^3$ CFU/mL for a PBS specimen) from a LRT culture in a subject with documented eradication at the EOT visit

[a]Relatedness will be determined by Genus, species and antibiogram at the discretion of the Sponsor, the pathogen from the TOC visit will be further tested by pulsed field gel electrophoresis to confirm relatedness to the baseline pathogen.

13.3.2.2. Per-subject Microbiologic Outcomes at the EOT and TOC Visits

Microbiological response at the EOT and TOC visits will be classified per-subject as microbiologic cure or microbiologic failure (Table 14).

Table 14: Per-subject Microbiologic Outcome Categories at the EOT and TOC Visits

Outcome	Definition
Microbiologic cure or presumed cure	All baseline pathogens are deemed eradicated/presumed eradicated or absence of respiratory material to culture at the EOT or TOC in a subject deemed a clinical cure.
Microbiologic failure or presumed failure	Any baseline pathogen is deemed persistent/presumed persistent or absence of material to culture in a subject deemed a clinical failure.
Indeterminate	Absence of respiratory material to culture at the EOT or TOC in a subject with Indeterminate clinical response

13.3.2.3. Emergent Infection

Qualifying pathogens other than the causative baseline pathogen isolated after baseline assessment will be assessed as a superinfection or new infection (Table 15). A qualifying emergent pathogen is defined as one meeting the threshold of $\geq 10^5$ CFU/mL (for an ETA specimen), $\geq 10^4$ CFU/mL (for a BAL or mini-BAL specimen), or $\geq 10^3$ CFU/mL (for a specimen obtained by PBS).

Table 15: New Pathogens

Outcome	Definition
Superinfection	Isolation of a pathogen, other than the causative baseline pathogen, from a post baseline LRT specimen obtained while the subject is still on study therapy.
New infection	Isolation of a pathogen other than the causative baseline pathogen from an LRT culture obtained after completion of study therapy.

13.4. Data and Safety Monitoring Board

An interim review will be performed at a single pre-defined interval by an independent Data Safety Monitoring Board (DSMB) to evaluate the safety of 3000 mg of ceftolozane/tazobactam compared with meropenem. The interim analysis of safety is planned after approximately 30% of subjects have been enrolled and have completed the study. The membership of the DSMB will comprise experts in infectious diseases, critical care, and biostatistics who are well versed in clinical research.

The DSMB review will include the following:

- Incidence and distribution between treatment arms of the following: deaths, related and unrelated SAEs, drug-related AEs, and premature discontinuation of study medication due to AEs
- Day 28 all-cause mortality rate
- Clinical response at the TOC visit
- Relevant safety lab results.

The DSMB will be provided with additional data upon request. The governance of the DSMB, including its decision rules, will be specified in the DSMB charter in accordance with applicable regulatory guidance. To maintain blinding of the study staff, an independent statistical reporting group will provide data to the DSMB. The DSMB Charter along with minutes of the review meeting will be filed, as part of the Trial Master File. The minutes of the review meeting will be filed at the end of the study, after the database has been hard-locked.

Based on its review, the DSMB will make recommendations on the interim safety of ceftolozane/tazobactam compared to meropenem. The Sponsor will have the final decision regarding disposition of the study based on the DSMB's recommendation, its own review and discussions with relevant regulatory jurisdictions, as appropriate.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

- Determine the adequacy of the facilities;
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

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

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

Prior to study start, the Investigator will be informed of the anticipated frequency of the monitoring visits. The Investigator will also receive a notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or his/her sub Investigator(s) and other appropriate staff are available on the day of the visit in case any questions arise. The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.1.1. Protocol Deviations/Amendments

Any deviation from the protocol could result in a discontinuation from the study of the center involved. Both the Sponsor and the IRB/EC that granted the original approval of the study prior to their implementation (unless only logistical or administrative aspects of the trial are involved) must approve any amendment(s) to the protocol.

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

14.1.2. Discontinuation of the Study

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

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an Institutional Review Board or an Independent Ethics Committee (IRB/EC) may visit the site to perform audits or inspections, including source data verification. The purpose of a the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

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

On one or more occasions, the study site may be audited by either the Sponsor or by a third party on behalf of the Sponsor. The Investigator will be informed in advance of such a visit. On one or more occasions, the study site may be inspected by a regulatory agency.

14.3. Institutional Review Board

Prior to the initiation of the study, the Investigator will submit the following documents to an IRB/EC for approval:

- The study protocol and any amendments;
- The Informed Consent Form and any other written documents to be provided to the subject;
- Details of any compensation to subject;
- Any other requested document(s).

A copy of the approval will be sent to the Sponsor along with all other correspondence with the IRB/EC. The letter of approval should be dated and specify the protocol number and date of the protocol or amendment that was reviewed and approved. It should also specify the date of the subject Informed Consent Form that was reviewed and approved.

In order to comply with ICH GCP, the Investigator will submit a report to the IRB/EC at least annually updating the committee on the study's progress.

14.3.1. Informed Consent and Screening Data

Subject Informed Consent Forms will be based on a master document provided by the Sponsor and must be approved by the Sponsor (or designee) prior to submission to the IRB/EC. The Sponsor must approve any changes requested by the IRB/EC prior to the documents being used.

The Principal Investigator must obtain IRB/EC approval for the investigation. Initial IRB/EC approval, and all materials approved by the IRB/EC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices (GCPs) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

The study will be performed in accordance with the protocol, ethical principles that have their origin in the Declaration of Helsinki, and are consistent with ICH E6 GCP: Consolidated Guideline, and any applicable local regulations.

16.3. Written Informed Consent

The Investigator or a designee is to explain the study and Informed Consent Form to the patient or the patient's legally-authorized representative (LAR) and answer any questions. The Informed Consent Form is to be signed by the patient or the patient's LAR, before any study-related procedures are performed. A copy of the Informed Consent Form is to be provided to the patient or the patient's LAR. In some countries the consent may be signed by an authorized designee per local regulations or requirements, including but not limited to independent physicians qualified to provide consent for patients who are unable to provide consent for themselves.

The signed Informed Consent Form is to remain in each patient's study file and be available for verification by study monitors or authorized regulatory representatives at any time.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

The Sponsor supports the authorship criteria established by the International Committee of Medical Journal Editors.

Minimum criteria for authorship credit based on:

1. Substantial contributions to conception and design, (or) acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content; and
3. Final approval of version to be published

To be considered, all potential authors must meet conditions 1, 2, and 3.

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20. APPENDICES

APPENDIX A. SAFETY CONTACT INFORMATION

SAEs must be reported within the eCRF within 24 hours of the Investigator's awareness of the event. Follow-up information to SAE reports must also be promptly entered into the eCRF. The Investigator will be required to electronically sign each SAE report. In the event that the EDC system is nonfunctional, a completed and signed SAE form must be faxed or emailed within 24 hours to:

Global SAE Fax Number: PPD

Email: PPD

Medical Emergency Contact: PPD

APPENDIX B. Acute Physiological Assessment and Chronic Health Evaluation (Apache) II Scoring System

Physiologic Variable†	POINT SCORE								
	+4	+3	+2	+1	0	+1	+2	+3	+4
1 Temperature (°C)	≥41°	39–40.9°	—	38.5–38.9°	36–38.4°	34–35.9°	32–33.9°	30–31.9°	≤29.9
2 Mean arterial pressure (mm Hg) *Note: Mean Arterial Pressure can be calculated, if not available from a monitor/device, with the following equation: (2x diastolic + systolic) / 3*	≥160	130–159	110–129	—	70–109	—	50–69	—	≤49
3 Heart rate	≥180	140–179	110–139	—	70–109	—	55–69	40–54	≤39
4 Respiratory rate (non-ventilated or ventilated)	≥50	35–49	—	25–34	12–24	10–11	6–9	—	≤5
5 Oxygenation:	*Note: If a patient has both FiO_2 less than and greater than 0.5, both 5a and5b must be calculated to identify and complete using the worst value.*								
a) FIO_2 ≥0.5: use $A\text{-}aDO_2$	≥500	350–499	200–349	—	<200	—	—	—	—
b) FIO_2 <0.5: use PaO_2 (mm Hg)	—	—	—	—	>70	61–70	—	55–60	<55
6 Arterial pH *Note: if ABG is not available, use Serum HCO_3 instead **(#13)***	≥7.7	7.6–7.69	—	7.5–7.59	7.33–7.49	—	7.25–7.32	7.15–7.24	<7.15
7 Serum Na (mmol/L)	≥180	160–179	155–159	150–154	130–149	—	120–129	111–119	≤110
8 Serum K (mmol/L)	≥7	6–6.9	—	5.5–5.9	3.5–5.4	3–3.4	2.5–2.9	—	<2.5
9 Serum Creatinine (mg/dL) *Note: Double point score for **acute** renal failure(as diagnosed by investigator)*	≥3.5	2–3.4	1.5–1.9	—	0.6–1.4	—	<0.6	—	—
10 Hct (%)	≥60	—	50–59.9	46–49.9	30–45.9	—	20–29.9	—	<20
11 WBC (in1000s)	≥40	—	20–39.9	15–19.9	3–14.9	—	1–2.9	—	<1

Physiologic Variable†	**POINT SCORE**								
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
12 Glasgow Coma score (GCS)	Score =15 minus actual GCS *Note: The Glasgow Coma Scale should not be calculated on **obtunded or otherwise sedated subjects**. In these subjects if a reliable pre-sedation Glasgow Coma Scale score is available, this should be used in calculating the APACHE II score. If a reliable pre-sedation score is not available, a score of 15 should be recorded for the Glasgow Coma Scale component of the APACHE II score (resulting in 0 points on this APACHE II score component).*								
Acute physiology score is the sum of the 12 individual variable points.									
Add 0 points for age <44; 2 points, 45–54 yr; 3 points, 55–64 yr; 5 points, 65–74 yr; 6 points ≥ 75 yr.									
Add the following chronic health status points‡ if applicable: • 5 points for nonoperative or emergency postoperative subjects: • 2 points for elective postoperative subjects with immunocompromise or history of severe organ insufficiency as defined by: o LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma. o CARDIOVASCULAR: New York Heart Association Class IV o RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, ie, unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respiratory dependency. o RENAL: Receiving chronic dialysis o IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, eg, immune-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, eg, leukemia, lymphomas, AIDS. *Note: Organ insufficiency or immune-compromised state must have preceded current admission*									
(13)§ Serum HCO3 (venous–mmol/L) *Note: only included if arterial pH is not available **(#6)***	≥52	41–51.9	—	32–40.9	22–31.9	—	18–21.9	15–17.9	<15

Glasgow Coma Scale	(Circle appropriate response)	**B Age**	**Points**	**C Chronic Health Points**	**Apache-II Score (sum of A+B+C)**
Eyes open 4 - spontaneously 3 - to speech 2 - to pain 1 - no response Motor response 6 - to verbal command 5 - localizes to pain 4 - withdraws to pain 3 – flexion to pain 2 – extension to pain 1 - no response	verbal - <u>nonintubated</u> 5 - oriented 4 - confused 3 - inappropriate words 2 - incomprehensible sounds 1 - no response verbal - <u>intubated</u> 5 - seems able to talk 3 - questionable ability to talk 1 - generally unresponsive	Age ≤44 45-54 55-64 65-74 ≥75 **Age points =**	Points 0 2 3 5 6	Refer to bottom of the chart above for: **Chronic Health Status** **Points =**	**A** APS points **+ B** Age points **+ C** Chronic Health Points _____ = Total Apache II
*Note: The Glasgow Coma Scale should not be calculated on **obtunded or otherwise sedated subjects**. In these subjects if a reliable pre-sedation Glasgow Coma Scale score is available, this should be used in calculating the APACHE II score. If a reliable pre-sedation score is not available, a score of 15 should be recorded for the Glasgow Coma Scale component of the APACHE II score (resulting in 0 points on this APACHE II score component).*					

*APACHE II score = acute physiology score + age points + chronic health points. Increasing score is associated with increasing risk of hospital death.
†Choose worst value in the past 24 h.
‡Chronic health status: Organ insufficiency (eg, hepatic, cardiovascular, renal, pulmonary) or immunocompromised state must have preceded current admission.
§Optional variable; use only if no ABGs.
A-aDO2 = Alveolar–arterial oxygen gradient; FIO_2 = fractional inspired O_2.

Adapted from Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med. 1985;13:818–29 [26].

APPENDIX C. MODIFIED CLINICAL PULMONARY INFECTION SCORE

1. Temperature, °C
    - ≥36.5 and ≤38.4 = 0 point
    - ≥38.5 and ≤38.9 = 1 point
    - ≥39 or ≤36.4 = 2 points
2. Blood leukocytes, mm^3
    - ≥4 000 and ≤11 000 = 0 point
    - <4 000 or >11 000 = 1 point + band forms ≥50% = + 1 point
3. Tracheal secretions
    - Absence of tracheal secretions = 0 points
    - Presence of nonpurulent tracheal secretions = 1 point
    - Presence of purulent tracheal secretions = 2 points
4. Oxygenation: PaO_2/FiO_2
    - >240 or acute respiratory distress syndrome (ARDS) = 0 point
    - ≤240 and no ARDS = 2 points
5. Pulmonary radiography
    - No infiltrate = 0 points
    - Diffuse (or patchy) infiltrate = 1 point
    - Localized infiltrate = 2 points
6. Progression of pulmonary infiltrate
    - No radiographic progression = 0 points
    - Radiographic progression (after CHF and ARDS excluded) = 2 points
7. Lower Respiratory Tract Culture
    - No pathogenic bacteria growth = 0 points
    - Pathogenic bacteria cultured = 2 points

Adapted from Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):505-11 [27].

APPENDIX D. SEPSIS-RELATED ORGAN FAILURE ASSESSMENT (SOFA) SCORE

Points	**0**	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mmHg	>400	≤400	≤300	≤200 with respiratory support	≤100 with respiratory support
Coagulation Platelets× $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥12.0
Cardiovascular Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine > 0.1 or norepinephrine >0.1[a]
Central nervous system Glasgow Coma Score	15	13 - 14	10 – 12	6 – 9	<6
Renal Creatinine, mg/dL or urine output	<1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 or urine output of <500 mL/day	≥5.0 or urine output of 200 mL/day

[a] Adrenergic agents administered for at least 1 h (doses given are in µg/kg*min).

Adapted from Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al for the Working Group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998;26(11):1793-800 [28].

APPENDIX E. O_2 SATURATION TO PaO_2 CONVERSION TABLE

Oxygen Saturation (SO_2)	Estimated PaO_2 (mm Hg)
99	156
98	111
97	92
96	82
95	74
94	69
93	66
92	62
91	60
90	58
88	54
86	51
84	49
82	47
80	45
78	43
76	41
74	40
72	39
70	37

Calculated from Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol Respir Environ Exerc Physiol. 1979 Mar;46(3):599-602 [29].

APPENDIX F. THE ASSESSMENT PLAN OF SEPSIS

1. DEFINITION OF SEPSIS

Sepsis is defined as bacteremia (positive blood culture at baseline) in the setting of systemic inflammatory symptoms/findings [1].

2. RATIONALE OF SEPSIS ASSESSMENT

Sepsis is associated with high mortality. Delays of treatment lead to complications of a variety of organ failure (circulatory failure, acute respiratory syndrome, disseminated intravascular coagulation, etc) and a poor outcome. Therefore, prompt therapy with effective antibiotics has been shown to be critical for effective for the treatment of sepsis.

Sepsis assessment is based on the Japanese guidelines for clinical assessment of antibiotics on sepsis and definition of sepsis-1 of Society of Critical Care Medicine and American College of Chest Physicians [1,2,3,4].

3. TRIAL OBJECTIVES OF SEPSIS ASSESSMENT

The efficacy and safety of ceftolozane/tazobactam in the population of patients with sepsis will be evaluated under a Japan-specific amendment.

3.1. Study Objectives

Primary objectives:

- To evaluate the clinical response to ceftolozane/tazobactam in the treatment of sepsis at the TOC visit in the sepsis population.
- To evaluate the safety and tolerability of ceftolozane/tazobactam in the sepsis population.

Secondary objectives:

- To evaluate the microbiological response to sepsis treatment at the TOC visit in the sepsis population.

4. THE CRITERIA OF SEPSIS

To be included in the sepsis population, a subject must satisfy all of the following criteria:

1) Have at least 1 of the following clinical criteria within the 24 hours prior to the first dose of study drug:
   - Temperature >38°C (100.4°F) or < 36°C (96.8°F)
   - WBC count >12,000 cells/mm^3, <4,000 cells/mm^3 or >10 % immature neutrophils
   - Pulse rate (heart rate) >90 beats per minute
   - $PaO_2/FiO_2 \leq 240$ mmHg

- Systolic blood pressure <90 mmHg
- CRP ≥20 mg/dL

2) Have positive blood culture at baseline.

5. STATISTICS OF SEPSIS ASSESSMENT

This section outlines the statistical analysis strategy and procedures for the assessment.

5.1. Handling of Missing Data

For efficacy endpoints, missing data will be handled with a Treatment Failure Approach (TFA) for the sepsis population defined as follows:

- TFA: All subjects with an outcome of efficacy endpoints as indeterminate at TOC visit will be considered as treatment failures. In other words, all subjects with efficacy endpoint of indeterminate at the TOC visit who meet the sepsis population criteria will be included in the denominator.
- For microbiological outcome, missing of blood culture will be considered presumed eradication or indeterminate as defined in Table F-2.

5.2. Populations for Analysis

The definitions of population for analysis are outlined below.

5.2.1. Sepsis Population

Sepsis population will consist of all randomized subjects who received at least one dose of study treatment and who satisfy the sepsis criteria. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

5.3. Study Endpoints

Efficacy endpoints

- Primary Endpoint: Clinical response at the TOC visit in the sepsis population
- Secondary Endpoint: Microbiological response at the TOC visit in the sepsis population

Safety endpoint

- Adverse event in the sepsis population

5.4. Efficacy Endpoint Analyses

5.4.1. Primary Endpoint Analysis

The point estimates and 95% CI by the Clopper-Pearson method will be presented for the clinical response rate at TOC in the sepsis population in each treatment group [5]. In addition, the treatment difference in proportions and the 95% CI for the treatment difference by using the Meittinen & Nurminen (M&N) method will be presented [6]. The clinical response rate is defined as a proportion of subjects who are confirmed to have a clinical outcome for sepsis as “Cure”.

5.4.2. Secondary Endpoint Analysis

The point estimates and 95% CI by the Clopper-Pearson method will be presented for the microbiological response rate at TOC in the sepsis population in each treatment group. In addition, the treatment difference in proportions and the 95% CI for the difference by using the M&N method will be presented. The microbiological response rate is defined as a proportion of subjects who are confirmed to have a microbiological outcome for sepsis as "Eradication" or "Presumed eradication".

5.5. Safety Analysis

5.5.1. Adverse Events

The incidence (n and %) of TEAEs, SAEs, and early termination of study medication and/or study participation due to an AE will be presented for subjects in the sepsis population in each treatment arm. Additionally, AEs will be tabulated according to severity and relatedness to study treatment categories as reported by the Investigator. Adverse events will be presented in tables organized alphabetically by System Organ Class and Preferred Term. Each subject will be counted only once for each AE reporting level.

5.6. Evaluation Criteria of Sepsis

5.6.1. Definition of Clinical Response for Sepsis

Clinical outcome assessment for sepsis will be made at the TOC visit.

5.6.1.1. Clinical Outcome for Sepsis

Clinical response at the TOC visit will be classified as cure, failure, or indeterminate (Table F-1).

Table F-1: Clinical Response Categories for Sepsis at the TOC Visit

Outcome	Definition
Cure	All clinical signs and symptoms of sepsis were resolved at the TOC visit, which means subject had all study data of the criteria of sepsis and did not meet any of the criteria of sepsis 1) in Section 4.
Failure	All clinical signs and symptoms of sepsis were not resolved at the TOC visit, which means subject met at least 1 of the available study data of the criteria of sepsis 1) in Section 4.
Indeterminate	Study data was not available for the evaluation of clinical outcome for any reason, which means at least 1 of study data of the criteria of sepsis 1) in Section 4 were not available even though subject had not met any of the other criteria of sepsis 1) in Section 4.

5.6.2. Definition of Microbiological Response for Sepsis

Microbiological outcome assessment for sepsis will be determined based on the results of last blood culture through TOC visit.

5.6.2.1. Microbiologic Outcome for Sepsis

Microbiological response for sepsis at the TOC visit will be classified per-subject as eradication, presumed eradication, persistence / new pathogen or indeterminate (Table F-2).

Table F-2: Microbiologic Outcome Categories for Sepsis at the TOC Visit

Outcome	Definition
Eradication	Last blood culture after the administration of the first dose of study drug through the TOC visit showed no growth of any pathogens.
Presumed eradication	A blood culture was not performed after the administration of the first dose of study drug, AND a subject deemed “a clinical cure” for clinical outcome of sepsis at the TOC visit.
Persistence / New Pathogen	Last blood culture after the administration of the first dose of study drug through the TOC visit showed the presence of baseline pathogen and/or any pathogens other than baseline pathogen.
Indeterminate	A blood culture after the administration of the first dose of drug is not performed and a subject deem other than clinical cure (failure or indeterminate) for clinical outcome of sepsis at the TOC visit.

6. LIST OF REFERENCES

1. Notification No1023-3, 2017 October 23, issued by the director of office of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health. Labour and Welfare. Japanese guideline for clinical assessment of antibiotics on sepsis.

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3. The JRS Guidelines for the Management of Pneumonia in Adults 2017 Creating Committee. The JRS Guidelines for the Management of Pneumonia in Adults 2017.

4. The JAID/JSC Guide and Guidelines for Management of Infection Creating Committee.Working Group for Sepsis. The JAID/JSC Guide and Guidelines for Management of Infectoin 2017-Sepsis and Catheter-related blood stream infections-.

5. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.

6. Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Statistics in Medicine 1985;4:213-26.