Official Protocol Title:	A Phase 3 Randomized Double-blind Study Comparing TR-701 FA and Linezolid in Ventilated Gram-Positive Nosocomial Pneumonia
NCT number:	NCT02019420
Document Date:	10-Aug-2018

Protocol Number: TR701-132 (MK-1986-002)

Study Drug: TR-701 FA

A Phase 3 Randomized Double-blind Study Comparing TR-701 FA and Linezolid in Ventilated Gram-positive Nosocomial Pneumonia

This protocol amendment is applicable only to Japan.

IND Number:	106307
EudraCT Number:	2013-004154-22
Sponsor:	Cubist Pharmaceuticals, LLC A wholly-owned indirect subsidiary of: Merck, Sharp & Dohme Corp. Weystrasse 20, 6000 Lucerne 6 Switzerland Telephone: PPD
Version History:	
Original Protocol	30 May 2013
Amendment 1	26 August 2013
Amendment 2	15 January 2014
Amendment 3	11 November 2014
Amendment 4	24-January-2017
Amendment 5	10-August-2018

PPD

10 Aug 2018
Date

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INVESTIGATOR'S AGREEMENT

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I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council on Harmonisation guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Cubist Pharmaceuticals, LLC or specified designees. I will discuss the material with them to ensure that they are fully informed about Cubist Pharmaceuticals, LLC and the study.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Please submit an original copy of this page to Cubist Pharmaceuticals, LLC and file a copy in the Investigator site file.

SYNOPSIS

Title	A Phase 3 Randomized Double-blind Study Comparing TR-701 FA and Linezolid in Ventilated Gram-positive Nosocomial Pneumonia
Objectives	The primary objective is to determine the noninferiority (NI) in all-cause mortality (ACM) within 28 days after randomization of intravenous (IV) TR-701 FA (tedizolid phosphate, MK-1986) compared with IV linezolid in the Intent to Treat (ITT) Analysis Set in ventilated patients with presumed gram-positive hospital-acquired bacterial pneumonia (HABP) or gram-positive ventilator-associated bacterial pneumonia (VABP), collectively defined as ventilated nosocomial pneumonia (VNP). Secondary objectives: • To compare the ACM observed with TR-701 FA and linezolid within 28 days after randomization in the microbiological ITT (Micro-ITT) Analysis Set • To compare clinical response for TR-701 FA and linezolid treatment at Test of Cure (TOC) in the ITT (European Medicines Agency [EMA] and Japan Ministry of Health, Labour, and Welfare primary endpoint) and Clinically Evaluable (CE) Analysis Sets. Clinical response at TOC is derived from the Investigator's assessment at the End of Therapy (EOT) and TOC Visits as detailed in the Statistical Analysis Plan (SAP) • To compare the per-patient favorable microbiological response rate at EOT in the Micro-ITT and Microbiologically Evaluable (ME)-1 Analysis Sets and at TOC in the Micro-ITT and ME-2 Analysis Sets • To evaluate the safety profile of TR-701 FA and compare with that of linezolid • To assess the population pharmacokinetic (PK) and PK/pharmacodynamic (PD) profile of TR-700 The protocol has been designed to meet Food and Drug Administration (FDA) and EMA regulatory requirements. In addition, the efficacy and safety of TR-701 FA in the Sepsis Population are evaluated under this Japan-specific amendment.
Methodology/ Study Design	This is a 1:1 ratio, randomized, double-blind, double-dummy, multicenter, global Phase 3 study of TR-701 FA 200 mg IV once daily for 7 days versus linezolid (Zyvox®, Zyvoxid®, etc.) 600 mg IV every 12 hours for 10 days for the treatment of ventilated patients with presumed gram-positive HABP or VABP. Patients with concurrent gram-positive bacteremia are to receive 14 days of active therapy in either treatment arm. Cubist Pharmaceuticals, LLC (hereafter referred to as Cubist) (with the exception of the Clinical Drug Supply manager and the Unblinded Global Study team), and the Investigators, study statistician, clinical study personnel, study staff participating in patient care or clinical evaluations, and patients will be blinded to therapy assignment until the database is locked. Pharmacy staff or designee, the independent Statistics Reporting Group (SRG), the Data and Safety Monitoring Board (DSMB), will be unblinded. All study drug infusion bags and IV tubing will be covered and sealed with tamper-evident material in order to maintain the blind. Approximately 300 sites will participate in this global study. Ventilated patients with HABP/VABP caused by presumed gram-positive pathogen(s) at baseline as determined by positive Gram stain will be randomized 1:1 to study drug treatment using an interactive voice response system. Randomization will be stratified by geographic region, age (≥65 years or <65 years), and underlying diagnosis (trauma or nontrauma admitting diagnosis).

Number of Patients	Approximately 726 patients will be randomized (ITT Analysis Set) and are expected to include approximately 363 (50%) patients with a gram-positive pathogen isolated based on respiratory culture (Micro-ITT Analysis Set). Data from approximately 580 patients are expected to be included in the CE Analysis Set.
Inclusion Criteria	Patients who meet all the following diagnostic and inclusion criteria are eligible for the study. 1. Males or females ≥18 years old 2. Adequate venous access for IV study drug administration 3. Intubated (via endotracheal tube, including tracheostomy patients) and mechanically ventilated, AND • For HABP, at least 1 of the following signs or symptoms presenting within 24 hours prior to intubation of a patient hospitalized, including patients institutionalized in long-term care facilities, for ≥48 hours. If the patient has been discharged, discharge must have been within 7 days: o A new onset of cough (or worsening of baseline cough) o Dyspnea, tachypnea, or respiratory rate >30/minute, particularly if any or all of these signs or symptoms are progressive in nature o Hypoxemia (eg, a partial pressure of oxygen <60 mm Hg while the patient is breathing on room air as determined by arterial blood gas [ABG] or oxygen saturation <90% while the patient is breathing on room air as determined by pulse oximetry), or worsening (decline from any earlier finding) of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), or respiratory failure requiring mechanical ventilation • For VABP, receiving mechanical ventilation ≥48 hours and at least one of the following: o Acute changes made in the ventilator support system to enhance oxygenation, as determined by ABG, or worsening PaO_2/FiO_2 o Hypoxemia (eg, a partial pressure of oxygen less than 60 millimeters of mercury while receiving FiO2 of 25%-30%, as determined by ABG or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) o New onset or worsening pulmonary symptoms or signs, such as cough, asymmetric breath sounds, tachypnea (eg, respiratory rate greater than 25 breaths per minute), need for increased oxygenation or ventilation support, 4. Chest radiograph shows the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia (based on Investigator evaluation; report from qualified medical professional who is not the Investigator to be provided) 5. Clinical findings to support diagnosis of HABP/VABP • New onset of suctioned respiratory secretions characterized by purulent appearance indicative of bacterial pneumonia • And at least 1 of the following: o Documented fever (oral ≥38°C [100.4°F] or a tympanic, temporal, rectal, or core temperature ≥38.3°C [101°F]) **OR** o Hypothermia (core body temperature ≤35°C [95.2°F]) **OR**

	○ Total peripheral white blood cell (WBC) count ≥10,000 cells/mm^3 **OR** ○ Leukopenia with total WBC ≤4500 cells/mm^3 **OR** ○ ≥15% immature neutrophils (bands; if local laboratory has capabilities to measure) 6. High probability of pneumonia caused by gram-positive bacteria only or in a mixed infection defined as follows: <u>Respiratory Sample</u> • Sample acquired and Gram stain performed within 36 hours prior to first infusion of study drug using an acceptable purulent respiratory specimen such as sputum or endotracheal aspirate sample (with <10 squamous epithelial cells [SEC] and >25 polymorphonuclear [PMN] cells per low-power field) showing gram-positive bacteria (with or without gram-negative bacteria) **OR** • Sample acquired and Gram stain performed within 36 hours prior to first infusion of study drug using an acceptable respiratory specimen such as protected specimen brush, bronchoalveolar lavage (BAL), mini-BAL, or sample from an exudative pleural effusion showing gram-positive bacteria (with or without gram-negative bacteria) **OR** • Culture from lower respiratory sample obtained within 72 hours prior to first infusion of study drug positive for methicillin-resistant *Staphylococcus aureus* (MRSA) **OR** • Rapid molecular diagnostic test (for example Xpert®) positive for MRSA
Exclusion Criteria	Patients who meet any of the following criteria are not eligible to participate in this study: 1. Known or suspected community-acquired bacterial pneumonia or viral, fungal (presence of *Candida* in lower respiratory tract is not exclusionary), or parasitic pneumonia 2. Any of the following health conditions: • *Legionella* infection (*Legionella pneumophila* pneumonia) • Cystic fibrosis • Human immunodeficiency virus (HIV) infection with last known CD4 count <200 cell/mm³ (HIV testing is not required) • Known or suspected *Pneumocystis jirovecii* pneumonia • Known or suspected active tuberculosis • Lung abscess • Evidence of endocarditis • Tracheobronchitis (if no evidence of pneumonia) 3. Received systemic or inhaled antibiotic therapy effective for gram-positive pathogens that cause VNP for >24 hours (for example, >1 dose of a once-daily antibiotic, >2 doses of a twice daily antibiotic) in the last 72 hours **EXCEPTIONS** • Progression of disease on the prior antibacterial regimen for this episode of VNP after >48 hours of treatment, **OR**

	• Patient developed symptoms of pneumonia and a new infiltrate while receiving the prior antibacterial regimen for reasons other than the current VNP, **OR** • Patient received systemic antibacterial therapy that does not cover the gram-positive pathogen isolated on respiratory culture, **OR** • Antibiotic therapy for gut decontamination or gut motility (example, low-dose erythromycin) or *C. difficile* infection 4. Receipt of monoamine oxidase A and B inhibitors (see Appendix 1) from 2 weeks prior to randomization or planned use through the EOT Visit 5. Planned use of agents with serotonergic activity (see Appendix 1 and Section 1.4) through the EOT Visit 6. Administration of linezolid or tedizolid phosphate ≤30 days before the first infusion of study drug, except for receipt of a single administration of linezolid, within 24 hours prior to the first administration of study drug to treat the current VNP 7. Bronchial obstruction or a history of postobstructive pneumonia (this does not exclude patients with pneumonia who have underlying chronic obstructive pulmonary disease) 7. Primary lung cancer or another malignancy metastatic to the lungs 8. Recent opportunistic infection where the underlying cause of the infection is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome) 9. Expected survival <72 hours or any 1 of the following: • Comfort care measures only • Acute respiratory distress syndrome/acute lung injury secondary to septic shock, or due to third degree burns or inhalation injury • Nonresolving pulmonary edema secondary to congestive heart failure 10. Burns >40% of total body surface area 11. Current or anticipated neutropenia with absolute neutrophil count <500 cells/mm^3 12. Severe renal disease requiring peritoneal dialysis. Patients with severe renal disease on hemodialysis, venovenous dialysis, or other forms of renal filtration may be enrolled 13. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥10× upper limit of normal OR severe hepatic disease with Child-Pugh score >9 14. Investigator's opinion of clinically significant electrocardiogram (ECG) finding such as ischemia, infarct, or ventricular arrhythmia with immediate potential for a fatal outcome, or, prior to the current infection, a history of New York Heart Association Class IV cardiac failure defined as severe limitations - experiences symptoms even while at rest, mostly bedbound patients, within 1 year 15. Patients with uncontrolled hypertension (defined as high blood pressure that is clinically an issue and uncontrolled on multiple medications), pheochromocytoma, carcinoid syndrome, or thyrotoxicosis 16. Treatment with investigational medicinal product ≤30 days before the first infusion of study drug or prior randomization in this protocol

	17. Investigational device present, or removed <30 days before the first infusion of study drug or presence of device-related infection 18. Hypersensitivity to oxazolidinones (eg, linezolid) or any component in the formulation 19. Women who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel], or male partner sterilization); excluding women ≥2 years postmenopausal or surgically sterile
Test Product(s), Dose, Mode of Administration, and Duration of Treatment	TR-701 FA 200 mg once daily in 250 mL sterile saline for injection as a single 60-minute IV infusion for 7 days (14 days for patients with gram-positive bacteremia). Linezolid 600 mg IV Injection twice daily in 300 mL sterile saline for injection as a 60-minute infusion for 10 days (14 days for patients with gram-positive bacteremia). In this double-dummy study, patients will receive placebo unique to each active treatment, placebo infusion unique for TR-701 FA (250 mL) and placebo infusion unique for linezolid (300 mL). No dosage adjustments are allowed.
Duration of Study	The overall duration of the study will be approximately 58 months. Patient participation will be up to 33 days from the Screening Visit to the Follow-up Visit, unless a patient is being monitored for an adverse event (AE). Patients will be monitored for AEs through the last study visit and serious AEs (SAEs) will be followed using the SAE report form until stabilization, resolution/death, or consent is withdrawn.
Efficacy Outcomes	The primary outcome is ACM within 28 days after randomization in the ITT Analysis Set. Secondary outcomes include the following: • ACM within 28 days after randomization (Micro-ITT Analysis Set) • Clinical response at TOC in the ITT (EMA and Japan Ministry of Health, Labour, and Welfare primary endpoint) and CE Analysis Sets. Clinical response at TOC is derived from the Investigator's assessment at the EOT and TOC Visits • Microbiological response at EOT and TOC (Micro-ITT, ME-1 and ME-2 Analysis Sets) • ACM in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) or MRSA (Micro-ITT Analysis Set) • Clinical response by Investigator in patients with MSSA or MRSA (Micro-ITT and ME-2 Analysis Sets)
Safety Variables	Safety will be evaluated through assessment of AEs, laboratory evaluations (hematology and chemistry), vital signs, and physical examinations including a neurologic examination and visual acuity examination
PK Variables	Include maximum plasma concentrations and estimated PK parameters (eg, area under the concentration-time curve)
Analysis Sets	1. ITT Analysis Set: data from all randomized patients 2. Safety Analysis Set: data from all patients in the ITT Analysis Set who receive any amount of study drug 3. Micro-ITT Analysis Set: data from all patients in the Safety Analysis Set who have gram-positive pathogen(s) confirmed by culture results from a respiratory

<table>
<tr><td></td><td>tract or pleural fluid specimen obtained within 36 hours (or if culture positive for MRSA within 72 hours) before first administration of study drug, and documented bacterial pathogen known to cause VNP against which the investigational drug has antibacterial activity
4. ME-1 Analysis Set: data from all patients in the Micro-ITT Analysis Set who did not receive an antibiotic (other than study drug) with activity against the baseline pathogen received up through 28 days after randomization
5. ME-2 Analysis Set: data from all patients in the Micro-ITT Analysis Set who did not receive an antibiotic (other than study drug) with activity against the baseline pathogen received up through the TOC Visit and also in the CE Analysis Set
6. CE Analysis Set: data from all patients in the Safety Analysis Set who had a TOC response assessment recorded (if the patient was assessed by the Investigator as a clinical failure at the EOT Visit, a response assessment at the TOC Visit is not required), had no confounding events or factors as detailed in the SAP</td></tr>
<tr><td>Statistical Methods</td><td>To demonstrate the NI of TR-701 FA to linezolid with respect to the difference in 28-day ACM rates, using an NI margin of 10%, a sample size of 726 randomized patients (363 per arm) in the ITT Analysis Set will have 92% power at a 1-sided significance level of 0.025, assuming a 28-day ACM rate of 20% in both TR-701 FA and linezolid arms.
The study is also sufficiently powered for the secondary outcome measure of clinical cure as derived from the Investigator's assessment at TOC in the ITT and CE Analysis Sets. A total of 726 patients will be randomized in the ITT Analysis Set, which provides 87% power to show NI assuming a 50% clinical success rate and an NI margin of 12.5%. If the clinical evaluability rate will be 80%, with a 12.5% NI margin, 80% power, a 1-sided alpha=0.0125, and a clinical cure rate of 60% in the CE Analysis Set, a total of 580 patients are required in the CE Analysis Set.
<table>
<tr><th></th><th>Primary Outcome (28-Day ACM)</th><th colspan="2">Secondary Outcome (Clinical Response*)</th></tr>
<tr><td>Analysis Set</td><td>ITT</td><td>ITT</td><td>CE</td></tr>
<tr><td>Outcome Rate</td><td>20%</td><td>50%</td><td>60%</td></tr>
<tr><td>Evaluability Rate</td><td>NA</td><td>NA</td><td>80%</td></tr>
<tr><td>Margin</td><td>10%</td><td>12.5%</td><td>12.5%</td></tr>
<tr><td>N</td><td>726</td><td>726</td><td>580</td></tr>
<tr><td>Power</td><td>92%</td><td>87%</td><td>80%</td></tr>
</table>
Abbreviations: CE=clinically evaluable; ITT=intent to treat; NA=not applicable
*As derived from the Investigator's assessment at the EOT and TOC Visits

The DSMB will be convened when approximately 30% (218 patients), 50% (363 patients), and 75% (545 patients) of patients have been randomized in the ITT Analysis Set and completed 28 days of follow-up. A DSMB will review safety and efficacy data including ACM, treatment-emergent adverse events (TEAEs), incidence of serious TEAEs, study drug-related TEAEs, and study drug discontinuation due to study drug-related TEAEs and other safety and efficacy related data at 30%, 50%, and 75% of patient enrollment. Only data for the first and the second interim looks will be unblinded (Treatment A vs Treatment B). At the first and second interim analysis, futility analysis based on the primary efficacy outcome of 28-day ACM in the ITT Analysis Set will be performed. The futility boundaries will be derived from the Gamma (-4.27) error spending function and constructed to be nonbinding. The futility boundaries will be calculated using the actual information fractions at the time of the DSMB interim analysis. The DSMB charter will detail the review of safety, efficacy data and the futility analyses. The study is designed to show the NI of TR-701 FA</td></tr>
</table>

	versus linezolid in ACM within 28 days after randomization in the ITT Analysis Set. A 2-sided 95% confidence interval (CI) for the difference in proportions for ACM rate will be calculated. TR-701 FA will be considered NI to linezolid if the lower limit of the 2-sided 95% CI around the difference is greater than minus 10%. Secondary efficacy analyses will be conducted to support the efficacy findings of the primary outcome. For the secondary outcome of 28-day ACM in the Micro-ITT Analysis Set, a 2-sided 95% CI for the difference in proportions for ACM will be calculated. For the secondary outcome measure of clinical response at TOC in the ITT and CE Analysis Sets, the risk difference in cure rates will be determined, and a 2-sided 95% CI and a 2-sided 97.5% CI will be calculated (method of Miettinen and Nurminen). The difference in proportions for 28-day ACM (TR-701 FA versus linezolid) in patients with MSSA and MRSA will also be determined and a 95% CI will be calculated. The risk difference in favorable microbiological response rates at EOT in the ITT and ME-1 Analysis Sets and at TOC in the ITT and ME-2 Analysis Sets will be determined and a 95% CI will be calculated. The risk difference in cure rates based on the Investigators assessment of clinical response at TOC in patients with MSSA and MRSA will also be determined and a 95% CI will be calculated. Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary outcomes but no formal conclusions of NI will be made. For other outcomes, descriptive statistics including the number and percentage will be provided and 2-sided 95% CIs for the risk difference will be determined (Miettinen and Nurminen). Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be used for continuous variables. The incidence of treatment-emergent AEs will be presented by system organ class and preferred term for each treatment group according to the Medical Dictionary of Regulatory Activities, relationship to study drug, and severity in the Safety Analysis Set. Descriptive statistics of clinical laboratory results (hematology and chemistry), vital sign measurements, and the change from Baseline will be presented, as will a summary of laboratory values classified based on Division of Microbiology and Infectious Disease (National Institute of Allergy and Infectious Disease, Department of Health and Human Services, United States) toxicity scale.

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SUMMARY OF CHANGES

PRIMARY REASONS FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Changes	Rationale
Synopsis, 2.0	Objectives, Study Objectives	Added text explaining that the efficacy and safety of TR-701 FA in patients with sepsis will be evaluated under this Japan-specific amendment.	To evaluate the efficacy and safety of TR-701 FA in patients with sepsis.
Appendix 12	Assessment Plan of Sepsis	Added the Assessment Plan of Sepsis.	To describe the plan for assessment of sepsis.

ABBREVIATIONS

Abbreviation	Definition
ABG	arterial blood gas
ABSSSI	acute bacterial skin and skin structure infection
ACM	all-cause mortality
AE	adverse event
ALT	alanine aminotransferase
AM	alveolar macrophages
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BCRP	breast cancer resistant protein
BSA	body surface area
CBA	colistin base activity
CBC	complete blood count
CLcr	creatinine clearance
CE	clinically evaluable
cfr	chloramphenicol-florfenicol resistance
CFR	Code of Federal Regulations
CI	confidence interval
CPIS	Clinical Pulmonary Infection Score
CSR	clinical study report
CT	computed tomography
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
e-CRF	electronic case report form
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	end of therapy
ERT	Evaluability Review Team
EU	European Union
FiO_2	fraction of inspired oxygen
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia

Abbreviation	Definition
HAP	hospital-acquired pneumonia
hCG	beta-human chorionic gonadotropin hormone
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ICU	intensive care unit
IRB	Institutional Review Board
ISI	international sensitivity index of a tissue factor (for calculating INR)
ITT	intent to treat
IVRS	interactive voice response system
IV	intravenous(ly)
LAR	legally-authorized representative
LRT	Lower respiratory tract
MAOI	monoamine oxidase inhibitor
ME	microbiologically evaluable
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MIC	minimum inhibitory concentration
Micro-ITT	microbiological intent to treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NI	noninferiority
NOAEL	no observed adverse effect level
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic(s)
PMN	polymorphonuclear
PT	prothrombin time
PTT	Partial thromboplastin time
REB	Research Ethics Board
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SEC	squamous epithelial cells
SOFA	Sepsis-related Organ Failure Assessment
SRG	Statistics Reporting Group

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TFA	Treatment failure approach
TOC	test of cure
ULN	upper limit of normal
WBC	white blood cell
VAP	ventilator-associated pneumonia
VABP	ventilator-associated bacterial pneumonia
VNP	ventilated nosocomial pneumonia

1.0 INTRODUCTION AND RATIONALE

Ventilator-associated bacterial pneumonia (VABP) and ventilated hospital-acquired bacterial pneumonia (HABP) are collectively termed ventilated nosocomial pneumonia (VNP). HABP is defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea; accompanied by a new or progressive infiltrate on a chest radiograph in a patient hospitalized for more than 48 hours or that develops within 7 days after hospital discharge. VABP is associated with the same clinical syndrome as HABP with increased oxygen requirements in patients receiving mechanical ventilation via an endotracheal tube for at least 48 hours. VABP is the leading cause of morbidity and mortality in intensive care units (ICUs) with an incidence ranging from 7% to 70% in different studies and mortality rates of 20 to 75% according to the study population (Alp 2006). Patients with VABP also have longer durations of mechanical ventilation, longer ICU stays, and prolonged hospitalization (Alp 2006).

Infections due to gram-positive cocci such as *Staphylococcus aureus* and particularly methicillin-resistant *S aureus* (MRSA) are common in HABP/VABP; other common pathogens include *P aeruginosa, Escherichia coli, Klebsiella pneumoniae,* and *Acinetobacter* species (ATS Guidelines 2005; Torres 2009). Currently, there are only 2 agents approved for the treatment of MRSA nosocomial pneumonia, vancomycin and linezolid. In a Phase 4 post-approval prospective, double-blind, controlled, multicenter study of intravenous (IV) linezolid versus vancomycin involving hospitalized adult patients with hospital-acquired or healthcare-associated MRSA pneumonia, clinical response at the end of 7 to 14 days of treatment in the per protocol analysis set was significantly higher with linezolid than with vancomycin but there was no difference in all-cause mortality (ACM) between the 2 agents (Wunderink 2012). Based on the ongoing decline in vancomycin activity in nosocomial pneumonia (Pletz 2010), interest in linezolid use has increased as first-line treatment for VNP due to MRSA.

The draft Food and Drug Administration (FDA) guidance for clinical study design for the HABP/VABP indication was discussed with key stakeholders at public workshops in November 2011, reaching consensus on the key elements to support development of new treatments for HABP and VABP in the US. In the European Union, a separate series of workshops hosted by the European Medicines Agency (EMA) in 2011 and 2012 led to the recent draft Addendum to the Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections to Address Indication-specific Clinical Data issued in July 2012. This protocol has been designed to integrate both US and European guidance and reflect recent interactions and scientific advice obtained from regulatory authorities. While the FDA established 28-day ACM in the Microbiological Intent to Treat (ITT) Analysis Set as the primary endpoint with a 1.71 noninferiority (NI) margin for the odds ratio (equivalent to a 10% NI margin for the risk difference), the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom stipulated the clinical response at Test of Cure (TOC; 7 to 14 days after the end of therapy [EOT] Visit) as derived from the Investigator's assessment at the EOT and TOC Visits as a primary endpoint with a

12.5% NI margin for the risk difference. More recently in 2013, FDA agreed with the Sponsor to use the Intent to Treat Analysis Set as the primary analysis set for evaluation of the primary outcome measure, instead of the microbiological ITT (Micro-ITT) Analysis Set. Additionally, the Sponsor met with the EMA in March 2013 and there was agreement on overall trial design, including the clinical response at TOC (as derived from the Investigator's assessment at the EOT and TOC Visits) in the ITT and Clinically Evaluable (CE) Analysis Sets as the primary outcome for support of registration for the EMA (EMA 2012). In Amendment 4, the Sponsor updated the primary endpoint to support registration for the EU to clinical response at TOC (as derived from the Investigator's assessment at the TOC Visit) in the ITT Analysis Set. According to the current draft of FDA Guidance for Industry (HABP and VABP: Developing Drugs for Treatment, May 2014): "The primary efficacy analysis should be based on the difference between treatment groups in the proportions of success on the primary outcome measure, assessing either non-inferiority or superiority." This protocol reflects this requirement.

TR-701 FA, also known as tedizolid phosphate and MK-1986, is a phosphate prodrug of the microbiologically active molecule TR-700 (tedizolid), a protein synthesis inhibitor that has potent bactericidal gram-positive activity. TR-701 FA administered as an IV infusion of 200 mg once daily for 7 days (or 14 days for gram-positive bacteremia) is predicted to achieve systemic and pulmonary levels with a high probability of antimicrobial efficacy against clinically relevant gram-positive pathogens in critically ill patients.

1.1 Relevant Nonclinical Findings

Results from relevant nonclinical studies of TR-701, TR-701 FA, and TR-700 are summarized in this section. Further information is provided in the Investigator's Brochure (IB).

Susceptibility testing results from multiple studies of TR-701 demonstrate that overall, TR-700 is 4- to 16-fold more potent than linezolid against all *S aureus,* and streptococcal species (including penicillin-susceptible and -resistant strains). The TR-700 MIC_{90} values for gram-positive pathogens were 0.25 to 0.5 µg/mL compared with 2 to 4 µg/mL for linezolid. TR-700 retained activity against vancomycin-resistant and linezolid-resistant staphylococcal and enterococcal clinical isolates. TR-700 has activity against strains harboring chromosomal 23S rRNA mutations and strains that contain the chloramphenicol-florfenicol resistance (*cfr*) transposon-borne gene that confers resistance to linezolid. Additional in vivo efficacy studies confirmed the greater potency of TR-700 versus linezolid against linezolid-resistant MRSA *cfr* strain CM/05. Resistance development to TR-700 was 16-fold lower than to linezolid. TR-700 demonstrated no antagonism or synergy against bacterial isolates with other antibacterial and antifungal agents of different classes. In vivo nonclinical studies have been conducted to evaluate the antibacterial activity of TR-700 and to determine the pharmacokinetic (PK) and pharmacodynamic (PD) parameters correlating with efficacy. TR-701 FA demonstrated advantages over linezolid and vancomycin in pulmonary penetration and exhibited potent staphylococcal killing. The key PD target for TR-700 is

free area under the concentration-time curve (AUC_{free})/minimum inhibitory concentration (MIC).

Once-daily dosing provided the same efficacy as the equivalent dose apportioned into multiple equally divided doses (Louie ECCMID 2009). Drusano and colleagues (Drusano 2011) found an enhancement of TR-700 staphylococcal killing in the presence of granulocytes in a mouse thigh model on the order of 25-fold compared to a neutropenic model. Lemaire and colleagues (Lemaire 2009) demonstrated that TR-700 penetrates into macrophages better than linezolid and kills intracellular staphylococci to a significantly greater extent (approximately 15-fold).

Pichereau and colleagues (Pichereau 2009) compared the efficacy of TR-701 to linezolid in a neutropenic murine model of staphylococcal pneumonia. Test mice required 4.6- to 5.5-fold less TR-701 compared with linezolid (on a mg/kg basis) to produce stasis and a 1-log reduction in colony forming units in lung tissue. The AUC_{free}/MIC values achieving stasis and 1-log kill at 24 hours after TR-701 administration were approximately 10 and 25, respectively. These ratios are considerably lower than observed in the neutropenic thigh infection model and may be due to greater partitioning of TR-700 into lung fluids. Tessier and colleagues (Tessier 2012) compared the antibacterial activity and pulmonary epithelial lining fluid (ELF) exposures of TR-700, linezolid, and vancomycin in an immunocompetent mouse pneumonia model. Overall, at these human-simulated ELF exposure levels, vancomycin resulted in minimal reductions in bacterial counts. TR-701 and linezolid regimens were not statistically different against the 3 MRSA isolates tested, although both treatments were significantly different from controls and considered effective. Vancomycin was less protective than either TR-701 or linezolid, with overall survival of 61.1% versus 94.7% and 89.5%, respectively. Based on these results, an exposure response relationship can be predicted for TR-701. The human ELF exposure level predicted from the proposed dose of TR-701 FA 200 mg IV once daily should be appropriate for treatment of MRSA pneumonia.

Population PK analysis and PD simulations have demonstrated that a 200 mg human-equivalent TR-701 FA dose corresponding to 165 mg of TR-700 is expected to provide maximal killing effect (Louie ICAAC 2009).

In subchronic studies, the primary target organs of TR-701/TR-701 FA toxicity were the hematopoietic system in rats and the gastrointestinal system in rats and dogs. Safety margins generated from repeat-dose toxicity studies in rats and dogs for proposed IV and oral human doses based on systemic exposure (AUC) were determined. After IV administration, the safety margin to the anticipated therapeutic dose in humans (200 mg) for systemic toxicity is 5.6- and 3.8-fold in male and female rats, respectively. In dogs, the safety margin is 3.4- and 4.4-fold in males and females, respectively. The no observed adverse effect level (NOAEL) for systemic toxicity of TR-701 is 7- to 14-fold greater than linezolid based on the ratio of NOAELs established in 1-month toxicology studies in rats and dogs, respectively, relative to the recommended oral dose in humans. Results from comprehensive in vivo and in vitro genotoxicity studies indicate little genotoxic risk to humans. In a fertility study of TR-701 FA

in rats, no effects on either male or female reproductive performance were observed at any dose tested. In addition, no effect on intrauterine survival of embryos or testicular sperm counts was observed.

1.2 Relevant Clinical Findings

Pharmacokinetic parameters for TR-700 generally increased linearly and proportionally with dose, with low to moderate intersubject variability and low accumulation of approximately 28% following multiple once-daily oral or IV administrations (TR701-101 and TR701-107). Steady-state concentrations are achieved within 3 days in most individuals and plasma concentrations achieved with the first dose are similar to steady-state concentrations.

Pharmacokinetic studies have demonstrated that TR-700 rapidly distributes into tissues (TR701-119, TR701-102). Both TR-701 and TR-700 are moderately highly protein bound in human plasma (70% to 90%), and binding appeared to be independent of concentration. Study TR701-119 examined the steady-state plasma PK and disposition of TR-700 into the ELF and alveolar macrophages (AM) of 20 healthy volunteers given TR-701 FA 200 mg once daily for 3 days. The TR-700 penetration ratio into the ELF and AM (ELF or AM AUC_{0-24} compared with the AUC_{0-24} in plasma, adjusted for protein binding) was 41.2 and 20.0, respectively. These results indicate that TR-700 concentrates in the ELF and AM and that TR-701 FA 200 mg once daily appears adequate for the treatment of lung infections caused by susceptible pathogens.

Results from the Phase 1 Study TR701-107 in healthy volunteers indicate that TR-701 FA was well tolerated when administered via peripheral vein as a single administration up to 400 mg and multiple administrations of 200 mg IV once daily. A placebo-controlled arm of study TR701-107 showed that peripheral administration of IV TR-701 over 3 days showed a venous tolerability similar to a placebo regimen. Results from studies in elderly (TR701-109) or in subjects with renal impairment (with or without hemodialysis) (TR701-123) or hepatic impairment (TR701-124) showed that TR-701 FA was well tolerated with no meaningful changes noted in laboratory, vital sign, physical examination, or electrocardiogram (ECG) data. Moreover, these studies have shown that the dosing regimen does not require adjustment in these patients. Hence, the 200 mg QD dose can be used in all patient populations investigated to date.

In vitro studies evaluated the potential of tedizolid (TR700) and tedizolid phosphate (TR701) to inhibit the efflux transporter breast cancer resistant protein (BCRP) in human colorectal adenocarcinoma (Caco2) cells (IB). The BCRP transporters were inhibited at TR701 concentrations achievable in the intestinal lumen, suggesting that orally administered TR701 could interact with and raise the AUC of BCRP substrates (eg, rosuvastatin, methotrexate and topotecan). Co-administration of oral TR701 and oral rosuvastatin resulted in a 70% increase in AUC values for rosuvastatin. However, IV TR701 does not reach systemic concentrations that could inhibit BCRP (IB). Because this protocol requires the use of IV TR701 and this is an exclusively oral interaction, there is no risk of interaction in this trial.

Two pivotal Phase 3 studies, TR701-112 and TR701-113, were NI, global, multicenter, randomized, double-blind, double-dummy studies evaluating the efficacy and safety of oral (TR701-112) or IV to oral (TR701-113) TR-701 FA 200 mg once daily for 6 days versus oral linezolid 600 mg every 12 hours for 10 days for the treatment of acute bacterial skin and skin structure infection (ABSSSI) in adult patients. In TR701-112, 79.5% of patients in the TR-701 FA group (N=332) and 79.4% in the linezolid group (N=335) were responders at the 48-72 Hour Visit (ITT Analysis Set). A total of 85.5% and 86.0% of patients in the TR-701 FA and linezolid groups, respectively, were considered to be a clinical success based on the Investigator's assessment of clinical response at post-treatment evaluation in the ITT Analysis Set. In TR701-113, 85.2% of patients in the TR-701 FA group (N=332) and 82.6% in the linezolid group (N=334) were responders at the 48-72 Hour Visit (ITT Analysis Set). A total of 88.0% and 87.7% of patients in the TR-701 FA and linezolid groups, respectively, were considered to be a clinical success based on the Investigator's assessment of clinical response at post-treatment evaluation in the ITT Analysis Set (see the IB for additional details). These 2 studies provide evidence that tedizolid phosphate is effective in ABSSSI, a moderately severe infection, and is safe and well tolerated by oral or IV route. Results from a multiple-dose 21-day study (TR701-101) of oral 200, 300, or 400 mg TR-701 once daily showed that TR-701 was generally well tolerated over the 21-day treatment period; however, over time, a higher incidence of adverse events (AEs) at the 400 mg TR-701 dose was noted. The most common treatment-emergent adverse events (TEAEs) were generally in the Nervous System and Gastrointestinal Disorders system organ class category, including headache, nausea, and stomach discomfort. No remarkable hematologic effects were observed at 200 mg TR-701 once daily over 21 days; however, at higher doses of TR-701, hematologic effects gradually increased over time and were generally similar between subjects receiving 400 mg TR-701 once daily or 600 mg linezolid twice daily.

Taken together, results from these studies support the selection of 200 mg IV TR-701 FA once daily for 7 or 14 days in HABP/VABP.

Recent study results indicate that use of continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) results in minimal loss of tedizolid. The amount of drug lost is unlikely to require an adjustment in dose for patients using CVVH or CVVHD. The study, performed at the University of Michigan, included the two most common membranes used in CVVH and CVVHD and measured the percent loss of drug at different hemofiltration rates. The findings showed that the rate of removal of tedizolid from the blood was low and similar to the amounts observed with normal renal excretion and previous testing performed with intermittent hemodialysis which showed decreases of approximately 10% (Flanagan 2014). There was significant loss of tedizolid (approximately 50%) due to adsorption to the membrane and/or apparatus. Despite the losses observed in the model, the tedizolid losses in humans should not be significant since very little tedizolid is in the circulation given its low unbound drug concentrations and high volume of distribution. These results have been submitted for presentation at the International Symposium of Intensive Care and Emergency Medicine 2015 with journal submission anticipated.

In countries where tedizolid (SIVEXTRO) is approved, please consult the local prescribing information for additional information.

1.3 Safety Precautions for TR-701 FA

1.3.1 Potential Side Effects

Integrated AE data from Phase 1 studies indicated that the most common TEAEs were infusion site erythema, hematoma, pain, and swelling; vessel puncture site hematoma and pain; and headache, nausea, and diarrhea. Within the peripheral IV administration groups, the most common TEAEs included infusion site pain, erythema, and swelling; and vessel puncture site hematoma. Integrated AE data from oral Phase 2 and 3 studies in patients indicated that the most common TEAEs were nausea, diarrhea, and vomiting, abscess limb, and headache. In this integrated analysis, the type of AEs reported was similar between the TR-701 FA and linezolid groups. Additional information is provided in the IB.

Information on AEs considered associated with TR-701 FA is presented in an appendix of the IB. Information on the necessary warnings and precautions for use and the known safety profiles of linezolid are provided in the package insert (use local brand name prescribing information).

1.3.2 Unknown Risks

It is possible that study drug-related AEs that are unknown at this time could occur. It is also unknown whether TR-701 FA will be as efficacious as the comparator treatment. As linezolid will be used as a comparator, the safety considerations recommended in the package insert will be extended to all patients as a precaution (use local linezolid prescribing information). The linezolid label contains warnings for myelosuppression and *C difficile*-associated diarrhea, and also has precautions for lactic acidosis, serotonin syndrome, peripheral and optic neuropathy, and convulsions. Please consult the summary of data and guidance for the Investigator in the IB for additional important safety information for TR-701 FA and the local brand name prescribing information for linezolid.

Because TR-701 and linezolid are in the same class of antibiotic, oxazolidinones, and both drugs will be used in a blinded manner in the present study, the safety warnings and restrictions of linezolid should extend to TR-701 FA treated patients, as a precaution. Visual effects, peripheral neuropathy, and lactic acidosis have been observed following prolonged linezolid therapy, generally after more than 28 days of treatment. Any such occurrences should be carefully monitored in this study.

The risks to the fetus are unknown at this time. It is also unknown whether TR-700 is excreted in breast milk. Therefore, women who are pregnant or nursing are excluded from this clinical study and women of childbearing potential must use appropriate birth control.

1.4 Safety Precautions for Patients Treated with Serotonergic Agents Prior to Randomization

Serotonin syndrome is a serious, life-threatening condition that has been reported when linezolid was coadministered with monoamine oxidase inhibitors (MAOIs) or other serotonergic drugs (Appendix 1). Although the risk is extremely low, with a postmarketing review of worldwide data identifying 29 possible cases between 1997-2005 (Lawrence 2006), the latest linezolid drug safety update (http://www.fda.gov/Drugs/DrugSafety/ucm265305.htm#hcp) states that linezolid should generally not be given to patients taking serotonergic drugs. However, life-threatening conditions, including nosocomial pneumonia caused by MRSA, may warrant the risk and justify the use of linezolid.

With the reduction in vancomycin effectiveness, linezolid is now viewed as the therapy of choice for MRSA pneumonia (Wunderink 2012). Given the rarity of serotonin syndrome, linezolid provides a health benefit with little risk of this serious adverse reaction and provides an advantage over vancomycin in critically ill patients with unstable hemodynamics or renal impairment where drug levels must be monitored. The current prescribing information for linezolid indicates a contraindication for use with MAOIs and a warning and precaution for use with serotonergic agents. For this reason, patients receiving MAOIs within 2 weeks prior to randomization are excluded from enrollment and patients taking serotonergic drugs prior to randomization must discontinue the drugs during the study. As indicated in the FDA safety update, all patients receiving potentially interacting drugs within 30 days prior to randomization will need to be closely monitored for symptoms of central nervous system toxicity through the treatment period and for 24 hours following the end of study drug therapy. There is no evidence that TR-701 FA interacts with serotonergic agents; however, clinical experience is limited. Therefore, the same precautions should apply to patients receiving either TR-701 FA or linezolid. Please refer to local linezolid prescribing information for additional information.

1.5 Study Design Rationale

This protocol, ventilated pneumonia treatment with tedizolid phosphate and linezolid (VITAL), is designed as an NI study to address both FDA and EMA regulatory requirements for developing antimicrobial drugs for treatment of HABP/VABP. The primary efficacy outcome for this protocol is defined as 28-day ACM in the ITT Analysis Set, as defined by Sorbello et al. (Sorbello 2010). Clinical response at TOC (derived from the Investigator's assessment at the EOT and TOC Visits) in the ITT Analysis Set will be used as the primary outcome for support of registration for the EMA (EMA 2012). The criteria for efficacy and selection of the NI margins in this protocol are also consistent with the draft FDA and EMA guidances. This study provides 7 days of TR-701 FA treatment and 10 days of linezolid treatment for VNP, increasing to 14 days of either drug in patients with gram-positive bacteremia due to the same pathogen causing VNP. Treatment duration of TR-701 FA is based on results from a study by Chastre et al. (Chastre 2003), who demonstrated that a short course of therapy was similar in terms of ACM and relapse/recurrence rates compared to a

15-day course of treatment, except for infections due to nonfermenting gram-negative bacilli. Current consensus recommends 7 to 8 days for treatment of uncomplicated hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) in patients who initially received appropriate therapy (ATS Guideline 2005, Torres 2009) and 14 days of therapy for patients with uncomplicated bacteremia (Liu 2011). Linezolid is currently approved for first-line therapy of nosocomial pneumonia due to gram-positive pathogens in adult and adolescent patients, with a recommended treatment duration of 10-14 days.

The dosage selected for this study, TR-701 FA 200 mg IV once daily, is predicted to achieve adequate systemic and lung exposures resulting in antimicrobial efficacy against gram-positive bacterial respiratory infections in adult and adolescent patients. Anticipated physiologic changes in critically ill patients (eg, changes in regional blood flow to target and clearance organs, plasma protein levels, total body volume changes, and other treatment modalities that may impact drug disposition) are not expected to significantly alter TR-700 kinetics. This prediction is based on a review of studies investigating nonclinical and clinical microbiology, pharmacology, PK, PK/PD and safety/efficacy of TR-701 FA as detailed in the IB. In addition, recent results from a Phase 3 clinical study in adults with ABSSSI have provided evidence of efficacy and safety of TR-701 FA 200 mg once daily and support the continuation of the development plan in the HABP/VABP indication.

2.0 STUDY OBJECTIVES

The study objectives accommodate the unique requirements of different regulatory jurisdictions. In addition, the efficacy and safety of TR701-FA in the population of patients with sepsis will be evaluated under a Japan-Specific amendment. Further details are provided in Appendix 12.

2.1 Primary Objectives

The primary objective is to determine the noninferiority in all-cause mortality within 28 days after randomization of intravenous TR-701 FA compared with IV linezolid in the ITT Analysis Set in ventilated patients with presumed gram-positive hospital-acquired bacterial pneumonia or gram-positive ventilator-associated bacterial pneumonia, collectively defined as ventilated nosocomial pneumonia.

2.2 Secondary Objectives

The secondary objectives are as follows:

- To compare the ACM observed with TR-701 FA and linezolid within 28 days after randomization in the Micro-ITT Analysis Set
- To compare the clinical response for TR-701 FA and linezolid treatment at TOC in the ITT (EMA and Japan Ministry of Health, Labour, and Welfare primary endpoint) and CE Analysis Sets. Clinical response at TOC is derived from the Investigator's assessment at the EOT and TOC Visits, as detailed in the statistical analysis plan (SAP)
- To compare the per-patient favorable microbiological response rate at EOT in the Micro-ITT and Microbiologically Evaluable (ME)-1 Analysis sets and at TOC in the Micro-ITT and ME-2 Analysis Sets
- To evaluate the safety profile of TR-701 FA and compare with that of linezolid
- To assess the population PK and PK/ PD profile of TR-700

2.3 Exploratory Objectives

Additional efficacy objectives of this study to further characterize any difference between treatment groups include the following:

- To compare the ACM rates following TR-701 FA and linezolid therapy within 28 days after randomization (CE, Microbiologically Evaluable-1 [ME-1], and ME-2 Analysis Sets) and 14 days after randomization (ITT, Micro-ITT, and ME-1 Analysis Sets)
- To evaluate the activity of study drug as measured by change from baseline in procalcitonin level at Day 7 in the ITT and Micro-ITT Analysis Sets

- To characterize the plasma concentrations of TR-700 in patients with HABP/VABP, including estimation of typical PK parameters (eg, AUC) and inter-individual and residual variability
- To estimate the effects in patient-specific covariate factors of TR-700 PK
- To provide individual metrics of TR-700 exposure for modeling probabilities of clinical cure, microbiologic response, or safety outcomes

2.4 Outcomes

The primary outcome is ACM within 28 days after randomization in the ITT Analysis Set.

Secondary outcomes include the following:

- ACM within 28 days after randomization (Micro-ITT Analysis Set)
- Clinical response at TOC (ITT and CE Analysis Sets). Clinical response at TOC is derived from the Investigator's assessment at the EOT and TOC Visits
- Microbiological response at EOT and TOC (Micro-ITT, ME-1, and ME-2 Analysis Sets)
- ACM in patients with methicillin-susceptible *S aureus* (MSSA) or MRSA (Micro-ITT Analysis Set)
- Clinical response by Investigator in patients with MSSA or MRSA (Micro-ITT and ME-2 Analysis Sets)

Key exploratory outcome variables to be analyzed include the following:

- ACM within 28 days after randomization (CE, ME-1, and ME-2 Analysis Sets)
- ACM within 14 days after randomization (ITT, Micro-ITT, CE, and ME-1 Analysis Sets)
- Proportion of patients discharged from the acute care hospital within 28 days after randomization (ITT and Micro-ITT Analysis Sets)
- Change from baseline in procalcitonin level at Day 7 (ITT Analysis Set)
- Per-pathogen clinical response rate at TOC (Micro-ITT, ME-1, and ME-2 Analysis Sets)
- Per-pathogen ACM rate at 28 days after randomization (Micro-ITT, and ME-1, ME-2 Analysis Sets)
- Number of days in the ICU through 28 days after randomization (ITT and CE Analysis Sets)

Number of days on a ventilator through 28 days after randomization (ITT and CE Analysis Set)

3.0 INVESTIGATIONAL PLAN

This is a 1:1 ratio, randomized, double-blind, double-dummy, multicenter, global Phase 3 study of TR-701 FA 200 mg IV once daily for 7 days versus linezolid (Zyvox®, Zyvoxid®, etc) 600 mg IV every 12 hours for 10 days for the treatment of ventilated patients with presumed gram-positive HABP and VABP. Patients with concurrent gram-positive bacteremia are to receive 14 days of active therapy in either treatment arm.

Cubist (with the exception of the Clinical Drug Supply manager, and the Unblinded Global Study team), and the Investigators, study statistician, clinical study personnel, study staff participating in patient care or clinical evaluations, and patients will be blinded to therapy assignment until the database is locked. Pharmacy staff or designee, the independent Statistics Reporting Group (SRG), and the Data and Safety Monitoring Board (DSMB), will be unblinded. All study drug infusion bags and IV tubing will be covered and sealed with tamper-evident material in order to maintain the blind.

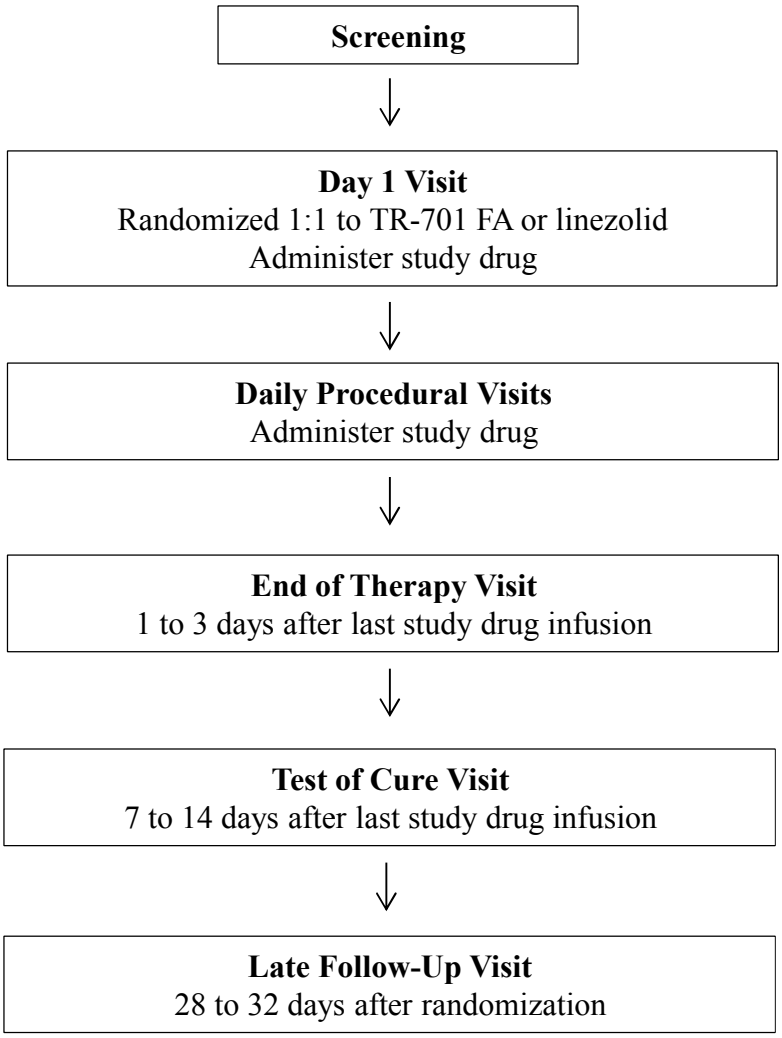
Approximately 300 sites will participate in this global study of approximately 726 randomized patients of which approximately 363 (50%) are expected to have a gram-positive pathogen isolated based on respiratory culture (Micro-ITT Analysis Set). Ventilated patients with HABP/VABP caused by presumed gram-positive pathogen(s) at baseline as determined by positive Gram stain will be randomized 1:1 to study drug treatment using an interactive voice response system (IVRS). Randomization will be stratified by geographic region, age (≥65 years or <65 years), and underlying diagnosis (trauma or nontrauma). A minimum of 50% of patients will have a diagnosis of VABP. Adjunctive therapy for appropriate gram-negative coverage will be selected based on Gram stain and site epidemiology (see Appendix 4).

The DSMB will be convened when approximately 30% (218 patients), 50% (363 patients), and 75% (545 patients) of patients have been randomized and complete 28 days of follow-up. A DSMB will review safety and efficacy data including ACM, TEAEs, incidence of serious TEAEs, study drug-related TEAEs, and study drug discontinuation due to study drug-related TEAEs, and other safety and efficacy related data. Only data for the first and the second interim looks will be unblinded (Treatment A vs Treatment B). At the first and second interim analysis, futility analysis based on the primary efficacy outcome of 28-day ACM in the ITT Analysis Set will be performed. The futility boundaries will be derived from the Gamma (-4.27) error spending function (Hwang 1990) and constructed to be nonbinding. The futility boundaries will be calculated using the actual information fractions at the time of the DSMB interim analysis. The DSMB charter will detail the review of safety, efficacy data and the futility analyses. The independent SRG will receive the blinded study data from Cubist and treatment assignment data directly from the IVRS vendor. The responsibility of SRG will be reviewing, analyzing, and preparing the DSMB interim data reports, including tables, listings, and figures, to be reviewed by DSMB members during DSMB meetings. The study is expected to complete enrollment in approximately 58 months and the duration of patient participation is up to 33 days (the Screening Visit through the Follow-Up Visit), unless a patient is being monitored for an AE. Patients are to be monitored for all AEs until

the last study visit (ie, 28 to 32 days after randomization). Serious adverse events (SAEs) are to be followed until stabilization, resolution/death, or consent is withdrawn.

A schema showing the study visits is presented in Figure 1. A more detailed Schedule of Study Procedures is provided in Appendix 11.

Figure 1. Study Schema for Study TR701-132



4.0 POPULATION

4.1 Selection and Withdrawal of Patients

Patients who meet the diagnostic criteria and all of the other inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

4.2 Inclusion Criteria

Patients who meet all of the following criteria are eligible to participate in this study:

1. Males or females ≥18 years old
2. Adequate venous access for IV study drug administration
3. Intubated (via endotracheal tube, including tracheostomy patients) and mechanically ventilated, AND
    - For HABP, at least 1 of the following signs or symptoms presenting within 24 hours prior to intubation of a patient hospitalized, including patients institutionalized in long-term care facilities, for ≥48 hours. If the patient has been discharged, discharge must have been within 7 days:
        - A new onset of cough (or worsening of baseline cough)
        - Dyspnea, tachypnea, or respiratory rate >30/minute, particularly if any or all of these signs or symptoms are progressive in nature
        - Hypoxemia (eg, a partial pressure of oxygen <60 mm Hg while the patient is breathing on room air as determined by arterial blood gas [ABG] or oxygen saturation <90% while the patient is breathing on room air as determined by pulse oximetry), or worsening (decline from any earlier finding) of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), or respiratory failure requiring mechanical ventilation
    - 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 ABG, or worsening PaO_2/FiO_2
        - Hypoxemia (eg, a partial pressure of oxygen less than 60 millimeters of mercury while receiving FiO_2 of 25-30%, as determined by ABG or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2)
        - New onset or worsening pulmonary symptoms or signs, such as cough, asymmetric breath sounds, tachypnea (eg, respiratory rate greater than 25 breaths per minute), need for increased oxygenation or ventilation support

4. Chest radiograph shows the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia (based on Investigator evaluation; report from qualified medical professional who is not the Investigator to be provided)
5. Clinical findings to support diagnosis of HABP/VABP
    - New onset of suctioned respiratory secretions characterized by purulent appearance indicative of bacterial pneumonia
    - And at least 1 of the following:
        - Documented fever (oral ≥38°C [100.4°F] or a tympanic, temporal, rectal, or core temperature ≥38.3°C [101°F]) **OR**
        - Hypothermia (core body temperature ≤35°C [95.2°F]) **OR**
        - Total peripheral white blood cell (WBC) count ≥10,000 cells/mm^3 **OR**
        - Leukopenia with total WBC ≤4500 cells/mm^3 **OR**
        - ≥15% immature neutrophils (bands; if local laboratory has capabilities to measure)
6. High probability of pneumonia caused by gram-positive bacteria only or in a mixed infection defined as follows:

    Respiratory Sample

    - Sample acquired and Gram stain performed within 36 hours prior to first infusion of study drug using an acceptable purulent respiratory specimen such as sputum or endotracheal aspirate sample with <10 squamous epithelial cells (SEC) and >25 polymorphonuclear (PMN) cells per low-power field showing gram-positive bacteria (with or without gram-negative bacteria) **OR**

    - Sample acquired and Gram stain performed within 36 hours prior to first infusion of study drug using an acceptable respiratory specimen such as protected specimen brush, bronchoalveolar lavage (BAL), mini-BAL, or sample from an exudative pleural effusion showing gram-positive bacteria (with or without gram-negative bacteria) **OR**

    - Culture from lower respiratory sample obtained within 72 hours prior to first infusion of study drug positive for methicillin-resistant *S aureus* (MRSA) **OR**

    - Rapid molecular diagnostic test (for example Xpert®) positive for MRSA

4.3 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to participate in this study:

1. Known or suspected community-acquired bacterial pneumonia or viral, fungal (presence of *Candida* in lower respiratory tract is not exclusionary), or parasitic pneumonia
2. Any of the following health conditions:
   - *Legionella* infection (*Legionella pneumophila* pneumonia)
   - Cystic fibrosis
   - Human immunodeficiency virus (HIV) infection with last known CD4 count <200 cell/mm³ (HIV testing is not required)
   - Known or suspected *Pneumocystis jirovecii* pneumonia
   - Known or suspected active tuberculosis
   - Lung abscess
   - Evidence of endocarditis
   - Tracheobronchitis (if no evidence of pneumonia)
3. Received systemic or inhaled antibiotic therapy effective for gram-positive pathogens that cause VNP for >24 hours (for example, >1 dose of a once-daily antibiotic, >2 doses of a twice daily antibiotic) in the last 72 hours

   EXCEPTIONS

   - Progression of disease on the prior antibacterial regimen for this episode of VNP after >48 hours of treatment, **OR**
   - Patient developed symptoms of pneumonia and a new infiltrate while receiving the prior antibacterial regimen for reasons other than the current VNP, **OR**
   - Patient received systemic antibacterial therapy that does not cover the gram-positive pathogen isolated on respiratory culture, **OR**
   - Antibiotic therapy for gut decontamination or gut motility (example, low-dose erythromycin) or *C difficile* infection
4. Receipt of monoamine oxidase A and B inhibitors (see Appendix 1) from 2 weeks prior to randomized or planned use through the EOT Visit
5. Planned use of agents with serotonergic activity (see Appendix 1 and Section 1.4) through the EOT Visit
6. Administration of linezolid or tedizolid phosphate ≤30 days before the first infusion of study drug, except for receipt of a single administration of linezolid, within 24 hours prior to the first administration of study drug to treat the current VNP

7. Bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients with pneumonia who have underlying chronic obstructive pulmonary disease)
8. Primary lung cancer or another malignancy metastatic to the lungs
9. Recent opportunistic infection where the underlying cause of the infection is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome)
10. Expected survival <72 hours or any 1 of the following:
    - Comfort care measures only
    - Acute respiratory distress syndrome/acute lung injury secondary to septic shock, or due to third degree burns or inhalation injury
    - Nonresolving pulmonary edema secondary to congestive heart failure
11. Burns >40% of total body surface area
12. Current or anticipated neutropenia with absolute neutrophil count <500 cells/mm^3
13. Severe renal disease requiring peritoneal dialysis. Patients with severe renal disease on hemodialysis, venovenous dialysis, or other forms of renal filtration may be enrolled
14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥10× upper limit of normal OR severe hepatic disease with Child-Pugh score >9
15. Investigator's opinion of clinically significant ECG finding such as ischemia, infarct, or ventricular arrhythmia with immediate potential for a fatal outcome, or, prior to the current infection, a history of New York Heart Association Class IV cardiac failure defined as severe limitations - experiences symptoms even while at rest, mostly bedbound patients, within 1 year
16. Patients with uncontrolled hypertension (defined as high blood pressure that is clinically an issue and uncontrolled on multiple medications), pheochromocytoma, carcinoid syndrome, or thyrotoxicosis
17. Treatment with investigational medicinal product ≤30 days before the first infusion of study drug or prior randomization in this protocol
18. Investigational device present, or removed <30 days before the first infusion of study drug or presence of device-related infection
19. Hypersensitivity to oxazolidinones (eg, linezolid) or any component in the formulation
20. Women who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel], or male partner sterilization); excluding women ≥2 years postmenopausal or surgically sterile

4.4 Patient Withdrawal from the Study

Patients may withdraw or be withdrawn from the study at any time. Patients may be discontinued from the study at the request of the Investigator or Cubist. Reasonable efforts are to be made to complete all protocol-specified assessments listed for the EOT Visit at the time of withdrawal (Section 6.6) and to perform follow-up safety assessments as specified in Section 6.8 at the protocol-defined time points. The safety assessments at the EOT Visit are to be completed before beginning new antibiotic therapy. Patients who withdraw or are withdrawn will not be replaced.

4.5 Discontinuation of Treatment

Reasons for discontinuation of study drug include, but are not limited to, the following:

- Patient or legally authorized representative requests discontinuation of the study drug or withdrawal from the study
- Unacceptable toxicity

In the case of unacceptable toxicity leading to consideration of study drug discontinuation, the Medical Monitor is to be consulted immediately for additional advice regarding patient management and data collection requirements.

- AEs or laboratory changes considered clinically relevant, documented to be worsening from the Screening Visit on repeat testing, and considered to be at least possibly related to study drug; eg, anemia or hemoglobin <8 g/dL, thrombocytopenia or platelet count <50,000 plts/mm^3, leukopenia/neutropenia or total WBC count ≤1000 cells/mm^3 or absolute neutrophil count ≤500 cells/mm^3, or pancytopenia
- Evidence of new or worsening hepatic function during study treatment, ie, ALT or AST ≥3× upper limit of normal (ULN) with either elevated total bilirubin ≥2× ULN or international normalized ratio (INR) >1.5 or AST/ALT >3× ULN with the appearance of right upper quadrant pain or tenderness, or peripheral eosinophilia (>5%), rash, and/or fever. Study drug is to be discontinued and serum ALT, AST, alkaline phosphatase, and total bilirubin and/or INR testing are to be repeated at 48 to 72 hours after discontinuation of study drug and until medically stable (FDA Guidance, Drug-Induced Liver Injury 2009)
- Evidence of optic neuropathy (AEs including new or worsening visual impairment not explained by an alternative cause, such as persistent and/or worsening blurred vision, visual field cut, color blindness, or reduction in light perception). Development of optic neuropathy should prompt a consultation with an ophthalmologist. Investigators are strongly recommended to have patients consult with a neurologist as appropriate
- Evidence of serious peripheral neuropathy or serious cranial neuropathy (eg, facial nerve palsy) not explained by an alternative cause. Development of serious peripheral neuropathy or serious cranial neuropathy should prompt a consultation with a neurologist (if appropriate) who will decide whether an electromyogram and/or nerve conduction studies are appropriate

- Patient becomes pregnant
- Investigator-assessed treatment failure (patient should receive rescue therapy following Investigator's judgment)
- Investigator considers a change of therapy would be in the best interest of the patient

Patients **MAY** be discontinued from the study if culture results from the respiratory sample taken at the Screening Visit shows either only gram-negative bacteria **OR** gram-positive bacteria that is below the prospective site-specific and respiratory specimen-specific quantitative threshold (sites may use either qualitative results or thresholds). Prior to discontinuation, Investigators should consider the initial Gram stain result and the timing of antibiotic therapy in relation to respiratory sample acquisition. In some instances, prior antibiotic use may affect culture results if administered prior to sample acquisition.

4.6 Study Discontinuation

Cubist reserves the option to terminate the study at any time. Reasons for terminating the study or terminating the participation of a specific site include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies with the study drug indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- The Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- The Institutional Review Board (IRB)/Ethics Committee (EC)/Research Ethics Board (REB) decides to terminate or suspend approval for the study or the Investigator
- The Investigator asks to withdraw from study participation

4.7 Prohibited Medications

Receipt of MAOIs is prohibited in the 2 weeks prior to randomization through the EOT Visit (see Appendix 1). Receipt of the following medications is prohibited between the first study drug infusion through the EOT Visit: serotonergic agents including antidepressants such as SSRIs, tricyclic antidepressants, and serotonin 5-HT1 receptor agonists (triptans), meperidine (or other phenylpiperidines), or buspirone. Considerations should be made to use alternatives to meperidine.

5.0 STUDY TREATMENT

5.1 Description of Study Drug

5.1.1 TR-701 FA

TR-701 FA is formulated as a sterile lyophilized powder for injection for IV administration. *TR-701 FA for Injection, 200 mg*, is formulated with TR-701 FA, mannitol, and sodium hydroxide that are lyophilized in a 10 mL clear glass vial with a 20 mm gray butyl stopper, and a 20 mm seal with flip-off top. The resulting drug product is a white to off-white cake that results in a clear, colorless to light-yellow solution after reconstitution.

The vial should be reconstituted with 4 mL of Sterile Water for Injection and added to a 250 mL IV bag containing 0.9% Sodium Chloride Injection, USP for IV administration. Study drug should be prepared by qualified clinical staff following directions provided in the Pharmacy Manual.

TR-701 FA for Injection is manufactured according to Good Manufacturing Practice. Additional information is provided in the Pharmacy Manual.

Placebo for TR-701 FA for Injection, 200 mg, is a sterile saline solution in a 250 mL infusion bag.

5.1.2 Linezolid

Linezolid IV Injection (300 mL bag), 600 mg, a marketed ready-to-use product, is supplied by Cubist, a designee, or the site if approved by the Sponsor, and blinded by the site.

Placebo for Linezolid IV Injection is a sterile saline solution in a 300 mL infusion bag.

5.1.3 Adjunctive Therapy

Refer to Appendix 4 for information on adjunctive therapy. Adjunctive therapy will be supplied by the site unless otherwise approved by Cubist. Local prescribing guidance is to be followed regarding use of specific adjunctive therapy.

5.2 Packaging, Labeling, and Storage

A lyophilized vial of *TR-701 FA for Injection, 200 mg* (50 mg/mL) is to be prepared by qualified clinical staff following directions provided in the Pharmacy Manual.

TR-701 FA for Injection, 200 mg, should be stored at 20 to 25°C (68°F to 77°F); excursions are permitted to 15°C and 30°C (59°F to 86°F). The study drug should be administered within 12 hours after reconstitution.

All medication (linezolid and adjunctive therapy) is to be stored according to the instructions in the package insert.

The unblinding procedures are described in Section 5.5.

5.3 Dose, Blinding, and Administration

5.3.1 Dose

Patients will receive IV TR-701 FA 200 mg once daily for 7 days or IV linezolid 600 mg twice daily for 10 days. If the patient has gram-positive bacteremia (see Appendix 5 for the list of pathogens), treatment duration for either study drug is 14 days. Bacteremia is defined as 1 positive blood culture for *S aureus*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes*, or 2 positive blood cultures for any other gram-positive lung pathogen.

5.3.2 Blinding

All infusion bags will be sealed with tamper-evident material. Cubist (with the exception of the Clinical Drug Supply manager and Unblinded Global Study team), and the Investigator, study staff participating in direct patient care or clinical evaluations (study drug administration, efficacy and safety measurements, etc) and patients will be blinded to treatment assignment. The staff responsible for IV study drug preparation will be unblinded to treatment and will prepare all infusion bags and attached tubing. The unblinded pharmacy staff or designee are responsible for ensuring that a current record of inventory and drug accountability is maintained. A designated unblinded study monitor will be responsible for verifying drug accountability at the sites. Infusion bags will be returned to a secure location accessible only to staff unblinded to treatment, unless otherwise approved by Cubist. Detailed information on means of blinding of the infusion bags and tubing is included in the Pharmacy Manual. Additionally, a DSMB will review unblinded safety and efficacy data.

5.3.3 Administration

Flush IV line before and after study drug administration. No other IV therapy should be administered through the same lumen concurrent with the study drug.

Patients will receive 10 days of study drug administration, some of which may be placebo administration, or if the patient has gram-positive bacteremia, 14 days of active study drug. Bacteremia is defined as 1 positive blood culture for *S aureus*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes*, or 2 positive blood cultures for any other gram-positive lung pathogen. Personnel who are blinded to treatment are to notify the pharmacy staff or designee if blood cultures from the Screening Visit are positive, and the patient requires extended therapy (14 days). Patients will receive 3 infusions daily. The daily study drug administration schedule for patients without bacteremia is presented in Table 1 and with bacteremia in Table 2.

The entire contents of the infusion bag will be administered. All infusions will be 60±10 minutes and start and stop time will be recorded in the source documents and e-CRFs. Each odd-numbered IV dose (through dose 13 or 27, see Table 1 and Table 2) will consist of 2 separate and serial infusions: Infusion A will be administered over 60 minutes

(±10 minutes) and followed by a saline line flush, and then Infusion B will be administered over 60 minutes (±10 minutes). As shown in Table 1 and Table 2, Infusion A will always be active TR-701 FA or placebo TR-701 FA and Infusion B will always be active linezolid or placebo linezolid. An infusion schema is provided in Figure 2.

Doses should be given every 12 hours ± 2 hours from start of Infusion A of odd numbered dose (eg, Dose 1) to next even numbered dose (eg, Dose 2). Initiate gram-negative therapy at Study Day 1 and continue according to Investigator's judgment. Gram-negative adjunctive therapy will be administered to all patients based on initial Gram stain results or a rapid diagnostic test, patients and site epidemiology, and then adjusted by the Investigator based on the results of the microbiology assessments (see Appendix 5).

Figure 2. Infusion Schema

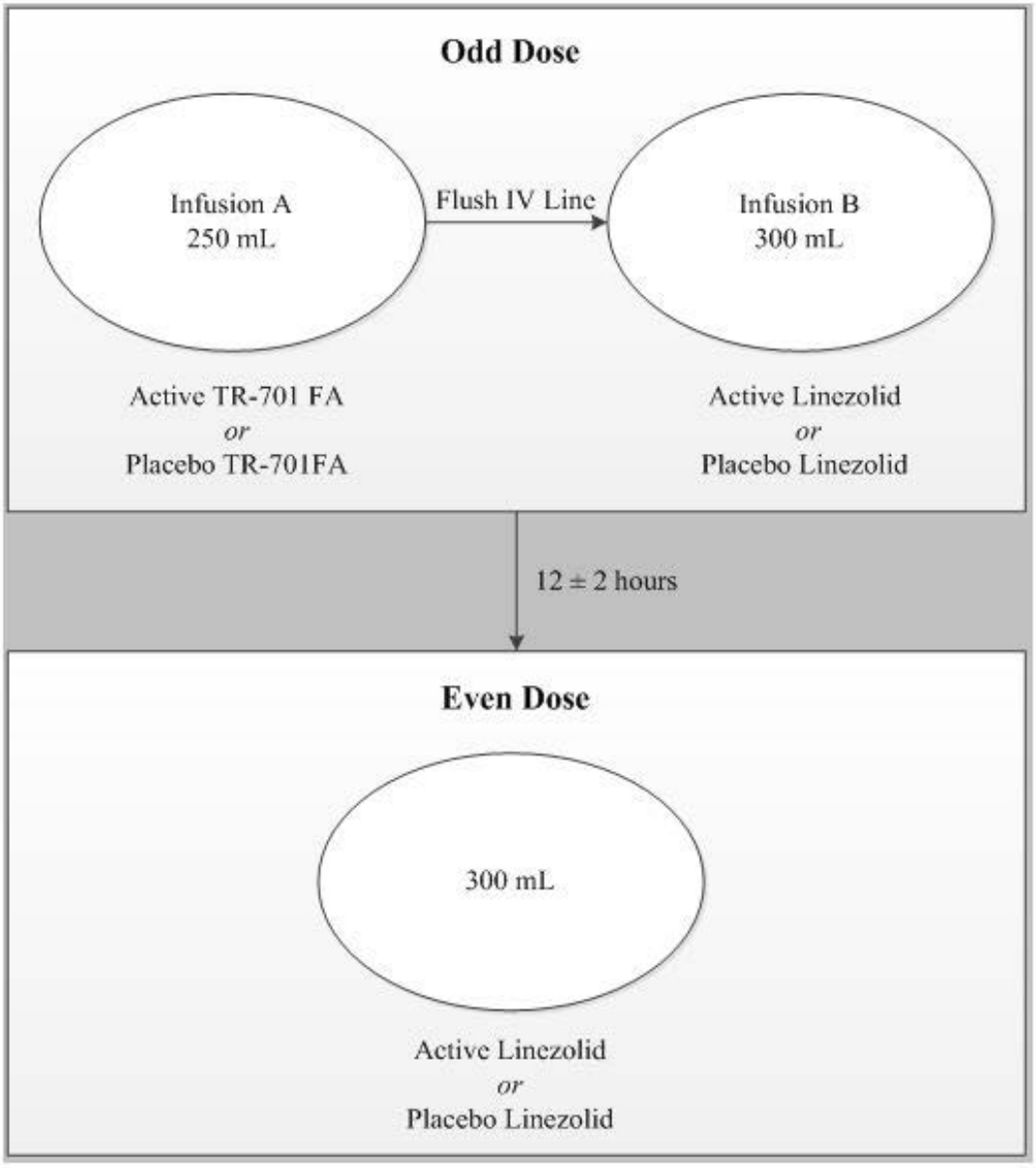


Table 1. Daily Dose Schedule by Treatment Group

Dose	TR-701 FA (TR) Group	Linezolid (LZ) Group
Dose 1	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 2	Placebo LZ	Active LZ
Dose 3	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 4	Placebo LZ	Active LZ
Dose 5	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 6	Placebo LZ	Active LZ
Dose 7	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 8	Placebo LZ	Active LZ
Dose 9	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 10	Placebo LZ	Active LZ
Dose 11	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 12	Placebo LZ	Active LZ
Dose 13	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 14	Placebo LZ	Active LZ
Dose 15	Placebo LZ	Active LZ
Dose 16	Placebo LZ	Active LZ
Dose 17	Placebo LZ	Active LZ
Dose 18	Placebo LZ	Active LZ
Dose 19	Placebo LZ	Active LZ
Dose 20	Placebo LZ	Active LZ

Abbreviations: LZ=linezolid infusion bag (300 mL); TR=TR-701 FA infusion bag (250 mL).
Note: Shading represents treatment days with active study drug.

Table 2. Daily Dose Schedule by Treatment Group: Patients with Gram-positive Bacteremia

Dose	TR-701 FA (TR) Group	Linezolid (LZ) Group
Dose 1	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 2	Placebo LZ	Active LZ
Dose 3	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 4	Placebo LZ	Active LZ
Dose 5	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 6	Placebo LZ	Active LZ
Dose 7	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 8	Placebo LZ	Active LZ
Dose 9	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 10	Placebo LZ	Active LZ
Dose 11	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 12	Placebo LZ	Active LZ
Dose 13	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 14	Placebo LZ	Active LZ
Dose 15	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 16	Placebo LZ	Active LZ
Dose 17	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 18	Placebo LZ	Active LZ

Dose	TR-701 FA (TR) Group	Linezolid (LZ) Group
Dose 19	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 20	Placebo LZ	Active LZ
Dose 21	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 22	Placebo LZ	Active LZ
Dose 23	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 24	Placebo LZ	Active LZ
Dose 25	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 26	Placebo LZ	Active LZ
Dose 27	Infusion A: Active TR Infusion B: Placebo LZ	Infusion A: Placebo TR Infusion B: Active LZ
Dose 28	Placebo LZ	Active LZ

Abbreviations: LZ=linezolid infusion bag (300 mL); TR=TR-701 FA infusion bag (250 mL).
Note: Shading represents treatment days with active study drug.

5.4 Method of Assigning Patient to Study Treatment

Patients are to be assigned to receive TR-701 FA or linezolid in a 1:1 ratio with stratification by geographic region, age (18 to <65 and ≥65 years), and underlying diagnosis (trauma or nontrauma based on the most current diagnosis prior to intubation and mechanical ventilation) using block randomization via the IVRS. Patients randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule.

5.5 Maintaining the Randomization Codes and Breaking the Study Blind

Cubist designee (eg, study statistical team, IVRS vendor) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained, and that only Cubist personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes, unblinded team monitoring study drug accountability, or SAE reporting).

Investigators are not to break the study treatment blind except when information concerning the study drug is necessary for the medical treatment of the patient. If a medical emergency requiring unblinding occurs, the Investigator (or designated physician) is strongly encouraged to contact the Regional Medical or Safety Monitor to assess the necessity of breaking the study treatment blind. If unblinding is warranted, the site is to call the IVRS for information. Every effort is to be made to limit study site personnel unblinding to only those individuals providing direct care to that patient. Any intentional or unintentional breaking of the blind is to be reported immediately to Cubist.

The other circumstances in which unblinding may be necessary are at the request of a patient or the patient's legally authorized representative in the case of pregnancy during the study or for regulatory reporting purposes. The unblinding procedure outlined above is to be followed in the event of a pregnancy (see also Section 9.5). The procedure for unblinding by Cubist for regulatory reporting of an expedited SAE is outlined in Section 9.2 and more details are available in the internal safety plan.

After the database is locked and the SAP is final, the study blind codes will be broken.

5.6 Measures of Treatment Compliance

The infusion date and start and stop times will be recorded in the source documents and electronic case report form (e-CRF). In the event of a missed dose, please contact Cubist or designee to discuss how to continue therapy.

5.7 Study Drug Accountability and Retention

All TR-701 FA required for completion of this study will be provided by Cubist or Cubist's designee, except saline for injection. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Linezolid IV is supplied by Cubist, a designee, or the site if approved by the Sponsor. Accurate records of all study drug (TR-701 FA and linezolid) received and dispensed are to be maintained. A Study Monitor will be responsible for checking study drug accountability at the study site. Inventory records must be available for inspection by Cubist, a designee of Cubist, or the FDA at any time. The Investigator will be responsible for ensuring the study drug is used in accordance with this protocol.

Additional information regarding study drug accountability and retention is provided in the Pharmacy Manual.

All unused IV materials and packaging are to be retained at the study site until receipt of written instruction from Cubist regarding disposition. All records related to study drug supply and disposition are to be maintained by the study site.

6.0 DESCRIPTION OF STUDY PROCEDURES

The Schedule of Study Procedures is provided in Appendix 11.

6.1 Screening

- Review and obtain informed consent before any study procedures are performed.

The following assessments are to be performed within 24 hours before the first infusion, unless otherwise noted:

- Record medical and surgical history for the previous 5 years
- Perform a directed physical examination
- Record prior medications taken ≤30 days before the first infusion
- Record height and weight (estimate if necessary)
- Record lowest and highest vital signs in the last 24 hours (blood pressure, heart rate, respiration rate)
- Record lowest and highest core (or core approximate, such as esophageal, pulmonary artery catheter (Swan-Ganz), urinary bladder, or rectal), temporal, or tympanic temperature in the last 24 hours
- Perform 12-lead ECG and record Investigator's interpretation
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available
- Record highest minute ventilation (L/min) and highest FiO_2 in the last 24 hours
- Determine Acute Physiology and Chronic Health Evaluation (APACHE) II score (if all components available, see Appendix 7)
- Determine Glasgow Coma Scale score (see Appendix 8)
- Collect and document CPIS (Appendix 2) and SOFA (Appendix 3) scores, if data from all components are available
- Obtain chest x-ray (lateral and posteroanterior or portable when the patient's condition does not permit transport to radiology), performed in supine position if possible. Computed tomography (CT) scan is also acceptable. Perform within 36 hours prior to infusion
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.

- Obtain and send clinical laboratory samples to the local laboratory and, for patients who are randomized, also send samples to the central laboratory, as shown in Table 3.

Table 3. Screening Samples for Safety Laboratory Assessments

Sample Test	**Laboratory**		**Comments**[b]
	Local	**Central**[a]	
Blood			
Hematology panel, Complete blood count (CBC) with differential	×	×	
Serum chemistry panel	×	×	
Coagulation parameters	×		Prothrombin time, partial thromboplastin time, and international normalized ratio
Procalcitonin		×	
Pregnancy	×		All females of childbearing potential (excludes females who are ≥2 years postmenopausal or surgically sterile)

[a]Send samples to the central laboratory only for patients who will be randomized. (Central laboratory evaluations will not be performed on patients who fail screening).
[b]Use local laboratory results for patient eligibility and timely treatment decisions. A list of laboratory evaluations is provided in Appendix 9.

- Calculate whether the patient's prothrombin time (PT) is prolonged compared with the control PT using the values provided by the local laboratory as follows:
  - PT prolongation (seconds prolonged) = [*insert patient's PT in sec*] – [*insert control time in sec*]
  - OR
- Calculate the patient's INR using the patient and control PT values provided by the local laboratory and the international sensitivity index (ISI) of a tissue factor as follows:
  - $$\left[\text{INR} = \frac{(\textit{insert patient's PT in seconds})}{(\textit{insert control PT in seconds})}^{ISI} \right]$$

- Calculate the patient's Child-Pugh score according to the following chart:

Parameter	Points		
	1	2	3
Ascites	None	Medically controlled	Poorly controlled
Encephalopathy*	None	Medically controlled	Poorly controlled
Total bilirubin (mg/dL)	<2	2 – 3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
INR	<1.7	1.7 – 2.3	>2.3
(or PT prolongation in sec)	(<4)	(4 – 6)	(>6)

*If sedated, use last known encephalopathy status before sedation

- Estimate the patient's creatinine clearance (CLcr) using the serum creatinine value provided by the local laboratory, actual body weight, and the appropriate Cockcroft-Gault formula. If necessary, convert serum creatinine values from µmol/L to mg/dL by dividing by 88.4. For example, 100 µmol/L divided by 88.4 equals 1.131 mg/dL

  Males:

  $$\text{CLcr} = \frac{(140 - [\textit{insert age in years}]) \times [\textit{insert weight in kg}]}{72 \times [\textit{insert serum creatinine in mg/dL}]}$$

  Females:

  $$\text{CLcr} = \mathbf{0.85} \times \frac{(140 - [\textit{insert age in years}]) \times [\textit{insert weight in kg}]}{72 \times [\textit{insert serum creatinine in mg/dL}]}$$

- Document any rapid diagnostic test or polymerase chain reaction (PCR) respiratory sample results if done at admission and/or within 72 hours prior to screening. Document the most recent nasal swab since admission to hospital or ICU
- Obtain microbiological specimen(s) from blood, urine for *Legionella* antigen assay, and the lower respiratory tract and/or pleural fluid within 36 hours (or if culture positive for MRSA within 72 hours) before administration of any antibiotic, if possible, and send to the local laboratory; for patients who are randomized, also send isolates to the central laboratory as shown in Table 4. If blood culture is positive for gram-positive pathogen, extend treatment to 14 days

Table 4. Screening Samples for Microbiology Assessments

Screening Samples for Microbiology Assessments	Laboratory		Comments
	Local	Central[a]	
Lower respiratory tract (LRT) specimen or pleural fluid specimen, unless there is isolation of MRSA from the LRT in the 72 hours prior to screening/enrollment			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 squamous epithelial cells [SEC] and >25 polymorphonuclear [PMN] cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on *S aureus* isolates is required.
Gram stain, culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory except for those listed as never a pathogen in Appendix 5.
Blood Cultures			From each of 2 different veins or vascular access catheters, collect 1 vial for aerobic testing and 1 for anaerobic testing (if available) from each vein for a total of 4 vials. If anaerobic testing is not available at the site, collect only 1 vial for aerobic testing from each vein for a total of 2 vials
Gram stain (optional), culture, and susceptibility testing	×		Send all vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	All isolates from a local laboratory culture are to be sent to the central laboratory If positive, repeat within 24 hours
Urine *Legionella pneumophila* antigen	×		If positive, patient should not be randomized

[a]Send samples to the central laboratory only for patients who will be randomized. (Central laboratory evaluations will not be performed on patients who fail screening).

- Record any pretreatment AEs
- Verify patient meets inclusion and exclusion criteria

6.2 Study Day 1

Study Day 1 is defined as the calendar day on which the first infusion is administered.

- If original consent was provided by someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- Once Investigator has determined that the patient is eligible for entry into the study, randomize the patient using the IVRS as close to administration of the first infusion of study drug as possible
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.
- Administer study drug Dose 1 as 2 separate and serial 60-minute infusions (±10 minutes). Initiate Infusion A, flush the line, and then initiate Infusion B
- Record any medications received after study drug administration and reason for use
- Record lowest and highest vital signs (blood pressure, heart rate, respiration rate) obtained on the calendar day (Note: Perform only if Day 1 is different calendar day from Screening)
- Record lowest and highest core (or core approximate, such as esophageal, pulmonary artery catheter (Swan-Ganz), urinary bladder, or rectal), temporal, or tympanic temperature obtained on the calendar day (Note: Perform only if Day 1 is different calendar day from Screening)
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available. (Note: Perform only if Day 1 is different calendar day from Screening)
- Select gram-negative adjunctive therapy as needed (see Appendix 4)
- If approved by ethics and/or local regulatory authorities, collect 1 blood sample for PK analysis between 5 and 80 minutes after the completion of Dose 1, Infusion A, and 1 sample between 4 and 12 hours after the completion of Dose 1, Infusion A; see Appendix 10
- Record any pretreatment AEs
- Record treatment-emergent adverse events (TEAEs) including any local reactions that develop during or after the infusion; document procedures performed due to an AE
- Document hospitalization status and ventilator status

6.3 Study Day 2

- If original consent was provided by someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.
- Record any new concomitant medication and the reason for its use
- Record the daily lowest and highest temperature while the patient is hospitalized and receiving IV study drug therapy
- Record lowest and highest vital signs obtained on the calendar day (blood pressure, heart rate, respiration rate)
- Perform directed physical examination
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available
- Record highest minute ventilation (L/min) and highest FiO_2 obtained on the calendar day
- If clinically indicated (see Section 8.2), obtain microbiological specimen(s) from the lower respiratory tract and/or pleural fluid, send to the local laboratory and send isolates to the central laboratory as shown in Table 5

Table 5. Day 2 Samples for Microbiology Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Lower respiratory tract specimen or pleural fluid specimen (if clinically indicated, such as increased purulence, fever, expansion of the infiltrate on the x-ray, increased minute ventilation, etc.)			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 SEC and >25 PMN cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on S aureus isolates is required.
Gram stain (optional), culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5.

- Re-evaluate selection of adjunctive therapy based on microbiology and susceptibility results
- Administer study drug
- Assess any ongoing or new AEs including any local reactions that develop during or after the infusion; document procedures performed due to an AE
- Document hospitalization status and ventilator status

6.4 Study Day 3

- If original consent was provided by someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.
- Record any new concomitant medication and the reason for its use
- Record the lowest and highest temperature obtained on the calendar day while the patient is hospitalized and receiving IV study drug therapy
- Record lowest and highest vital signs (blood pressure, heart rate, respiration rate) obtained on the calendar day
- Determine Glasgow Coma Scale score (see Appendix 8)
- Perform directed physical examination
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available.
- Record highest minute ventilation (L/min) and highest FiO_2 if patient remains ventilated
- If clinically indicated (see Section 8.2), obtain microbiological specimen(s) from blood and/or the lower respiratory tract/or pleural fluid. Send specimens to the local laboratory and isolates to the central laboratory as shown in Table 6.

Table 6. Day 3 Samples for Microbiology Assessments

Sample Test	Laboratory		Comments
	Local	**Central**	
Lower respiratory tract specimen or pleural fluid specimen (if clinically indicated, such as increased purulence, fever, expansion of the infiltrate on the x-ray, increased minute ventilation, etc.)			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 SEC and >25 PMN cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on *S aureus* isolates is required.
Gram stain (optional), culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory except for those listed as never a pathogen in Appendix 5.
Blood Cultures (if clinically indicated)			From each of 2 different veins or vascular access catheters, collect 1 vial for aerobic testing and 1 for anaerobic testing (if available) from each vein for a total of 4 vials. If anaerobic testing is not available at the site, collect only 1 vial for aerobic testing from each vein for a total of 2 vials
Gram stain (optional), culture, and susceptibility testing	×		Send all vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	All isolates from a local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5. If blood culture is positive, repeat within 24 hours

- Re-evaluate selection of adjunctive therapy and adjust according to microbiology and susceptibility results (Appendix 4)
- Administer study drug
- Assess any ongoing or new AEs including any local reactions that develop during or after the infusion; document procedures performed due to an AE
- Document hospitalization status and ventilator status

6.5 Study Days 4 to 10 for Nonbacteremic Patients; Study Days 4 to 14 for Gram-positive Bacteremic Patients

- If original consent was provided by someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- If the patient is medically able (ie, alert and extubated) on any Study Day, perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.
- Record any new concomitant medication and the reason for its use
- Record the lowest and highest temperature obtained on the calendar day while the patient is hospitalized and receiving IV study drug therapy
- Record lowest and highest vital signs (blood pressure, heart rate, respiration rate) obtained on the calendar day
- Determine Glasgow Coma Scale score (see Appendix 8; Day 7 only)
- Perform directed physical examination
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available.
- Record highest minute ventilation (L/min) and highest FiO_2 if patient remains ventilated
- Obtain and send clinical laboratory samples to the local and central laboratories on Day 7, Day 10, and, for bacteremic patients only, on Day 14, as shown in Table 7

Table 7. Day 7 and Day 10 (and Day 14 for bacteremic patients only) Samples for Safety Laboratory Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Blood			
Hematology, CBC with differential		×	
Serum chemistry panel		×	
Procalcitonin [a]		×	
Repeat test for any previous laboratory result of potential safety concern	×		At the Investigator's discretion; use local laboratory results for timely patient treatment decisions

[a]Obtain sample on Day 7.

- **Day 4 or Day 5, and Day 7 only**. Day 4 or Day 5: obtain blood sample for PK analysis before Infusion A (Dose 7 or Dose 9). Day 7: obtain 3 samples for PK analysis, 2 samples between 5 and 80 minutes after the completion of Infusion A (Dose 13) and 1 sample between 4 and 12 hours after the completion of Infusion A (Dose 13); see Appendix 10

- Obtain microbiological specimen(s) from blood and the lower respiratory tract/or pleural fluid, if clinically indicated. Send specimens to the local laboratory and isolates to the central laboratory as shown in Table 8

Table 8. Days 4 to 10 (Days 4 to 14 for gram-positive bacteremic patients) Samples for Microbiology Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Lower respiratory tract specimen or pleural fluid specimen (if clinically indicated, such as increased purulence, fever, expansion of the infiltrate on the x-ray, increased minute ventilation, etc.)			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 SEC and >25 PMN cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on *S aureus* isolates is required.
Gram stain (optional), culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory except for those listed as never a pathogen in Appendix 5.
Blood Cultures (if clinically indicated)			From each of 2 different veins or vascular access catheters, collect 1 vial for aerobic testing and 1 for anaerobic testing (if available) from each vein for a total of 4 vials. If anaerobic testing is not available at the site, collect only 1 vial for aerobic testing from each vein for a total of 2 vials
Gram stain (optional), culture, and susceptibility testing	×		Send all vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	All isolates from a local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5. If blood culture is positive, repeat within 24 hours

- Re-evaluate adjunctive therapy and adjust therapy based on microbiology and susceptibility results
- Administer study drug
- Assess any ongoing or new AEs including any local reactions that develop during or after the infusion; document procedures performed due to an AE
- Document hospitalization status and ventilator status

6.6 End of Therapy Visit (EOT; up to 3 days after last study drug infusion)

Complete the EOT Visit procedures after infusion is completed for all patients who receive any study drug. The EOT Visit is to occur up to 3 days after last study drug infusion except for patients considered a clinical failure, for whom EOT assessments should be completed as close to the date of failure as possible, and prior to initiating rescue therapy, if feasible.

Note: Do not initiate SSRI/MAOI medications until at least 24 hours after the end of the last study drug infusion.

- If original consent was provided by someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.
- Record any new concomitant medication and the reason for its use
- Record lowest and highest temperature obtained on the calendar day
- Record lowest and highest vital signs (blood pressure, heart rate, respiration rate) obtained on the calendar day
- Perform directed physical examination
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG, if available.
- Record highest minute ventilation (L/min) and highest FiO_2 if patient remains ventilated
- Determine Investigator's Assessment of Clinical Response (See Section 8.1.2 for definition)
- Obtain and send clinical laboratory samples to the local and central laboratories, as shown in Table 9

Table 9. End of Therapy Samples for Safety Laboratory Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Blood			
Hematology, CBC with differential		×	
Serum chemistry panel		×	
Repeat test for any previous laboratory result of potential safety concern	×		At the Investigator's discretion; use local laboratory results for timely patient treatment decisions

- Obtain microbiological specimen(s) from blood and the lower respiratory tract/or pleural fluid if clinically indicated and send to the local laboratory and send isolates to the central laboratory as shown in Table 10

Note: If the Investigator assesses the patient as a treatment failure at any time during study therapy, rescue antimicrobial therapy may be initiated at the Investigator's discretion. Microbiologic assessments should be completed prior to initiation of alternative antimicrobial therapy when possible.

Table 10. End of Therapy Samples for Microbiology Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Lower respiratory tract specimen or pleural fluid specimen (if clinically indicated, such as increased purulence, fever, expansion of the infiltrate on the x-ray, increased minute ventilation, etc.)			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 SEC and >25 PMN cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on *S aureus* isolates is required.
Gram stain (optional), culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory except for those listed as never a pathogen in Appendix 5.
Blood Cultures (if clinically indicated)			From each of 2 different veins or vascular access catheters, collect 1 vial for aerobic testing and 1 for anaerobic testing (if available) from each vein for a total of 4 vials. If anaerobic testing is not available at the site, collect only 1 vial for aerobic testing from each vein for a total of 2 vials
Gram stain (optional), culture, and susceptibility testing	×		Send all vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	All isolates from a local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5. If blood culture is positive, repeat within 24 hours

- Assess any ongoing or new AEs including any local reactions that develop during or after the infusion; document procedures performed due to an AE
- Document hospitalization status and ventilator status

6.7 Test of Cure Visit (7 to 14 days after last study drug infusion or at time of failure)

Complete the TOC Visit procedures for all patients who receive any study drug. For patients considered a failure at the EOT Visit, complete procedures for safety follow-up only. If the patient was categorized as a cure at the EOT Visit and has since been recategorized as a failure, perform the TOC Visit procedures as soon as possible after the assessment of failure.

- If original consent was provided by the someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.
- Record any new concomitant medication and the reason for its use
- If patient remains hospitalized, record lowest and highest temperature obtained on the calendar day. If patient is NOT hospitalized, record temperature
- If patient remains hospitalized, record lowest and highest vital signs obtained on the calendar day. If patient is NOT hospitalized, record vital signs (blood pressure, heart rate, respiration rate)
- Perform directed physical examination
- In patients who are receiving supplemental O_2, determine oxygenation status in the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available.
- Record highest minute ventilation (L/min) and highest FiO_2 if patient remains ventilated
- Determine Investigator's Assessment of Clinical Response (See Section 8.1.2) for definition
- Obtain and send clinical laboratory samples to the local and central laboratories, as shown in Table 11

Table 11. Test of Cure Samples for Safety Laboratory Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Blood			
Hematology, CBC with differential		×	
Serum chemistry panel		×	
Repeat test for any previous laboratory result of potential safety concern	×		At the Investigator's discretion; use local laboratory results for timely patient treatment decisions

- Obtain microbiological specimen(s) from blood and the lower respiratory tract/or pleural fluid if clinically indicated and send to the local laboratory and send isolates to the central laboratory as shown in Table 12.

Table 12. Test of Cure Samples for Microbiology Assessments

Sample Test	Laboratory		Comments
	Local	Central	
Lower respiratory tract specimen or pleural fluid specimen (if clinically indicated, such as increased purulence, fever, expansion of the infiltrate on the x-ray, increased minute ventilation, etc.)			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 SEC and >25 PMN cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on *S aureus* isolates is required.
Gram stain (optional), culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5.
Blood Cultures (if clinically indicated)			From each of 2 different veins or vascular access catheters, collect 1 vial for aerobic testing and 1 for anaerobic testing (if available) from each vein for a total of 4 vials. If anaerobic testing is not available at the site, collect only 1 vial for aerobic testing from each vein for a total of 2 vials
Gram stain (optional), culture, and susceptibility testing	×		Send all vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	All isolates from a local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5. If blood culture is positive, repeat within 24 hours

- Assess any ongoing or new AEs; document procedures performed due to an AE

6.8 Late Follow-Up Visit (28 to 32 days after randomization)

- If original consent was provided by someone other than the patient, the patient must be re-consented at any time during the study should he/she become medically able to do so.
- If the patient is medically able (ie, alert and extubated), perform a neurologic examination (including a cranial nerve examination [see Appendix 6] and screening for peripheral sensory and motor neuropathy) and a visual acuity examination.

- Record any new concomitant medication and the reason for its use (only for patients with clinical relapse or who require treatment for an AE).
- Determine survival status (contact patient and/or legally authorized representative if patient has been discharged from the hospital to ascertain if patient is alive or deceased; record date and cause[s] of death. Obtain autopsy report if available.)
- Assess for clinical relapse
- Assess any ongoing or new AEs
- Review laboratory results, and document any new abnormalities or clinically significant changes from Day 1
- If an on-site follow-up visit is clinically indicated (eg, new or ongoing AEs or laboratory findings that require follow-up), or the patient has persistent or recurrent signs or symptoms of pneumonia or evidence of any complications, collect lower respiratory tract sample (if feasible), blood sample for culture, and/or blood samples for chemistry and hematology panels. Send samples to the local laboratory and central laboratory as shown in Table 13 and Table 14**.**

Table 13. Late Follow-Up Samples for Safety Laboratory Assessments

Sample Test	**Laboratory**		**Comments**
	Local	**Central**	
Blood			
Hematology, CBC with differential		×	
Serum chemistry panel		×	
Repeat test for any previous laboratory result of potential safety concern	×		At the Investigator's discretion; use local laboratory results for timely patient treatment decisions

Table 14. Late Follow-Up Samples for Microbiology Assessments

Sample Test	Laboratory		Comments
	Local	**Central**	**Comments**
Lower respiratory tract specimen or pleural fluid specimen (if clinically indicated, such as increased purulence, fever, expansion of the infiltrate on the x-ray, increased minute ventilation, etc.)			All samples must be collected via valid sampling technique: sputum or endotracheal aspirate (with <10 SEC and >25 PMN cells per low-power field), protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion. Quantitative cultures are recommended but not required. Any quantitative or semiquantitative results are to be entered into the e-CRF. Local susceptibility testing of oxacillin on *S aureus* isolates is required.
Gram stain (optional), culture, and susceptibility testing	×		
Isolates from local laboratory culture for confirmation of identification and susceptibility testing		×	All isolates from the local laboratory culture are to be sent to the central laboratory except for those listed as never a pathogen in Appendix 5.
Blood Cultures (if clinically indicated)			From each of 2 different veins or vascular access catheters, collect 1 vial for aerobic testing and 1 for anaerobic testing (if available) from each vein for a total of 4 vials. If anaerobic testing is not available at the site, collect only 1 vial for aerobic testing from each vein for a total of 2 vials
Gram stain (optional), culture, and susceptibility testing	×		Send all vials to same local laboratory
Isolates from blood culture for confirmation of identification and susceptibility testing		×	All isolates from a local laboratory culture are to be sent to the central laboratory, for samples collected on study drug dosing days, except for those listed as never a pathogen in Appendix 5. If blood culture is positive, repeat within 24 hours

7.0 PHARMACOKINETIC ANALYSIS

Unless otherwise approved by Cubist, sites will collect blood samples from all patients for pharmacokinetic analysis. Blood samples are to be collected at the following timepoints for TR-700 plasma concentration measurement, and time of blood draw and time of study drug administration are to be recorded:

- Day 1: Collect 2 blood samples after completion of Dose 1, Infusion A:
  - 1 sample between 5 minutes and 80 minutes after the completion of Dose 1, Infusion A
  - 1 sample between 4 and 12 hours after the completion of Dose 1, Infusion A
- Day 4 or 5: Collect 1 blood sample before Infusion A (Dose 7 or Dose 9)
- Day 7: Collect 3 blood samples after the completion of Dose 13 Infusion A:
  - 2 samples between 5 and 80 minutes after the completion of Dose 13, Infusion A
  - 1 sample between 4 and 12 hours after the completion of Dose 13, Infusion A

Two samples are to be collected on Day 1, a single sample on Day 4 or Day 5, and 3 samples on Day 7. One of the 2 samples collected on Day 7 between 5 and 80 minutes will be used in an optional exploratory analysis for metabolite identification (to be reported separately). Plasma samples will be analyzed for TR-700 concentrations (and optionally TR-701) using a validated tandem mass spectrometric assay in patients randomized to receive TR-701 FA only. Analysis for linezolid plasma concentrations in patients randomized to receive linezolid will be optional. Variables to be assessed include maximum plasma concentration, AUC, average plasma concentration, and half-life.

Population PK analysis will be conducted and results will be reported separately.

Detailed instructions on collecting and processing blood PK samples are provided in Appendix 10 and the PK manual.

8.0 EFFICACY

8.1 Assessment of Efficacy – Response Definitions

8.1.1 All-Cause Mortality

The primary efficacy outcome is ACM, defined by alive or deceased within 28 days after randomization into the clinical study.

8.1.2 Investigator's Assessment of Clinical Response

Clinical response (cure, failure, or indeterminate) will be determined. Clinical response at TOC (7 to 14 days after the last administration of study drug) is the primary efficacy endpoint for the EMA and Japan Ministry of Health, Labour, and Welfare, and a secondary endpoint for the FDA and is derived from the Investigator's assessment at the EOT and TOC Visits as detailed in the SAP.

The Investigator will make an assessment of clinical response at the EOT Visit (up to 3 days after the last administration of study drug) and the TOC Visit as detailed in Table 15. Patients whose disease is progressing or who receive rescue or additional prohibited antimicrobial therapy prior to the EOT Visit will be considered a clinical failure at the EOT and TOC Visits. Patients who are a failure at the EOT Visit or who relapse between the EOT and TOC Visits and receive antimicrobial therapy will be considered a failure at the TOC Visit.

Table 15. Investigator's Assessment of Clinical Response - Definitions at the EOT and TOC Visits

Clinical Outcome	Definition
Cure	• Complete resolution of most or all 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 or gram-positive bacteremia except for adjunctive therapy that was given for 14 days, AND • Patient is alive
Failure	• Progression, relapse, or recurrence of new symptoms or complications attributable to VNP or gram-positive bacteremia due to the same pathogen isolated at baseline, OR • 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, OR • Patient died of any cause
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Diagnosis of gram-negative VNP with no gram-positive pathogen isolated within 5 days after randomization • Lost to follow-up • Withdrawal of consent • Insufficient clinical documentation precluding the classification of the clinical outcome of VNP • Randomized but did not receive study drug • Extenuating circumstances that preclude the classification of clinical outcome of VNP

The Investigator will make an assessment of clinical response at the LFU Visit using definitions provided in Table 16.

Table 16. Investigator's Assessment of Clinical Response - Definitions at the LFU Visit

Clinical Outcome	Definition
Sustained Clinical Cure	• Complete resolution or marked improvement or return to baseline of all signs, AND • Symptoms of pneumonia and improvement or lack of progression of all chest x-ray abnormalities, such that no additional antibacterial therapy is required for the treatment of the current infection
Relapse	• Recurrence of signs or symptoms of pneumonia or new radiographic evidence of pneumonia or death due to pneumonia or pneumonia-related complications in a patient assessed as cured at the TOC visit
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Lost to follow-up • Withdrawal of consent • Death unrelated to pneumonia • Extenuating circumstances that preclude the classification as cure or relapse

8.2 Microbiologic Response Definitions

Microbiological response definitions are presented in Table 17. Note that microbiological samples are required only at the Screening Visit. At subsequent visits, samples are required in patients with no improvement or as clinically indicated for worsening respiratory status suggesting a treatment failure or new infection, and if respiratory specimens are easily accessible. Patients with an unfavorable microbiologic response (persistence or presumed persistence) at the EOT Visit will be assigned an unfavorable microbiological response at TOC. Microbiological response will be determined programmatically based on the data from the central laboratory and the Investigator's assessment of clinical response.

Table 17. Microbiologic Response Definitions

Term	Definition
Eradication	Absence of the baseline pathogen(s)
Presumed eradication	No source specimen to culture in a patient assessed as a clinical cure by the Investigator
Persistence	Continued presence of the original baseline pathogen(s)
Presumed persistence	No source specimen to culture in a patient assessed as a clinical failure by the Investigator
Indeterminate	The patient's clinical response is Indeterminate or there is another circumstance that precludes a microbiologic evaluation
Superinfection	Isolation of a new pathogen (not present at baseline) in clinically significant quantities from the respiratory tract or bloodstream while the patient is on study drug and the patient has worsening or new signs or symptoms of VNP
New infection	Isolation of a new pathogen (not present at baseline) in clinically significant quantities from the respiratory tract or bloodstream after the patient discontinues/completes study drug and the patient has worsening or new signs or symptoms of VNP

Note: Response is per pathogen and the per-patient outcome is based on all pathogens present at baseline.

9.0 SAFETY

Safety will be evaluated through assessment of AEs, vital signs, physical examinations including a neurologic examination (Appendix 6), visual acuity examinations, and laboratory evaluations (hematology and chemistry; Appendix 9).

9.1 Definition of Adverse Events

Adverse Events

According to 21 Code of Federal Regulations (CFR) 312.32 (a) effective September 2011 and FDA draft guidance "Safety Reporting Requirements for INDs and BA/BE Studies" dated December 2012, an AE is defined as follows:

> "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose."

Medical conditions present at the Screening Visit are considered medical history, and not AEs. However, any worsening of a pre-existing medical condition during the AE reporting period (see Section 9.1.1) is to be reported as an AE.

Suspected Adverse Reaction

A suspected adverse reaction (SAR) is defined as follows:

> "Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug (IND) safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

Adverse Reaction

An adverse reaction is defined as follows:

> "An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event."

Unexpected

"An adverse event or suspected adverse reaction is considered unexpected if "it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater severity) if the IB listed only cerebral vascular accidents. 'Unexpected,' as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation."

Known complications of VNP and mechanical ventilation including pleural effusion, empyema, pneumothorax, acute lung injury, acute respiratory distress syndrome, progression of VNP, and death unrelated to study drug are considered expected events for this protocol.

Serious

A serious AE is defined as follows:

> "An adverse event or suspected adverse reaction is considered 'serious' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
>
> - Death
> - A life-threatening AE (*Life-threatening refers to a situation in which the patient 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*)
> - Inpatient hospitalization or prolongation of existing hospitalization
> - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
> - A congenital anomaly/birth defect
> - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

Life-Threatening

"An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death."

Pretreatment Adverse Event

A pretreatment event is an untoward medical occurrence in a clinical investigational patient on Study Day 1 prior to Dose 1 of study drug; it does not necessarily have any causal relationship with study participation. If a patient experiences a worsening or complication of a pretreatment condition or AE after receiving Dose 1 of study drug, the worsening or complication is to be recorded as a treatment-emergent adverse event (TEAE). Investigators are to ensure that the AE term recorded captures the change in condition (eg, "worsening of…").

Treatment-Emergent Adverse Event

A TEAE is an event that emerges, or a pre-existing event that worsens, any time after the patient receives Dose 1 of study drug through the end of the AE reporting period (see Section 9.1.1).

Report laboratory test, vital sign, and ECG abnormalities as TEAEs only if the event leads to medical intervention (eg, additional concomitant medication, discontinuation of study drug).

The Investigator is responsible for ensuring that all events occurring during the AE reporting period (Section 9.1.1) are reported. Record the following information for each event: onset and stop dates, duration, severity, seriousness, causality, action taken, and outcome.

Study center personnel are to ask patients neutral questions when they are assessing the patient for AEs (eg, "How are you feeling?" or "Have you noticed any changes in your health?").

9.1.1 Reporting Period for Adverse Events

Collect AEs from Study Day 1 through the Late Follow-Up Visit. Ongoing AEs will be evaluated and documented at the last visit. Follow ongoing AEs as described in Section 9.4.

9.1.2 Severity of Adverse Events

Categorize the severity of each AE as follows:

Severity	Definition
Mild	Minor and does not cause significant discomfort to patient; patient aware of symptoms but symptoms easily tolerated without treatment
Moderate	An inconvenience or concern to patient, but patient able to tolerate. Treatment of symptom(s) may be needed
Severe	Symptom(s) of a sufficient severity to cause the patient severe discomfort. Severity may cause cessation of treatment with the study drug. Treatment for symptom(s) needed

9.1.3 Relationship of Adverse Events to Study Drug

The Investigator will make a determination of the relationship of the AE to the study drug using a 4-category scale (not related, possible, probable, or definite) according to the definitions below. Clinical failure, in and of itself, is considered unrelated to the toxicity of the study drug and is only related to the lack of efficacy of the study drug.

Category	Definition
Not Related	AE does not follow a reasonable temporal sequence from study drug administration and can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment
Possible	AE follows a reasonable temporal sequence from the study drug administration (including the course after study drug withdrawal) and cannot be excluded as possibly being caused by study drug (eg, existence of similar reports attributed to the suspected drug and/or its analogues; reactions attributable to the pharmacologic effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable
Probable	AE follows a reasonable temporal sequence from study drug administration (including the course after study drug withdrawal) and can be excluded as possibly being caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment
Definite	AE follows a reasonable temporal sequence from study drug administration (including the course after study drug withdrawal), follows a known or hypothesized cause-effect relationship, and (if appropriate) satisfies the following: • positive results obtained in drug sensitivity tests • toxic level of the drug present in blood or other body fluids

9.2 Reporting Serious Adverse Events

Investigators are to report SAEs to Cubist or designee that occur during the reporting period (Section 9.1.1) within 24 hours after becoming aware of the SAE.

The SAE form (both the paper SAE form and the AE eCRF), which is to be completed in English and signed by the Investigator (or designee), is to include as much information as possible, but at a minimum must contain the following:

- A short description of the event and the reason why the event was categorized as serious
- Patient identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

Follow SAEs as described in Section 9.1.1. The timelines and procedures for follow-up reports are the same as those for the initial report.

Cubist or designee will send copies of expedited reports for SAEs that are unexpected and at least possibly related to the study treatment to all concerned regulatory authorities and active Investigator(s). The Investigator is responsible for sending reports to the IRBs/ECs/REBs in accordance with local and site-specific requirements.

9.3 Adverse Events Requiring Additional Information

Investigators are to report AEs requiring additional information to Cubist or designee that occur during the reporting period (Section 9.1.1) only at the request of the Sponsor (including, but not limited to, optic neuropathy and peripheral neuropathy or cranial neuropathy or other events deemed appropriate by the Medical Monitor).

The additional information form, which is to be completed in English and signed by the Investigator (or designee), is to include as much information as possible, but at a minimum must contain the following:

- A short description of the event and the reason why the event is being reported
- Patient identification number
- Investigator's name
- Causality assessment
- Results of consultation and diagnostic tests

9.4 Follow-Up of Adverse Events

The Investigator is to follow AEs occurring during the AE reporting period (Section 9.1.1) with a clinically appropriate effort. Patients are to be monitored for all AEs until the last study visit (ie, 28 to 32 days after randomization). SAEs are to be followed using the SAE report form until stabilization, resolution/death, or consent is withdrawn. AEs ongoing at the end of the study are to be recorded as 'ongoing' on the e-CRF. Information received after the subject's last study contact is to be recorded on the paper SAE form.

9.5 Pregnancy

Instruct patients to notify the Investigator if they become pregnant. If any patient is found to be pregnant during the study, she is to immediately discontinue any Cubist -supplied study drug and to have only safety assessments performed. Report the pregnancy within 24 hours as outlined for SAEs in Section 9.2. Follow reported pregnancies to final outcome, using the pregnancy form. Report the outcome, including any premature termination, to Cubist. Follow live births for a minimum of 30 days or until the first well-baby visit. Additional details are available in the internal safety plan.

If the patient gives permission for her primary physician to be informed, the Investigator is to notify the patient's primary physician that she was participating in a clinical study at the time she became pregnant, and provide details of the treatment that the patient received.

9.6 Overdose of TR-701 or TR-701 FA

As of November 2016, no known incidents of overdose have occurred. In Phase 1 clinical studies, the highest single oral dose of TR-701 administered was 1200 mg and the highest oral multiple dose was 400 mg once daily for 21 days.

The signs and symptoms of overdose in humans are unknown at this time. In animals, signs of acute oral toxicity were alopecia, salivation, and decreased locomotor activity at ≥1000 mg/kg in rats and emesis in dogs at 400 mg/kg.

An overdose is defined as deliberate or accidental administration of study drug, to or by a study patient, at a dose greater than the total 24-hour dose assigned to that patient according to the protocol. Report signs and symptoms of an overdose, if any, as AEs as outlined in Section 9.1.

10.0 STATISTICAL METHODS

10.1 Sample Size

The study is designed to show NI in the primary outcome measure of 28-day ACM in the ITT Analysis Set and the secondary outcome measure of clinical response (as derived from the Investigator's assessment at the EOT and TOC Visits) in the ITT and CE Analysis Sets. Thus, a total of 726 patients will be randomized (ITT Analysis set).

Analyses of previous studies presented by the FDA (Antibacterial Drugs 2011) indicate that the true rate of 28-day ACM is approximately 20% for mechanically-ventilated patients with HABP/VABP receiving antibiotics. To demonstrate the NI of TR-701 FA to linezolid with respect to the difference in 28-day ACM rates, using an NI margin of 10%, a sample size of 726 randomized patients (363 per arm) in the ITT Analysis Set will have 92% power at a 1-sided significance level of 0.025, assuming a 28-day ACM rate of 20% in both TR-701 FA and linezolid arms. The study is also sufficiently powered for the secondary outcome measure of clinical cure at TOC in the ITT and CE Analysis Sets as derived from the Investigator's assessment at the EOT and TOC Visits. A total of 726 patients will be randomized in the ITT Analysis Set, which provides 87% power to show NI assuming a 50% clinical success rate and an NI margin of 12.5%. Data from the linezolid label and the Zephyr study (Wunderink 2012) indicate that the clinical cure rate for linezolid is approximately 60% in the CE Analysis Set. If the clinical evaluability rate will be 80%, with a 12.5% NI margin, 80% power, a 1-sided alpha=0.0125, and a clinical cure rate of 60% in the CE Analysis Set, a total of 580 patients are required in the CE Analysis Set. The sample size, outcome rates, and power for the primary and secondary outcomes are provided in Table 18.

Table 18. Sample Size and Power for the Primary and Secondary Efficacy Outcomes

	Primary Outcome (28-Day ACM)	**Secondary Outcome (Clinical Response*)**	
Analysis Set	ITT	ITT	CE
Outcome Rate	20%	50%	60%
Evaluability Rate	NA	NA	80%
Margin	10%	12.5%	12.5%
N	726	726	580
Power	92%	87%	80%

Abbreviations: ACM=all-cause mortality; CE=clinically evaluable; ITT=intent to treat; NA=not applicable.
*As derived from the Investigator's assessment at the EOT and TOC Visits.

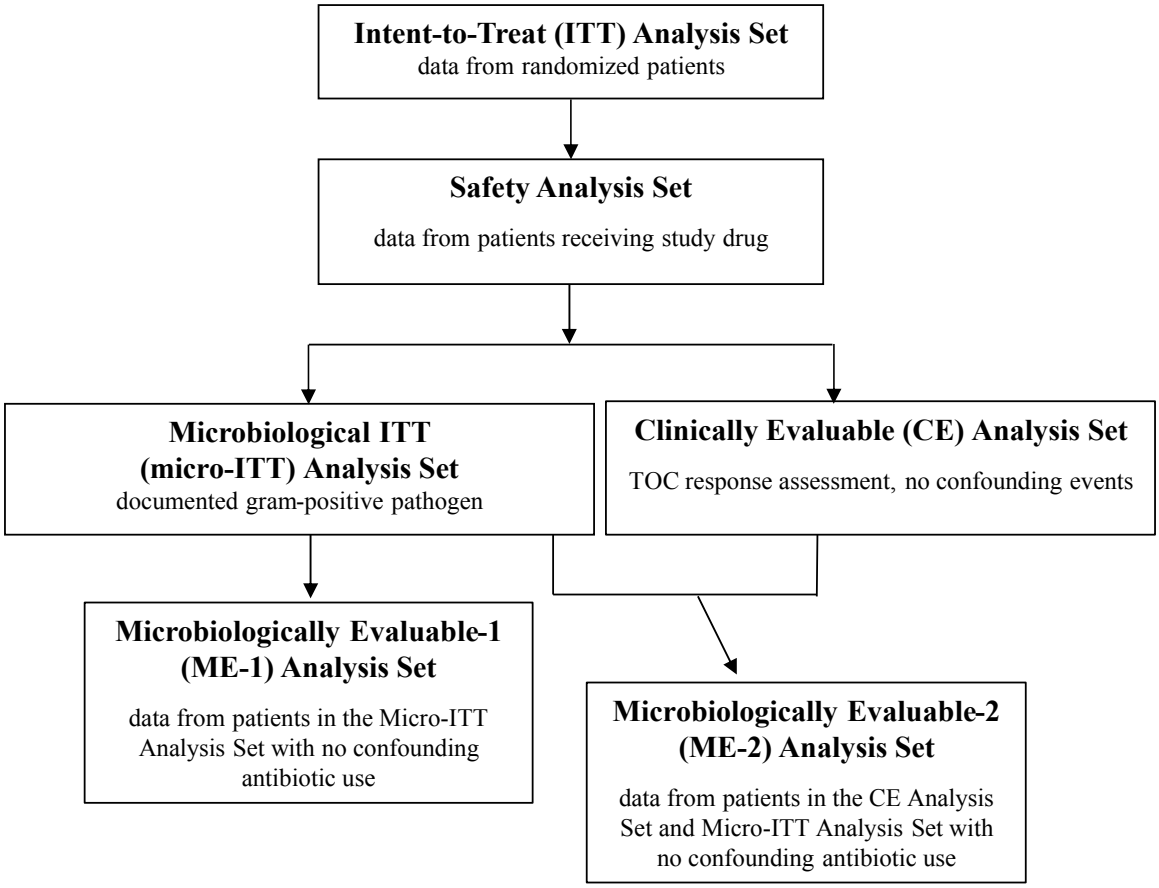
10.2 Analysis Sets

The Analysis Sets are defined below; additional information is provided in the SAP.

1. ITT Analysis Set: data from all randomized patients
2. Safety Analysis Set: data from all patients in the ITT Analysis Set who received any amount of study drug
3. Micro-ITT Analysis Set: data from all patients in the Safety Analysis Set who have gram-positive pathogen(s) confirmed by culture results from a respiratory tract or pleural fluid specimen obtained within 36 hours (or if culture positive for MRSA within 72 hours) before first administration of study drug, and documented bacterial pathogen known to cause VNP (see Appendix 5) against which the investigational drug has antibacterial activity
4. ME-1 Analysis Set: data from all patients in the Micro-ITT Analysis Set who did not receive an antibiotic (other than study drug) with activity against the baseline pathogen received up through 28 days after randomization
5. ME-2 Analysis Set: data from all patients in the Micro-ITT Analysis Set who did not receive an antibiotic (other than study drug) with activity against the baseline pathogen received up through the TOC Visit and also in the CE Analysis Sets
6. CE Analysis Set: data from all patients in the Safety Analysis Set who had a TOC response assessment recorded (if the patient was assessed by the Investigator as a clinical failure at the EOT Visit, a response assessment at the TOC Visit is not required), had no major confounding events or factors as detailed in the SAP

The relationship between the 6 analysis sets is shown in Figure 3.

Figure 3. Overview of the Analysis Sets



Abbreviations: TOC=test of cure

10.2.1 Process for Determining Inclusion in Analysis Sets

Inclusion into the ITT and Safety Analysis Sets will be determined programmatically from the e-CRF data. Inclusion into the ME-1, CE, and ME-2 Analysis Sets will be determined programmatically from the e-CRF data and the manual review conducted by the Evaluability Review Team (ERT) who may review patient data to confirm that analysis set criteria are satisfied. Inclusion into the Micro-ITT Analysis Set will be determined programmatically and based on a manual review conducted by the ERT of the respiratory culture data. The ERT will determine whether each isolate is considered a pathogen based on a review of the local and central laboratory genus and species identification, central laboratory (or local if central data not available) susceptibility data, and other microbiological and clinical data, if needed.

10.3 General Statistical Considerations

For analyses of dichotomous endpoints, 2-sided 95% CIs for the difference in proportions between TR-701 FA versus linezolid will be calculated. For negative endpoints, eg, 28-day ACM, the difference will be calculated as linezolid minus TR-701 FA; for positive endpoints, eg, clinical response at TOC, the difference will be calculated as TR-701 FA minus linezolid. A 2 sided 95% CI will be constructed for the observed difference using the method of Miettinen and Nurminen (Miettinen 1985).

For time-to-event endpoints, Kaplan-Meier curves that are stratified by age (≥65 years or <65 years), underlying diagnosis (trauma or nontrauma admitting diagnosis), and geographic region 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. Patients who do not have the event outcome recorded will not be excluded from these analyses, but will be right-censored as of the patient's last available evaluation, unless otherwise specified. All tests will be 2-sided and will be conducted at the 0.05 significance level.

For time to event endpoints, summaries will include the number of patients, the number of patients who achieved the event of interest, the number of patients 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.

Differences between treatment groups for baseline characteristics will be analyzed using Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal variables and continuous variables.

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. Exploratory analyses may also be performed. Listings of individual patient's data will be produced. A comprehensive SAP will be submitted to regulatory authorities prior to initiation of the study.

10.4 Patient Population and Characteristics

Enrollment, protocol deviations, and discontinuations from the study drug and the study will be summarized by treatment group. Demographics (age, race, sex), medical and surgical history, APACHE II score, SOFA score, CPIS, baseline assessment of the clinical signs and symptoms, microbiological assessment, and study drug administration data will also be summarized. Differences between treatment groups will be analyzed using Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal variables and continuous variables.

10.5 Efficacy Analysis

For all efficacy analyses, patient data will be analyzed in the group to which the patient was randomized. For the analysis of the primary efficacy outcome, patients who are randomized to the wrong stratum will be analyzed in the stratum to which they were randomized. A sensitivity analysis will be conducted in which these patients are analyzed in the stratum with which they correctly belong.

10.5.1 Primary Efficacy Analysis

The primary statistical goal of this study is to establish NI of TR-701 FA to linezolid with respect to the difference in the Day 28 all-cause mortality rates using a 10% NI margin in the ITT population.

The hypotheses for NI are as follows where p1 is the proportion of deceased patients on Day 28 treated with linezolid and p2 is the proportion of deceased patients on Day 28 treated with TR-701 FA:

Null Hypothesis, H0: $p1 - p2 \leq -10\%$

Alternative Hypothesis, H1: $p1 - p2 > -10\%$.

A 2-sided 95% CI around the difference (linezolid minus TR-701 FA) in the Day 28 all-cause mortality rates will be constructed, not adjusting for the stratification factors. The estimated difference in proportions between the 2 groups and the 2-sided 95% CI for the difference will be calculated using the method of Miettinen and Nurminen without stratification. TR-701 FA will be considered NI to linezolid if the lower limit of the 2 sided 95% CI around the difference is greater than minus 10% (D'Agostino 2003).

10.5.1.1 Additional Analyses of the Primary Efficacy Outcome

The primary efficacy outcome will also be assessed across the stratification factors of age (≥65 years or <65 years), underlying diagnosis (trauma or nontrauma admitting diagnosis), and geographic region. For each stratum, a 2-sided 95% CI for the treatment difference of 28-day ACM will be calculated for the ITT Analysis Set.

A Kaplan-Meier analysis in the ITT Analysis Set of the time to death in days from the date of the first administration of study drug will be conducted. All patients will be monitored until the last trial evaluation. Data from patients whose survival status is not known at the last trial evaluation will be censored on the date of last contact. Mortality will be summarized by treatment group using the methodology described in Section 10.3.

Three sensitivity analyses of the primary outcome will be conducted using the ITT Analysis Set. The first analysis will be an adjusted analysis (adjusted for the randomization stratification factors) based on the stratification factors to which the patient was randomized

and the second will be an adjusted analysis based on the stratification factors to which the patient correctly belongs. Adjusted 95% CIs will be computed for the difference in 28-day ACM rates using the stratified method of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CIs. The third sensitivity analysis will consider all patients who are lost to follow-up prior to 28 days as alive. The difference in 28-day ACM will be determined and a 95% CI for the difference will be computed.

10.5.2 Secondary Efficacy Analyses

The number and percentage of patients in each treatment group categorized with a clinical cure, clinical failure, or indeterminate based on the clinical response as derived from the Investigator's assessment at the EOT and TOC Visits as detailed in the SAP, will be determined at TOC for the ITT Analysis Set (EMA and Japan Ministry of Health, Labour, and Welfare primary endpoint) and CE Analysis Set (by definition, patients in the CE Analysis Set cannot have a response of indeterminate). In the ITT Analysis Set, patients with an indeterminate response are included in the denominator and thus, are essentially considered a clinical failure. Patients categorized as clinical failure at the EOT Visit will be considered to have clinical failure at TOC. A 2-sided 95% CI and a 2-sided 97.5% CI will be constructed for the observed difference (TR-701 FA group minus linezolid group) in the clinical cure rate using the method of Miettinen and Nurminen without stratification. Clinical response as derived from the Investigator's assessment will also be assessed in those patients with a confirmed pathogen of MSSA and MRSA (micro-ITT and ME-2 Analysis Sets). The difference between the treatment groups in the clinical cure rate will be presented along with the 2-sided 95% CI for the difference.

A sensitivity analysis of the secondary efficacy outcome of clinical response will be conducted whereby adjusted (adjusted for the randomization stratification factors to which the patient was randomized) 95% and 97.5% CIs for the difference in clinical cure rate will be determined using the stratified method of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CIs.

The number and percentage of patients who are alive and deceased at 28 days after randomization in the Micro-ITT Analysis Sets will be provided. Patients who are lost to follow-up (ie, are not known to be alive or deceased on Day 28) will be defined as indeterminate for the secondary analysis and are included in the denominator for the calculation of the 28-day ACM. Thus, patients with an indeterminate outcome are considered deceased for the secondary analysis. The 28-day ACM rate in each treatment group will be reported along with the treatment difference and unadjusted 2-sided 95% CI. The 28-day ACM rate will be determined in those patients with a confirmed pathogen of MSSA and MRSA. The number of patients who are alive in each treatment group, the treatment difference and the unadjusted 2-sided 95% CI will be provided.

The per-patient microbiological response at EOT in the Micro-ITT and ME-1 Analysis Sets and at TOC in the Micro-ITT and ME-2 Analysis Sets will be determined to support the clinical findings. Per-patient microbiological response is based on per-pathogen outcomes. To have an overall favorable microbiological response, the outcome for each baseline pathogen must be favorable. The number and percentage of patients classified with a favorable (eradication and presumed eradication) and unfavorable (persistence and presumed persistence) microbiological response will be tabulated for both treatment groups. A 2-sided 95% unstratified CI will be constructed for the observed difference in the per-patient favorable microbiological response rate between the TR-701 FA and linezolid groups using the method of Miettinen and Nurminen.

Two sensitivity analyses of 28-day ACM will be conducted for the Micro-ITT Analysis Set. The first analysis will be an adjusted analysis (adjusted for the randomization stratification factors) based on the strata to which the patient was randomized. Adjusted 95% CIs will be computed for the treatment difference in 28-day ACM rates using the stratified method of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CIs. The second sensitivity analysis will consider all patients who are lost to follow-up prior to 28 days as alive, and a 95% CI for the treatment difference will be computed.

The secondary efficacy outcomes of clinical response in the ITT and CE Analysis Sets and 28-day ACM in the Micro-ITT Analysis Set will also be assessed across the stratification factors of age (≥65 years or <65 years), underlying diagnosis (trauma or nontrauma admitting diagnosis), and geographic region. For each stratum, a 2-sided 95% CI for the difference (clinical response and 28-day ACM) will be calculated.

10.5.3 Additional Efficacy Analyses

Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary outcomes. Confidence intervals will be provided for descriptive purposes as indicated below, but no conclusions of NI will be made.

The number and percentage of patients who are alive or deceased at 14 days after randomization in the ITT, Micro-ITT, and ME-1 Analysis Sets; and at 28 days after randomization in the ME-1 and CE, Analysis Sets will be provided. Patients who are lost to follow-up (ie, are not known to be alive or deceased on Day 14 or Day 28) will be defined as indeterminate and are included in the denominator for the calculation of the 14-day ACM and 28-day ACM rate. Thus, patients with an indeterminate outcome are considered deceased in this analysis. The unadjusted 2-sided 95% CIs will be computed for the difference in 14-day ACM and 28-day ACM rates using the method of Miettinen and Nurminen.

Descriptive summaries, including change from baseline, in the clinical findings that support the diagnosis of VNP (eg, temperature, WBC count) as well as the respiratory system findings will be provided for the ITT and CE Analysis Sets. The respiratory system findings include presence of purulent respiratory secretions, cough, rales, rhonchi and/or bronchial breath sounds, respiratory rate and presence of dyspnea, ABG, minute ventilation, and PaO_2/FiO_2 ratio. Procalcitonin levels and change from baseline to Day 7 will also be summarized in the ITT Analysis Set.

The number and percentage of patients in each treatment group with a favorable (eradication or presumed eradication) or unfavorable (persistence or presumed persistence) microbiological response at EOT and TOC, 28-day ACM, Investigator' assessment of clinical success at TOC, for each baseline pathogen will be tabulated. Analyses of per-pathogen microbiological response, per-pathogen 28-day ACM and the per-pathogen clinical response will be conducted in those patients with a culture positive pathogen from the Micro-ITT, ME-1 (for the EOT timepoint), and ME-2 (for the TOC timepoint) Analysis Sets.

10.6 Safety Analysis

Safety will be assessed through summaries of TEAEs, laboratory evaluations (hematology and chemistry), vital signs, and physical examinations. All safety analyses will be based on the Safety Analysis Set, as defined in Section 10.2 and will be summarized for each treatment group. Patients who receive the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

10.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Adverse events reported on Day 1 before Dose 1 of study drug is administered (pretreatment AEs) will be collected and presented in a listing; no analyses will be performed. Summary tables of TEAEs will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to study drug discontinuation, death, and all SAEs will be provided. The AE reporting period is defined in Section 9.1.1.

10.6.2 Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. The change from baseline to each postbaseline visit and to the overall worst postbaseline value will also be summarized by treatment group. Laboratory values will be classified according to a modified *Division of Microbiology and Infectious Diseases Adult Toxicity Scale, November 2007* criteria, and shifts in toxicity grade from baseline to postbaseline will be summarized. Selected laboratory values will also be classified as substantially abnormal from normal limits and summary data presented for the worst postbaseline value.

10.6.3 Additional Safety

Additional safety assessments include vital signs, physical examinations, including a neurologic examination (cranial nerve examination and screening for peripheral sensory and motor neuropathy) and a visual acuity examination using the Snellen or other similar eye chart. Descriptive statistics of the vital sign parameters will be presented by treatment group and study visit, as well as the change from baseline at each study visit. The percentage of abnormalities based on the physical examination including neurological examination, as available, will be presented. Visual acuity scores will be categorized as normal vision, near-normal vision, moderate low vision, severe low vision, and profound low vision or worse than profound low vision (see SAP for definitions) and will be presented by treatment group.

10.6.4 Interim Analysis

Two unblinded interim analyses of safety and efficacy will be conducted. The interim analyses of safety and efficacy will occur when 30% and 50% of the patients in the ITT Analysis Set (218 and 363 patients) have been randomized and monitored through Day 28. A futility analysis based on the primary efficacy outcome of 28-day ACM will be conducted. The futility boundaries will be derived from the Gamma (-4.27) error spending function (Hwang 1990) and constructed to be nonbinding. The futility boundaries will be calculated using the actual information fractions at the time of each DSMB interim analysis (as indicated in the DSMB charter and SAP). The DSMB may recommend that the study be stopped due to futility.

10.6.5 Monitoring Committees

The DSMB will be convened when approximately 30% (218 patients), 50% (363 patients), and 75% (545 patients) of patients have been randomized in the ITT Analysis Set and completed 28 days of follow-up. A DSMB will review safety and efficacy data including ACM, treatment-emergent adverse events (TEAEs), incidence of serious TEAEs, study drug-related TEAEs, and study drug discontinuation due to study drug-related TEAEs and other safety and efficacy related data at 30%, 50%, and 75% of patient enrollment. Only data for the first and the second interim looks will be unblinded (Treatment A vs Treatment B).

The DSMB will include at least 4 members: 1 biostatistician and 3 clinicians with relevant expertise in critical care medicine, internal medicine, and/or infectious diseases. The DSMB will operate in a fashion consistent with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (2006). The DSMB may recommend changes to study conduct on the basis of emerging safety information to protect the safety and welfare of clinical study patients. Additional details will be provided in the DSMB charter.

10.7 Handling of Missing Data

Missing values will not be imputed (except as detailed in the SAP) and only observed values will be used in the data analyses and presentations. For the primary outcome measure, 28-day ACM, if the patient's status is unknown or missing at Day 28, the patient will be assumed deceased and time to death will be censored at the last study contact. A sensitivity analysis of the primary outcome will be conducted in which patients with a missing status at Day 28 are considered to be alive and a time to death analysis will be conducted in which data from patients with missing survival status are censored at the last study contact.

For the secondary outcome measure of clinical response as derived from the Investigator's assessment at the EOT and TOC Visits, if the response is unknown or missing, the patient will be assigned a response of indeterminate. For the analysis in the ITT Analysis Set, indeterminate responses are included in the denominator and are thus considered failures. By definition, patients with an indeterminate response are excluded from the CE Analysis Set. More details will be provided in the SAP.

11.0 ADMINISTRATIVE CONSIDERATIONS

11.1 Ethical Conduct of the Study

This study will be conducted in accordance with applicable FDA clinical study regulations and guidelines, the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guideline (E6), the Basic Principles of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/), and the IRB/EC/REB and local legal requirements.

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

11.2 Institutional Review Board/Ethics Committee

In accordance with 21 CFR 56, the protocol, the Informed Consent Form (ICF), patient information sheets, and advertisements (as appropriate) are to be reviewed and approved by the IRB/EC/REB. Cubist will supply relevant material to the Investigator, and the Investigator is responsible for submitting the protocol to the IRB/EC/REB for review and approval.

The Investigator is to inform the IRB/EC/REB of any subsequent protocol amendment(s). In addition the Investigator is to send any reports of any serious, unexpected AEs that have implications for the conduct of the study, as described in Section 9.2. If requested, the Investigator is to permit audits and inspections by Cubist, the IRB/EC/REB, and any regulatory authority by providing direct access to source data/documents and ensuring study center personnel are available to answer questions.

11.3 Informed Consent

Cubist will review and endorse the draft ICFs before submission to the IRB/EC/REB, and the final IRB/EC/REB-approved documents are to be provided to Cubist for regulatory purposes. Cubist reserves the right to reject proposed modifications to the ICFs.

The Investigator or a designee is to explain the study and ICF to the patient or the patient's legally-authorized representative (LAR) and answer any questions. The ICF is to be signed by the patient or the patient's LAR, before any study-related procedures are performed. A copy of the ICF 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 ICF is to remain in each patient's study file and be available for verification by study monitors or authorized regulatory representatives at any time.

11.4 Confidentiality

11.4.1 Patient Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted is prohibited.

Information obtained during the conduct of this study is to be collected, processed, and transmitted to or for the benefit of Cubist in accordance with applicable law, as discussed below. Information contained therein is to be maintained in accordance with applicable law protecting patient privacy and may be inspected by the clinical researcher, the researcher's staff, and Cubist and its representatives to check, process, evaluate, and use the information collected during the study. Processing, evaluation, or use of the information is to be performed by a health professional for medical and study purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional. Information is to be transmitted and processed as Cubist may direct, including to Cubist and its representatives in the United States or elsewhere. Information obtained from the study is likely to be used by Cubist in connection with study drug development, including possible filing of regulatory dossiers with governmental authorities for marketing approval, and for other pharmaceutical and medical research purposes. The Investigator is obliged to provide Cubist with complete test results and data developed in this study. This information will be disclosed to the FDA/applicable regulatory agencies as deemed necessary by Cubist, or to local health authorities as required by law. Patient-specific information may be provided to other appropriate medical personnel only with the patient's or the patient's LAR's permission.

Investigators and other research study personnel who process information from the study must take appropriate measures to prevent unauthorized or unlawful processing or disclosure of data.

To ensure compliance with current Federal Regulations and the ICH GCP E6 guideline, data generated by this study including source documentation must be available for inspection upon request by representatives of regulatory authorities (FDA, EMA, and national and local health authorities), Cubist, and the IRB/EC/REB for each study center.

11.4.2 Confidentiality of Investigator Information

The investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

11.4.3 Confidentiality of IRB/IEC Information

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

11.5 Compliance with Financial Disclosure Requirements

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

11.6 Case Report Forms and Study Records

Data will be collected using e-CRFs. All e-CRF data are to be completed by the study coordinator or other designated site personnel. Data entry, modification, or deletion is to be

recorded automatically in the electronic audit trail. Data changes are to be clearly indicated with a means to locate prior values.

Electronic data entered by the site (including the electronic audit trail) is to be maintained or made available at the site in compliance with 21 CFR Part 11 and other applicable retention regulations. Those entering data at the site are responsible for logging into the system using their unique identifier and for all actions performed on the system under their identifier, for logging off the system when leaving the work station, and for ensuring that their identifier is not used by others. The computerized system is able to generate accurate and complete copies of records in paper or electronic form for inspection and review by applicable regulatory authorities, the IRB/EC/REB, and auditors or other designees authorized by Cubist.

In addition to capturing the user identification as part of the audit trail for data entry, the e-CRF allows for application of electronic signatures. After review of the data in the e-CRF, the Investigator is to confirm the validity of each patient's data by electronic signature. This electronic signature is to be certified as outlined in 21 CFR Part 11.

Cubist will retain the original e-CRF data and audit trail. An electronic or certified paper copy of completed e-CRF data, including query resolution correspondence, will be provided to the Investigator at the end of the study.

11.7 Protocol Deviations

Protocol deviations are to be recorded and categorized by type of deviation. Deviations include, but are not limited to, the following:

- Enrollment of a patient who did not satisfy the entry criteria
- Failure to withdraw a patient who developed withdrawal criteria during the study
- Administration of the incorrect dose
- Receipt of an excluded concomitant treatment

11.8 Data Quality Assurance

Cubist or designee will perform logic and consistency checks on data entered into the e-CRFs to ensure accuracy and completeness.

Training sessions, regular monitoring of Investigators by Cubist or designated personnel, distribution of instruction manuals, data verification, cross-checking, and data audits are to be performed to ensure the quality of the study data. Investigator meetings and/or on-site study initiations are to be performed to prepare Investigators and other study personnel for appropriate collection of study data.

11.9 Investigator Requirements

Each Investigator is to adhere to GCP guidelines, regulatory guidelines, local laws and regulations, and the protocol as detailed in this document. The Investigator must obtain written approval of any changes to the protocol from Cubist prior to seeking approval from the IRB/EC/REB. Each Investigator is responsible for enrolling only patients who meet protocol inclusion and exclusion criteria.

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

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

11.10 Sponsor Requirements

11.10.1Study Monitoring

An authorized Cubist representative will conduct study center visits to inspect study data, patient's medical records, ICFs, e-CRFs, and clinical study material storage and accountability procedures in accordance with current ICH GCP guidelines and the respective national or regulatory government regulations and guidelines. Monitors will be blinded to treatment group but unblinded monitors will support study drug accountability. The Cubist representative will ensure that regulatory documents are complete and monitor protocol compliance. Study-related documentation is to be made available to the Cubist representative.

11.10.2Study Auditing

Cubist personnel or their designee may perform an audit at any time during or after completion of the clinical study. If requested, the Investigator will provide study-related documentation to the designated auditor. In addition, study center personnel will be available to answer any questions. The Investigator will permit authorized representatives of Cubist and the respective national or local health authorities to inspect facilities and records relevant to this study.

11.10.3Designation of Coordinating Investigator

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in a n EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the

trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (eg, availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

11.11 Retention of Data

The Investigator will retain records and documents pertaining to the conduct of this study including e-CRFs, source documents, ICFs, laboratory test results, and study drug inventory records for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. No study records shall be destroyed without prior authorization from Cubist.

11.12 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. The Sponsor of this trial will review this protocol and submit the information necessary to fulfill these requirements.

The Sponsor's entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

11.13 Publication Policy and Disclosure Policy

Cubist intends to pursue publication of the results of the study in cooperation with a lead Investigator, subject to the terms and conditions of the clinical study agreement between Cubist and Investigators. Cubist approval in writing is required for publication of any data subsets. Final authorship will be determined in accordance with the International Conference of Medical Journal Editors definition of authorship (eg, by contributions to study design, enrollment, data analysis, and/or interpretation of the results) (http://www.icmje.org/). Patient names and other personal data relating to an identified or identifiable patient (such as

photographs, audio, videotapes, or other factors specific to physical, physiological, mental, economic, cultural or social identity), may not be disclosed in any publication without prior written authorization from Cubist and the patient or the patient's LAR.

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13.0 APPENDICES

Appendix 1. Examples of Prohibited Concomitant Medications

Receipt of MAOIs is prohibited in the 2 weeks prior to randomization through the EOT Visit.

Monoamine Oxidase Inhibitors		
Iprindole	Moclobemide	Rasagiline
Iproniazid	Nialamide	Selegiline
Iproclozide	Opipramol	Toloxatone
Isocarboxazid	Phenelzine	Tranylcypromin

The following examples of prohibited concomitant medications are not all inclusive and should be used as a guide for exclusion from the protocol.

Receipt of the following medications is prohibited between the first study drug infusion through the EOT Visit: serotonergic agents including antidepressants such as SSRIs, tricyclic antidepressants, and serotonin 5-HT1 receptor agonists (triptans), meperidine (or other phenylpiperidines), or buspirone.

Examples		
Selective Serotonin Reuptake Inhibitors		
Citalopram	Fluoxetine	Sertraline
Dapoxetine	Fluvoxamine maleate	Vilazodone
Escitalopram oxalate	Paroxetine	
Serotonin Norepinephrine Reuptake Inhibitors		
Duloxetine	Desvenlaxifine	Venlafaxine
Tricyclic Antidepressants		
Amitriptyline	Doxepin	Protriptyline
Clomipramine	Imipramine	Trimipramine
Desipramine	Lofepramine	
Dosulepin	Nortriptyline	
Triptans and other medications with potential serotonergic activity		
Amoxapine	Mirtazapine	Trazodone
Bupropion	Naratriptan	Trimeperidine
Buspirone	Nefazodone	Zolmitriptan
Maprotiline	Rizatriptan	
Meperidine	Sumatriptan	

Appendix 2. Modified Clinical Pulmonary Infection Score (CPIS)

The following data will be collected in the case report form in order to calculate the CPIS score.

(Adapted from Pugin 2002 and Wunderink 2012[a])

Parameter	Criteria	Score
Temperature (ºC)	>36.0 to 38.4	0
	≥38.5 to 38.9	1
	≤36.0 or ≥39.0	2
Leukocytosis (Peripheral white blood cell count, cells/mm3)	4000 to 11,000	0
	<4000 or >11,000	1
	<4000 or >11,000 AND Bands (immature forms) >500	2
Tracheal secretions	Absent	0
	Nonpurulent	1
	Purulent	2
Oxygenation (PaO2/FiO2, mmHg)	>240 or ARDSb	0
	≤240 and no ARDS	2
Chest Radiography	No infiltrate/minimal	0
	Diffuse or patchy infiltrate	1
	Focal (localized) infiltrate	2
Radiographic response	Total clearing (<3 days)	-3
	No change/minimal improvement	0
Sputum/tracheal culture	No growth or ≤1+ (rare/light) growth	0
	Pathogenic bacteria >1+ (moderate or heavy) growth	1
	Same pathogen identified on Gram stain and on culture	2
Minute ventilation	<10 L/min or off ventilator	0
	10–13 L/min	1
	>13 L/min	2

[a]Pugin J. Clinical signs and scores for the diagnosis of ventilator-associated pneumonia. Minerva Anestesiol 2002:68:261-265.
Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: A randomized, controlled study. Clin Infect Dis. 2012:54(5):621-9.
[b]ARDS=acute respiratory distress syndrome, defined clinically as having all of the following criteria: acute bilateral pulmonary infiltrates; PaO_2/FiO_2 <200; pulmonary arterial wedge pressure ≤18 mmHg (no heart failure or volume overload as the principal cause of pulmonary infiltrates).

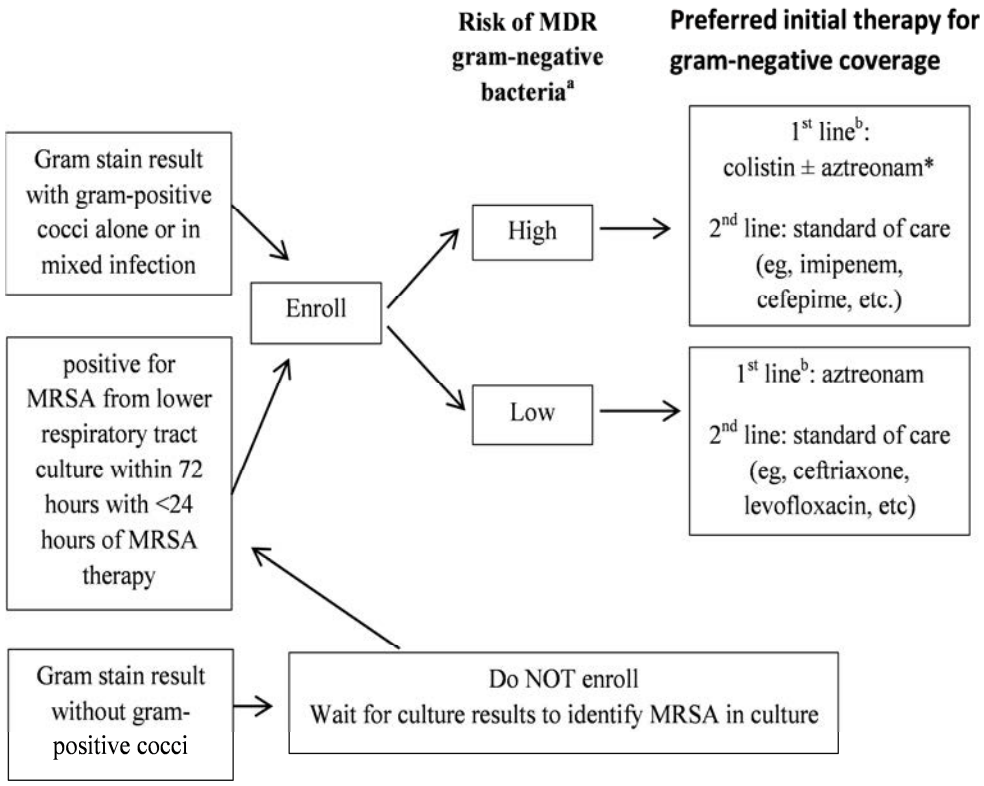
Appendix 3. Sepsis-related Organ Failure Assessment (SOFA) Score

The following data will be collected in the case report form in order to calculate the SOFA score.

Score	0	1	2	3	4
Respiration PaO_2/FiO_2	≥400	<400 to 300	<300 to 200	<200 to 100	<100
Coagulation Platelets (10^3 plts/mm^3)	≥150	<150 to 100	<100 to 50	<50 to 20	<20
Liver Total Bilirubin (mg/dL) [µmol/L]	<1.2 [<20]	1.2 to 1.9 [20-32]	2.0 to 5.9 [33-101]	6.0 to 11.9 [102-204]	≥12.0 [≥204]
Cardiovascular Hypotension	None	MAP <70	Dopamine ≤5 µg/kg/min or any Dobutamine	Dopamine >5 µg/kg/min or Epinephrine or Norepinephrine ≤0.1 µg/kg/min	Dopamine >15 µg/kg/min or Epinephrine or Norepinephrine >0.1 µg/kg/min
Central Nervous System Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Serum Creatinine (mg/dL) [µmol/L] or urine output (mL/day)	<1.2 [<110]	1.2-1.9 [110-170]	2.0-3.4 [171-299]	3.5-4.9 [300-440] or <500 mL	≥5.0 [>440] or <200 mL

Source: adapted from Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction /failure. Intensive Care Med. 1996;22:707–710.

Appendix 4. Adjunctive Therapy Decision Tree (before respiratory tract specimens from the Screening Visit culture results are available)



Abbreviations: MDR=multidrug resistant; MRSA=methicillin-resistant *S aureus*.

[a]Risk of multidrug resistant gram-negative bacteria is determined by each individual site and its history of resistant bacteria requiring broad-spectrum antibiotics.

[b]If first-line therapy is contraindicated or not available, use second-line therapy. Avoid additional coverage for gram-positive organisms when choosing antibiotic regimens.

Note: On Day 3, once culture results have returned, an assessment of the gram-negative coverage should be performed and therapy may be changed for a different antibiotic; however, antibiotics with gram-positive coverage should be avoided, if possible.

The following are not acceptable adjunctive therapy due to overlapping MRSA coverage:

- Vancomycin
- Linezolid
- Teicoplanin
- Tigecycline

- Ceftaroline
- Any rifamycin (ex rifampin, rifampicin etc)

***Recommended aztreonam and colistin administration**

Recommended aztreonam IV administration:

- Normal renal function: 2 g every 6-8 hours
- CLcr = 10 to 50 mL/min; if receiving continuous renal replacement therapy such as continuous veno-venous hemofiltration: 2 g load, then 1 g every 6-8 hours
- CLcr <10 mL/min: 2 g load, then 500 mg every 8 hours; if receiving hemodialysis, an additional 500 mg after hemodialysis

Recommended colistin base activity (CBA) administration based on target steady state of 2.5 mg/L (Garonzik 2011). Higher doses of colistin may be used for serious infections with a target of 3.0 mg/L or 3.5 mg/L. These targets may be inserted in the equations below if the investigator believes it is warranted. However, maintenance dosing should not exceed 475 mg CBA/day under any circumstance.

Dosing is given in CBA because there are 2 options for colistimethate sodium and the recommended dosing varies by drug (Li 2006):

- Colomycin is used as the CBA below with an IU conversion of 12,500 IU/mg.
- Coly-mycin M: total dose of colistimethate sodium in this form is 2.4 times the CBA dose and IU conversion from CBA dosing is 30,000 IU/mg. Convert doses as shown below:

Ask your pharmacist for help for CBA dosing with the option that is available at your site.

Loading Dose = body weight x 2.0 x target steady state (2.5 mg/L), but not to exceed 300 mg

Weight (kg)	Loading dose (mg)
40	200
50	250
60	300
>60	300

Maintenance doses (starting 24 hours after loading dose):

Daily Maintenance Dose (mg to be divided to twice or three times daily) = target steady state (2.5 mg/L) x (1.5 x CLcr +30)

Creatinine Clearance (mL/min//1.73m^2)	Daily Dose (mg/day)	Frequency	Dose (mg)
5	93.75	Twice daily	46.9
10	112.5	Twice daily	56.25
20	150	Twice daily	75
30	187.5	Twice daily	93.75
40	225	Twice daily	112.5
50	262.5	Twice daily	131.25
60	300	Three times daily	100
≥70	337.5	Three times daily	112.5

Dosing on Continuous Renal Replacement (regardless of weight or calculated CLcr):

- 480 mg/day divided twice daily = 240 mg/dose twice daily

Dosing on Intermittent Hemodialysis (regardless of weight or calculated CLcr):

- Nonhemodialysis day: 75 mg/day twice daily = 37.5 mg/dose twice daily
- Hemodialysis day (given after hemodialysis): 97.5 mg/day BID = 48.75 mg/dose twice daily

Weight is the lower value of the either the ideal body weight or the actual body weight

Creatinine Clearance is the Cockcroft-Gault calculation normalized for a body surface area (BSA) of 1.73 m^2:
Glomerular filtration rate = [(140-age) x (weight in kg) x (0.85 if female)] / (72 x serum creatinine) x patient's BSA/1.73 m^2

Source: Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug-resistant gram-negative bacterial infections. Lancet Infect Dis 2006;6:589-601

Appendix 5. Microbiological Sampling and Pathogen Determination

Appropriate specimens (sputum or endotracheal aspirate [with <10 SEC and >25 PMN cells per low-power field], protected specimen brush, BAL, and mini-BAL, or exudative pleural effusion) will be collected at various time points (see Appendix 11). Note that microbiological samples are required only at the Screening Visit. At subsequent visits, samples are required in patients with no improvement or as clinically indicated for worsening respiratory status suggesting a treatment failure or new infection.

It is recommended that the first aspirated specimen from an intubated patient be discarded and the second specimen and any subsequent aliquots aspirated after instillation of sterile saline should be collected for Gram stain and culture. All cultures should be processed within 2 hours from the collection time; alternatively these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8ºC before processing. See Microbiology Laboratory Manual for additional detailed instructions.

Lower respiratory specimens should be sent to the site's local laboratory (or other designated regional laboratory) for Gram stain and culture. Blood samples should be sent to the site's local laboratory for culture (or other designated regional laboratory; Gram stain optional). Isolates should be identified using the local laboratory's usual procedures. All unique organisms from the respiratory or pleural fluid specimens and/or blood samples will be stored and sent to the Cubist -designated central laboratory for confirmation of identification and susceptibility testing.

Backup samples of all organisms isolated from the respiratory or pleural fluid specimens and of blood should be stored frozen at each site's local laboratory. The local laboratory should store these backup samples until the site/Investigator is notified by Cubist to discard them or ship them to Cubist designated Central Laboratory.

Additional information is provided in the Microbiology Laboratory Manual.

Recommendation for Gram stain Protocol from American Society of Microbiology:

1) Using a loop spread the respiratory sample onto a clear slide. Fix the cells to the slide using heat so the excess liquid evaporates.

2) Flood the slide with crystal violet staining reagent for 1 minute.

3) Wash slide in a gentle and indirect stream of tap water for 2 seconds.

4) Flood slide with the mordant: Gram's iodine for 1 minute.

5) Wash slide in a gentle and indirect stream of tap water for 2 seconds.

6) Flood slide with decolorizing agent. Wait 15 seconds or add drop by drop until decolorizing agent running from the slide runs clear. This step is critical and time-dependent as over-decolorizing the sample will make gram-positive bacteria appear to be gram-negative.

7) Flood slide with counterstain: safranin. Wait 30-60 seconds.

8) Wash slide in a gentle and indirect stream of tap water until the fluid running off the slide runs clear then blot dry with absorbent paper.

9) Use low power (10x) to count squamous cells and white blood cells

10) Use high power (100x) with oil immersion to view bacteria

11) To remove oil immersion from the slide without damaging the smear, lay a piece of lens tissue on the slide and add a drop or two of xylene. Draw the lens tissue across the slide and repeat as necessary.

All reagents can be made or purchased commercially from biological supply houses:

1) Primary Stain: Crystal Violet Staining Reagent

   a. Solution A

      Crystal violet (certified 90% dye content), 2 g

      Ethanol, 95% (vol/vol), 20 mL

   b. Solution B

      Ammonium oxalate, 0.8 g

      Distilled water, 80 mL

   Mix Solutions A and B to obtain the crystal violet staining reagent. Store for 24 hours and filter through filter paper before using.

2) Mordant: Gram's Iodine

   Iodine, 1.0 g

   Potassium iodide, 2.0 g

   Distilled water, 300 mL

Grind the iodine and potassium iodide in a mortar and add water slowly with continuous grinding until the iodine is dissolved. Store in amber (dark) bottles.

3) Decolorizing Agent

Ethanol, 95% (vol/vol)

Alternatively, a 1:1 mixture of acetone and 95% ethanol may be used.

4) Counterstain: Safranin

a. Stock Solution

Safranin O, 2.5 g

Ethanol, 95% (vol/vol), 100 mL

b. Working Solution

Stock Solution, 10 mL

Distilled water, 90 mL

Gram Stain Requirements

Gram stains should be read and reported per your institution's procedures so that required Gram stain data can be recorded on the e-CRF.

Determine the presence of WBCs in 20-40 fields of the smear under low power. Skip fields where there are no cells or bacteria and do not record these.

Report the presence of WBCs as follows:

- No WBCs
- 1 to 25 WBCs per low-power field
- >25 WBCs per low-power field

- Report the presence of squamous cells as follows:
  - No squamous cells
  - 1 to 9 squamous cells per low-power field
  - ≥10 squamous cells per low-power field
- Report the bacterial cell morphologies seen under high power (oil immersion) magnification in 20-40 fields of the smear as follows:
  - 1+ (scant)
  - 2+ (light)
  - 3+ (moderate)
  - 4+ (heavy)

Pathogen Determination

Pathogen determination is based on the genus and species identification from the central laboratory. Three categories of pathogen classification are defined as follows:

1. Always a pathogen. If the organism was isolated from the culture, the following are always considered a pathogen:

   Staphylococcus aureus

   Streptococcus pneumoniae

   Streptococcus pyogenes

   Pseudomonas aeruginosa

   Acinetobacter species

   Stenotrophomonas maltophilia

   Escherichia coli

   Enterobacter species

   Klebsiella species

   Proteus species

   Serratia species

Citrobacter species

Morganella species

Haemophilus species

Hafnia species

2. Never a pathogen. If the organism was isolated from the culture, the following are never a pathogen:
   S. saprophyticus

   Corynebacterium spp.

   S. epidermidis

   Bacillus species

   Diphtheroids

   Micrococci

3. Case-by-case review. All organisms isolated from a blood culture and all isolates not defined by criteria 1 and 2 above will be assessed case-by-case with a manual review by Cubist. If needed, patient clinical (eg, type of infection, type of specimen, patient underlying conditions) and microbiological information (eg, Gram stain) will be used to assist in determining if the isolate is a pathogen.

Appendix 6. Cranial Nerve Examination

Cranial Nerve Assessment			
Nerve	**Name**	**Function**	**Test (examples)**
I	Olfactory	Smell	Have patient smell a familiar odor
II	Optic	Visual field	Check peripheral vision
III	Oculomotor	Pupillary Reaction	Shine light in the eye
IV	Trochlear	Eye Movement	Have patient follow a finger without moving the head
V	Trigeminal	Facial Sensation; Motor Function	Touch the face; Have patient hold mouth open
VI	Abducens	Motor Function	Check lateral eye movements
VII	Facial	Motor Function; Taste	Have patient smile, wrinkle face, puff cheeks; Evaluate taste
VIII	Acoustic	Hearing; Balance	Snap fingers by the ears; Romberg's test
IX	Glossopharyngeal	Swallowing and Voice	Have patient swallow and say "Ah"
X	Vagus	Gag Reflex	Use tongue depressor to evaluate
XI	Spinal Accessory	Neck Motion	Evaluate shoulder shrugging
XII	Hypoglossal	Tongue Movement and Strength	Have patient stick out tongue; apply resistance with a tongue depressor

Appendix 7. Acute Physiology and Chronic Health Evaluation (APACHE) II Score

Point Value	4	3	2	1	0	1	2	3	4	Total
Glasgow Coma Score	Score = 15 minus actual Glasgow Coma Score									
Temperature (rectal, ºC)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9	
Mean Arterial Pressure (mmHg)[a]	≥160	130-159	110-129		70-109		50-69		≤49	
Heart Rate (bpm)	≥180	140-179	110-139		70-109		55-69	40-54	≤39	
Respiration Rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5	
PaO_2 (mmHg) or Alveolar-Arterial Oxygen Gradient (if FiO_2≥50%)	≥500	350 to 499	200 to 349		<200 >70	61-70		55-60	<55	
Arterial pH OR Serum HCO_3 (mEq/L) -(venous-if ABG not performed)	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15	
Serum Na+ (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110	
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	
Serum creatinine (mg/dL)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6			
Acute renal failure[b]	×2 creatinine point score if patient has acute renal failure									
Hematocrit, %	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20	
WBC, (10^9 cells/L or mm^3)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1	
Severe organ failure (liver, heart, or lung) or immunocompromised[c]	Add 5 points if patient is medical (no surgery) or postoperative for emergency surgery Add 2 points if patient is postelective surgery									
Age (years) points	≤44=0 45-54=2 55-64=3 65-74=5 ≥75=6									
									Sum of all rows	

Footnotes for Appendix 7: Acute Physiology and Chronic Health Evaluation (APACHE) II Score

Source: Adapted from Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine* 13 (10): 818–29.

[a]Mean arterial pressure =$\frac{\text{Systolic blood pressure + 2 (diastolic blood pressure)}}{3}$

[b]Acute Renal Failure = a 0.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≤1.9 mg/dL, a 1.0 mg/dL increase in serum creatinine if the baseline serum creatinine was 2.0 to 4.9 mg/dL, and a 1.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≥5.0 mg/dL.

[c]Organ insufficiency or immunocompromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

- **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.
- **Cardiovascular** – New York Heart Association Class IV.
- **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 (>40 mmHg), or respirator dependency.
- **Renal** – receiving chronic dialysis.
- **Immunocompromised** – the patient has received therapy that suppresses resistance to infection (eg, immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, eg, leukemia, lymphoma, AIDS).

Appendix 8. Glasgow Coma Scale

Sedating and paralytic agent use may confound the assessment of the Glasgow Coma Score. If sedation is reduced and patients awakened daily to perform neurologic assessments, assess the score during the period when the patient is not sedated. If daily awakenings are not performed, please record the score as if the patient did not have sedating or paralytic agents preventing response.

Neurologic Response		**Score**
Best Eye Response (E)	Spontaneous-open with blinking at baseline	4
	Opens to verbal command, speech or shout	3
	Opens to pain (not applied to face)	2
	None	1
Best Verbal Response (V)	Oriented	5
	Confused conversation, but can answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best Motor Response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1
Total Score		

Source: Teasdale G, Jennet B. "Assessment of coma and impaired consciousness". *Lancet* 1974; ii: 81–83.

Appendix 9. Clinical Laboratory Evaluations

<table>
<tr><th colspan="2">Clinical Laboratory Evaluations</th></tr>
<tr><td rowspan="4">Chemistry Panel
Total Bilirubin[a]
Direct Bilirubin
Indirect Bilirubin
Albumin[a]
Alkaline Phosphatase
Alanine aminotransferase (ALT)[a]
Aspartate aminotransferase (AST)[a]
Gamma-glutamyl transpeptidase (GGT)
Lactate dehydrogenase (LDH)
Urea Nitrogen
Creatinine[a]
Glucose
Uric Acid
Calcium
Phosphorus
Total Protein
Cholesterol
Creatine kinase/creatine phosphokinase
Sodium[b]
Potassium[b]
Bicarbonate[b]
Chloride
Magnesium</td><td>Hematology/Differential Panel
Hemoglobin
Hematocrit[b]
Red blood cell count
White blood cell count[a]
Neutrophils (%, absolute)[a]
Lymphocytes (%, absolute)
Monocytes (%, absolute)
Eosinophils (%, absolute)
Basophils (%, absolute)
Bands (%, absolute)[b]
Platelet count</td></tr>
<tr><td>Pregnancy Test (all females of childbearing potential, excludes females ≥2 years postmenopausal or surgically sterile)
Serum beta-human chorionic gonadotropin (beta-hCG) at Screening (local only)[a]</td></tr>
<tr><td>Urine Panel
pH
Bilirubin
Glucose
Ketones
Urobilinogen</td></tr>
<tr><td>Coagulation Panel (local only)[a]
Prothrombin time (PT)
Partial thromboplastin time (PTT)
International Normalized Ratio (INR)</td></tr>
</table>

[a]Local laboratory evaluations required at Screening; PT **or** INR are acceptable; PTT or activated PTT are acceptable.
[b]Local laboratory evaluations required at Screening if local laboratory has capability to measure.

Appendix 10. Pharmacokinetic Sampling

Blood will be collected from all patients to evaluate the systemic plasma concentrations of TR-700 and optionally TR-701 after administration of TR-701 FA using a validated assay. Detailed information on sample collection and processing is provided in the PK Manual.

Perform the following:

1. Collect blood in the tube provided by the Cubist-designated central laboratory
2. Slowly invert the tube at least 8 to 10 times
3. Place the tube in an ice water bath until centrifugation
4. Centrifuge the sample at 2000 × g at 5ºC for 15 minutes. If a refrigerated centrifuge is not available, place the tube in an ice bath immediately before and after the centrifugation for at least 5 minutes each time
5. Split the sample into 2 aliquots and store at -20ºC or colder
    - One aliquot will be shipped to the Cubist-designated central laboratory
    - The other aliquot is to be stored at the study site as a back-up sample until notified by Cubist or designee that the sample either is to be sent to the Cubist-designated central laboratory or is to be destroyed

Appendix 11. Schedule of Study Procedures

	Study Visits							
		Study Day				End of Therapy (EOT; 1-3 days after last study drug)	Test of Cure (TOC; 7-14 days after last study drug)	Late Follow-Up[b] (28-32 days after randomization)
Study Procedure	**Screening** (within 24 hours before the first infusion)	**1**	**2**	**3**	**4-10/14**[a]			
Informed consent (before any study procedures)[c]	X	At any time the patient is medically able (ie, alert and extubated)						
Verify patient meets inclusion and exclusion criteria	X							
Record relevant medical/surgical history (5 years)	X							
Record height and weight (estimate if	X							
Perform 12-lead electrocardiogram	X							
Determine APACHE II score (if all components available; see Appendix 7)	X							
Determine Glasgow Coma Scale score (see Appendix 8)	X			X	X (Day 7 only)			
Obtain chest x-ray or CT scan (within 36 hours prior to infusion)	X							
Randomize via IVRS		X						
Neurologic examination and screening for peripheral sensory and motor neuropathy (see Appendix 6) and visual acuity examination	At any time the patient is medically able (ie, alert and extubated)							
In patients who are receiving supplemental O_2, determine oxygenation status obtained on the last 24 hours by documenting the lowest percentage oxygenation saturation by pulse oximetry or the lowest PaO_2 by ABG if available. Perform at Day 1 only if different from calendar day of Screening.	X	X	X	X	X	X	X	
Record highest minute ventilation and FiO_2 obtained on the calendar day	X		X	X	X	X	X	
Collect and document components of CPIS and SOFA scores (see Appendix 2 and Appendix 3)	X							
Perform a physical examination	X		X	X	X	X	X	
Record prior and/or concomitant medications	X[d]	X	X	X	X	X	X	X[e]
Record lowest and highest vital signs[f]	X	X	X	X	X	X	X	
Record lowest and highest temperature[g]	X	X	X	X	X	X	X	

Appendix 11 (*continued*) Schedule of Study Procedures

	Study Visits							
		Study Day				End of Therapy (EOT; 1-3 days after last study drug)	Test of Cure (TOC; 7-14 days after last study drug)	Late Follow-Up[b] (28-32 days after randomization)
Study Procedure	**Screening** (within 24 hours before the first infusion)	**1**	**2**	**3**	**4-10/14**[a]			
Obtain lower respiratory tract or pleural fluid microbiological specimens[h]	X		X	X	X	X	X	X (on-site visit only)
Document rapid diagnostic, PCR or nasal swab results if applicable	X							
Collect blood sample for microbiology[i]	X			X	X	X	X	X (on-site visit only)
Collect urine sample for *Legionella* antigen	X							
Collect sample for serum pregnancy test[j]	X							
Collect blood sample for procalcitonin	X				X (Day 7 only)			
Collect blood samples for chemistry and hematology panels	X				X (only Days 7 and 10 [all]; Day 14 [bacteremic])	X	X	X (on-site visit only)
Collect blood samples for PK analysisk		X			X (Day 4 or 5 and Day 7 only)			
Collect blood sample for coagulation panel	X							
Calculate PT or INR; Child-Pugh; estimate CLcr	X							
Administer study drug		X[l]	X	X	X			
Select or re-evaluate gram-negative adjunctive therapy based on microbiology and susceptibility results (see Appendix 4)		X	X	X	X			
Determine Investigator's assessment of Clinical Response						X	X	
Assess for clinical relapse								X
Determine survival status								X
Assess AEs (pretreatment, treatment-emergent, or ongoing)	X	X	X	X	X	X	X	X

Footnotes from Appendix 11: Schedule of Study Procedures

Abbreviations: AE=adverse event; APACHE=Acute Physiology and Chronic Health Evaluation; CLcr=creatinine clearance; CPIS=Clinical Pulmonary Infection Score; EOT=end of therapy; hCG=human chorionic gonadotropin; INR=international normalized ratio; hCG=beta-human chorionic gonadotropin hormone; PK=pharmacokinetic; PT=prothrombin time; SOFA=Sepsis-related Organ Failure Assessment; TOC=test of cure.

[a] Days 4 to 10 for patients without bacteremia; Days 4 to 14 for patients with gram-positive bacteremia.

[b] For patients with bacteremia, this visit may be combined with and performed on the same day as the TOC.

[c] Obtain initial informed consent >24 hours before the first infusion. Patient must be re-consented at any time during the study should he/she become medically able to do so (only if original consent was provided by the patient's legally authorized representative).

[d] Record medications taken ≤30 days before the first infusion.

[e] Only for patients with clinical relapse or who require treatment for an AE.

[f] Record blood pressure, heart rate, and respiration rate on calendar day. Perform at Day 1 only if different from calendar day of Screening. At the TOC Visit, record highest and lowest vital signs values if patient remains hospitalized; if patient is not hospitalized, record vital signs.

[g] Record temperature on calendar day. Perform at Day 1 only if different from calendar day of Screening. At the TOC Visit, record highest and lowest temperature if patient remains hospitalized; if patient is not hospitalized, record temperature.

[h] Samples must be collected via valid sampling technique. All isolates from the local laboratory culture are to be sent to the central laboratory except for those listed as never a pathogen in Appendix 5. Microbiological samples are required only at the Screening Visit. At subsequent visits, samples are required in patients with no improvement or as clinically indicated for worsening respiratory status suggesting a treatment failure or new infection, and if respiratory specimens are easily accessible.

[i] Obtain blood samples on Days 3 to 10/14, and the EOT and TOC Visits, if clinically indicated. Repeat blood samples if clinically significant pathogen is isolated.

[j] Perform a serum hCG pregnancy test at the local laboratory for the Screening Visit for female patients of childbearing potential (may be omitted for females ≥2 years postmenopausal or surgically sterile).

[k] If approved by ethics and/or local regulatory authorities, collect blood samples for PK analysis on Day 1 between 5 and 80 minutes, and between 4 and 12 hours after the completion of Dose 1, Infusion A; on Day 4 or 5 before Dose 7 or 9; on Day 7 between 5 and 80 minutes after Dose 13 (2 samples) and between 4 and 12 hours after Dose 13.

[l] Administer study drug Dose 1 as 2 separate and serial 60-minute infusions (±10 minutes). Initiate Infusion A, flush the line, and then initiate Infusion B. Doses should be given every 12 hours ± 2 hours from start of infusion A of odd numbered dose to next even numbered dose.

Appendix 12. Assessment Plan of Sepsis

1.0 DEFINITION OF SEPSIS

Sepsis is defined as bacteremia (positive blood culture at baseline) with systemic inflammatory symptoms/findings (Office of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW], 2017).

2.0 RATIONALE OF SEPSIS ASSESSMENT

Sepsis is associated with high mortality rates. Delays in treatment lead to complications, including multiple organ failure (circulatory failure, acute respiratory syndrome, disseminated intravascular coagulation, etc.), and associated poor outcomes. Therefore, prompt therapy with appropriate antibiotics is essential in patients with sepsis.

Sepsis assessment in this study is based on the Japanese Guideline for Clinical Assessment of Antibiotics on Sepsis and the definition of sepsis of Society of Critical Care Medicine and American College of Chest Physicians (MHLW 2017, Bone et al. 1992, JRS Guidelines 2017, JAID/JSC 2017).

3.0 TRIAL OBJECTIVES OF SEPSIS ASSESSMENT

The efficacy and safety of TR-701 FA in patients with sepsis will be evaluated under this Japan-specific amendment.

3.1 Study Objectives

Primary objectives:

- To evaluate the clinical response to TR-701 FA in the treatment of sepsis at the TOC Visit in the Sepsis Population.
- To evaluate the safety and tolerability of TR-701 FA in the Sepsis Population.

Secondary objective:

- To evaluate the microbiological response to TR-701 FA in the treatment of sepsis at the TOC Visit in the Sepsis Population.

4.0 THE CRITERIA OF SEPSIS

A subject must satisfy all [that is, both 1) and 2)] 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 (heart rate) >90 beats per minute

- PaO_2*/FiO_2**≤240 mmHg
- Systolic blood pressure <90 mmHg

  *In case percentage of oxygenation saturation was measured instead of PaO_2, PaO_2 value is calculated based on the method by Severinghaus (Severinghaus 1979).

  **Fraction of air oxygen (21%) is substituted for calculation in patients who were removed from ventilation.

2) Meet the definition of bacteremia*(refer to Protocol Section 5.3.1) at baseline

   *Definition of bacteremia (refer to Protocol Section 5.3.1): Bacteremia is defined as 1 positive blood culture for *S aureus*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes*, or 2 positive blood cultures for any other gram-positive lung pathogen. (Refer to Appendix 5 for details of pathogens.)

5.0 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 patients with an outcome of efficacy endpoint as indeterminate at the TOC Visit will be considered as treatment failures. In other words, all patients 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 Appendix 12 Table 2.

5.2 Population for Analysis

Sepsis Population:

The Sepsis Population will consist of all randomized patients who received at least 1 dose of study treatment and satisfy the sepsis criteria. Patients who receive the wrong study drug for the entire course of treatment will be analyzed in the group based on the drug received.

5.3 Study Endpoints

5.3.1 Efficacy Endpoints

Primary Endpoints:

- Clinical response at the TOC Visit

Secondary Endpoints:

- Microbiological response at the TOC Visit

5.3.2 Safety Endpoint:

- The incidence (n and %) of TEAEs, SAEs, and TEAEs leading to study drug discontinuation

5.4 Efficacy Endpoint Analyses

5.4.1 Primary Endpoint Analysis

The point estimates and 95% CI using the Clopper-Pearson method will be presented for the clinical response rate at TOC in the Sepsis Population in each treatment group (Clopper & Pearson 1934). Also, the difference in proportions and the 95% CI for the difference using the Meittinen & Nurminen method will be presented (Miettinen & Nurminen1985). The clinical response rate is defined as a proportion of patients who are judged to have a clinical outcome for sepsis as "Cure". In addition, the analysis approach will be the same for this endpoint in patients with sepsis who also have blood cultures positive for MRSA at baseline.

5.4.2 Secondary Endpoint Analysis

The point estimates and 95% CI using the Clopper-Pearson method will be presented for the microbiological response rate at TOC in the Sepsis Population in each treatment group. Also, the difference in proportions and the 95% CI for the difference using the Meittinen & Nurminen method will be presented. The microbiological response rate is defined as a proportion of patients who are judged to have a microbiological outcome for sepsis as "Eradication" or "Presumed eradication". In addition, the analysis approach will be the same for this endpoint in patients with sepsis who also have blood cultures positive for MRSA at baseline.

5.5 Safety Analysis

The incidence (n and %) of TEAEs, SAEs, and TEAEs leading to study drug discontinuation will be presented for patients in the Sepsis Population 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.

5.6 Evaluation Criteria of Sepsis

5.6.1 Definition of Clinical Response for Sepsis

Clinical outcome assessment for sepsis will be based on the data collected from 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 (Appendix 12 Table 1).

Appendix 12 Table 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 did not meet any of the criteria of sepsis 1) in Appendix 12, 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 criteria of sepsis 1) in Appendix 12, Section 4.
Indeterminate	Study data was not available at TOC visit for the evaluation of clinical outcome for any reason, which means at least 1 item 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 Appendix 12, 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 up to and including the 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 or indeterminate (Appendix 12 Table 2).

Appendix 12 Table 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 gram-positive 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 gram-positive pathogens.
Indeterminate	A blood culture after the administration of the first dose of drug is not performed and a subject deemed other than clinical cure (failure or indeterminate) for clinical outcome of sepsis at the TOC Visit.

6.0 LIST OF REFERENCES

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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