Official Protocol Title:	A Multi-national Phase 3, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of Imipenem/ Cilastatin/Relebactam (MK-7655A) Versus Piperacillin/ Tazobactam in Subjects
NCT number:	NCT03583333
Document Date:	11-Nov-2020

Title Page

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Protocol Title: A Multi-national Phase 3, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Piperacillin/Tazobactam in Subjects with Hospital-Acquired Bacterial Pneumonia or Ventilator-Associated Bacterial Pneumonia

Protocol Number: 016-03

Compound Number: MK-7655A

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

EudraCT NUMBER: 2018-003202-82

Approval Date: 11 November 2020

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-7655A-016-00	15-FEB-2018	Original Protocol
MK-7655A-016-01	29-AUG-2018	The main drivers for this amendment were changes to the microbiological definitions at EOT and EFU as well as additional clarifications to procedures in the schedule of activities.
MK-7655A-016-02	18-SEP-2019	The main reason for this amendment was to change the upper age limit of participants from ≤75 years to ≤90 years of age due to the unmet medical need for treatment of HABP/VABP in the elderly population. In support of the age limit change, prior studies in the MK-7655A program enrolled all adults aged 18 years or older, and a comparable safety profile for IMI/REL was observed across all participants ≤90 years of age.
MK-7655A-016-03	11-NOV-2020	The main reason for this amendment were to allow for inclusion of participants with a gram stain result showing 'no organism seen' and to provide clarification for key inclusion/exclusion criteria and study procedures.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 03

Overall Rationale for the Amendment:

The reason for this amendment were to allow for inclusion of participants with a gram stain result showing 'no organism seen' and to provide clarification for key inclusion/exclusion criteria and study procedures.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.4 Beginning and End of Study Definition 5.1 Inclusion Criteria 8.1.1 Informed Consent 8.1.1.1 General Informed Consent 8.1.3 Participant Identification Card 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 10.1 Data Quality Assurance	Updated text for informed consent process	The protocol template was updated to align with current informed consent/assent procedures.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Footnote: "f" added indicating that "If blood samples for chemistry and hematology safety evaluations, and Chest X-ray were performed within 24 hours prior to the EOT Visit, additional blood samples for chemistry and hematology and Chest x-ray are not required at EOT."	To clarify study procedure requirements and allowable windows for collection/completion of key procedures.
1.3 Schedule of Activities (SoA) 5.1 Inclusion Criteria – Criterion 2	Notes revised to clarify that chest x-ray at randomization is only to be performed if prior chest x-ray has not been performed in association with the current infection within 48 hours prior to randomization. Added "within 48 hours prior to randomization" in criteria 2 to clarify the allowed window.	To clarify the allowable time window for clinical and radiographic criteria of HABP/VABP.
1.3 Schedule of Activities (SoA) 8.2.4.2 Other Lower Respiratory Tract Samples Following Randomization	Text added to notes in SOA and in 8.4.2 for Lower Respiratory Tract Specimen for Gram stain, Culture, and Susceptibility at EOT and EFU visit: "Cultures are not required at EOT or EFU if considered clinically cured ('cure,' 'improved,' or 'sustained cure')."	To clarify study procedure requirements and allowable windows for collection/completion of key procedures.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.2.4.3 Blood Cultures	Text added to notes in SOA and in 8.4.3 for Blood Specimen for Culture and Susceptibility: "A culture obtained within 48 hours prior to the randomization visit is acceptable, as long as the blood cultures collected meet the protocol requirement, ie, 2 sets of blood cultures, from 2 separate venipunctures (or 1 venipuncture and 1 catheter)." Changed the follow-up blood culture frequency from "daily" to "as clinically indicated" in subjects with positive blood cultures at screening.	To clarify study procedure requirements and allowable windows for collection/completion of key procedures.
2.2.2. Preclinical and Clinical Studies 2.2.3 Ongoing Clinical Studies	Final information regarding MK-7655A-014 added. MK-7655A-014 was removed as an ongoing clinical study. MK-7655A-020 and MK-7655A-021 added as ongoing studies.	Updated information regarding the completed and ongoing clinical studies.
5.1 Inclusion Criteria – Criterion 3 5.2 Exclusion Criteria – Criterion 1	Changed the list of acceptable Gram stain result patterns to clarify that "no organism" is acceptable. Details regarding acceptable Gram stain results were removed from inclusion criterion 3 and added to exclusion criterion 1.	To further clarify these criteria and to be consistent with PN014. Details of acceptable Gram stain results were moved and updated to provide additional clarification.
5.2 Exclusion Criteria – Criterion 6 6.5 Concomitant Therapy	Added the prohibited duration for maintenance glucocorticoid therapy (>40 mg/d prednisolone equivalent dose continuously administered for ≥7 days).	To clarify the prohibited treatment duration.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria – Criterion 15 6.5 Concomitant Therapy	Added a note to clarify that the use of valproic acid or divalproex sodium for seizure prophylaxis among subjects with no active or prior history of seizure disorder is acceptable for the specified uses. Added "during treatment with linezolid" to serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), monoamine oxidase inhibitors (MAOIs), meperidine and buspirone. Added "dopaminergic agents (during treatment with linezolid)" as a prohibited medication. Revised "concomitant systemic (IV or oral) antibacterial agents" to "concomitant systemic (IV, or oral), inhaled or intrapleural antibacterial agents."	To clarify prohibited treatment information. To maintain consistency with 6.5 Concomitant Therapy. To maintain consistency with study PN014.
8.2.3 Microbiological Response Table 8: Definitions of the By-Pathogen Microbiological Response Rating at the EOT Visit	Updated the response definition of 'Superinfection' at EOT, now defined as: "A lower respiratory tract culture grows a pathogen other than a baseline pathogen at the EOT visit." Revised footnote 'a' to be aligned with the updated definition.	To clarify definition of 'Superinfection' at EOT.

Section # and Name	Description of Change	Brief Rationale
8.2.3 Microbiological Response Table 9: Definitions of the By-Pathogen Microbiological Response Rating at the EFU Visit	Updated the response definition of 'New Infection' at EFU, now defined as: "A lower respiratory tract culture grows a pathogen other than a baseline pathogen at the EFU visit." Revised footnote 'a' to be aligned with the updated definition. Added footnote 'd': "If a culture is not available at EFU, an assessment can be made based on a culture collected at the EOT visit as long as it was collected at least 24 hours after the end of IV therapy and before the EFU visit."	To clarify the definition of 'New Infection' at EFU. To clarify study procedure requirements and allowable windows for collection/completion of key procedures.
10.6 Appendix 6: APACHE II Severity of Disease Classification System – APACHE II Score Form	Added footnote 'a' to clarify timing of collection of APACHE II variable during Screening: "The most severe value in the last 48 hours prior to a participant's randomization into the study should be used for each variable of the APACHE II score calculation. The calculation of the APACHE II score should be captured in the patient's medical chart or in a copy of the APACHE II Score form." Added footnote 'b' to clarify the temperature measurement: "The sponsor recommendation is to use rectal temperature measurement whenever possible. If rectal temperature is not possible, it is acceptable to use non-rectal temperature with no conversion as a substitute."	To clarify APACHE II Score assessment.

Section # and Name	Description of Change	Brief Rationale
	Added footnote ‘c’ to clarify the oxygenation measurement: “It is recommended that when assessing the Oxygenation variable for the APACHE II calculation, ABG measurements should be used. If ABG has not been performed for a participant, then the APACHE II score calculation should be recorded as 0 for Oxygenation variable.” Added footnote ‘d’ to clarify specific motor response categories: “Decerebrate for +2 points means extension to pain. Decorticate for +3 points means flexion to pain.” Added footnote ‘e’ to clarify verbal response for participants who are intubated and/or sedated/paralyzed: “Verbal response for participants that are intubated and/or sedated/paralyzed: If there is a reliable pre-sedation GCS score or all of the elements of the GCS score were documented in the medical record - then just use the pre-sedation GCS score (not just the verbal response piece, but the whole GCS score). But if there is no reliable pre-sedation GCS score, then the GCS section of the Acute Physiology Score would just be null overall. Investigators should note on the source documents and then commenting out on the APC2 eCRF that the GCS was not assessed.”	

Section # and Name	Description of Change	Brief Rationale
	Added footnote 'f' to clarify assessment of the Chronic Health Points (CHE) Score: "The CHE score can only be +5, +2, or 0. These additional points are to be given only once and not multiple times for each separate condition that has been observed."	
Throughout	Minor editorial and grammatical revisions.	Minor revisions were made for clarity and to correct grammatical errors.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Multi-national Phase 3, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Piperacillin/Tazobactam in Subjects with Hospital-Acquired Bacterial Pneumonia or Ventilator-Associated Bacterial Pneumonia

Short Title:

IMI/REL (MK-7655A) vs. PIP/TAZ for Treatment of Subjects with HABP/VABP

Objectives/Hypotheses and Endpoints:

The following objectives and endpoints will be evaluated in adult participants diagnosed with hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP):

Objective/Hypothesis	Endpoint
Primary	
• Objective: To determine the incidence rate of all-cause mortality through Day 28 post-randomization associated with treatment with imipenem/cilastatin/relebactam (IMI/REL) compared to treatment with piperacillin/tazobactam (PIP/TAZ) in the modified intention-to-treat (MITT) population. Hypothesis (H1): IMI/REL is non-inferior to PIP/TAZ as measured by the incidence rate of all-cause mortality through Day 28 post-randomization in the MITT population. If non-inferiority is established, the following hypothesis will be tested:	• All-cause mortality

Hypothesis (H2): IMI/REL is superior to PIP/TAZ as measured by the incidence rate of all-cause mortality through Day 28 post-randomization in the MITT population.	
Secondary	
• Objective: To evaluate favorable clinical response (CR) rate associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the following visits and analysis populations: - At the early follow-up (EFU) visit in the MITT population - At the EFU visit in the clinically evaluable (CE) population - At the end of treatment (EOT) visit in the MITT population - At the EOT visit in the CE population	• Favorable CR at EFU requires "sustained cure" or "cure" (see Table 6) • Favorable CR at EOT requires "cure" or "improved" (see Table 5)
• Objective: To evaluate favorable microbiological response (MR) rate associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the following visits and analysis populations: - At the EFU visit in the microbiologically evaluable (ME) population - At the EOT visit in the microbiologically modified intention-to-treat (mMITT) population - At the EOT visit in the ME population	• Favorable MR at EFU requires "eradication" or "presumed eradication" (see Table 9) • Favorable MR at EOT requires "eradication" or "presumed eradication" (see Table 8)
• Objective: To evaluate the safety and tolerability profile of IMI/REL compared with PIP/TAZ.	• Number of participants experiencing adverse events (AEs) • Number of participants discontinuing study drug due to adverse events

Overall Design:

Study Phase	3
Clinical Indication	Treatment for hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP)
Population	Adult patients with HABP/VABP.
Study Type	Interventional
Type of Design	Multi-site parallel-group design
Type of Control	Active control without placebo
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 31 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 270 subjects will be enrolled to obtain 270 MITT participants as described in Section 9.9.

Treatment Groups and Duration:

Treatment Groups	Treatment Group 1: IMI/REL administered intravenously (IV) as a fixed-dose combination (FDC) at a dosage of 500 mg IMI/250 mg REL once every 6 hours. Treatment Group 2: PIP/TAZ administered IV as an FDC at a dosage of 4000 mg PIP/500 mg TAZ once every 6 hours. Doses of IMI/REL and PIP/TAZ will be adjusted for participants with renal insufficiency. In both treatment groups, the use of initial empiric treatment with open-label IV linezolid (600 mg every 12 hours) for methicillin-resistant *Staphylococcus aureus* (MRSA) infection is required and will be administered in an open-label fashion.

Duration of Participation	Each participant will participate in the study for approximately 1 month from the time the participant provides documented informed consent through the final contact. After a maximum screening phase of 2 days, each participant will be receiving assigned treatment for a minimum of 7 days to a maximum of 14 days. After the end of treatment, each participant will be followed for 7 to 14 days. All participants must also have a study visit at Day 28 (up to an additional 3 days) following randomization. The total duration for each participant in the study will be up to 33 days.

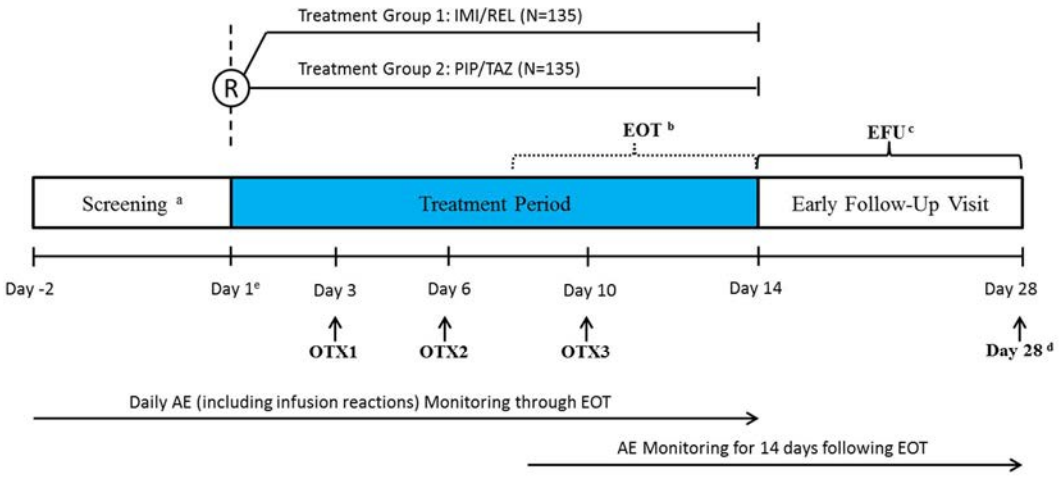
Study Governance:

Study Governance Committees	There are no governance committees in this study.

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.



OTX = on therapy, **EOT** = end of therapy, **EFU** = early follow-up, **Day 28** = Day 28 post-randomization
[a] The screening visit must occur ≤ 48 hours prior to randomization.
[b] The EOT visit must occur ≤ 24 hours after the last dose of IV study therapy. Minimum duration of IV therapy is 7 full days. Maximum duration must not exceed 14 days. Subjects with bacteremia or with Pseudomonas aeruginosa infection will receive 14 days of IV therapy.
[c] 7 to 14 days following EOT. The EFU and Day 28 visits may be combined as long as compliance with the visit windows is maintained for both visits.
[d] 28 days (up to an additional 3 days) following randomization.
[e] There is no day 0 in this study.

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Participant Identification Card	X								
Medical History	X								
Prior or Concomitant Medication Review	X	X	X	X	X	X	X	X	
Treatment Allocation/Randomization & Stratification		X							
Penicillin Skin Test (Per local guidance)	X	X							Must have a negative result prior to the first dose of IV study therapy. Test should be conducted on Screening or Day 1 within 72 hours prior to the IV study therapy with the same skin test agent; Otherwise, should be repeated.
Administration of IV Study Therapy		Daily (administered IV q6h)							Administered for 7 to 14 days, as described in Section 6.1. Refer to Table 2 and Table 3 for dose adjustments based on renal insufficiency.
Administration of Empirical IV Linezolid Therapy		Daily (administered at 600 mg IV q12h)							Administered for 7 to 14 days, as described in Section 6.1.

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Clinical Procedures/Assessments									
APACHE II Score	X								See Appendix 6 for details
Clinical Pulmonary Infection Score (CPIS)	X								See Appendix 7 for details
Full Physical Examination		X							
Directed Physical Examination			X	X	X	X	X	X	
Vital Signs (heart rate, blood pressure, respiratory rate, oral temperature)		Daily during IV study therapy				X	X	X	Assess prior to first dose of IV study medication on Day 1, then daily during IV study therapy; See Section 8.3.3
Height and Weight		X							Assess prior to first dose of IV study medication
Adverse Event Monitoring	X	Daily during IV study therapy				X	X	X	See Section 8.4 for details
Local Infusion Tolerability Monitoring		Daily during IV study therapy				X			See Section 8.4.8 for details
Review of Clinical Signs and Symptoms of HABP/VABP Infection		Daily during IV study therapy				X	X	X	Conduct prior to first dose of IV study medication. See Section 8.2.2.1 for details.

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Chest X-ray	X	X	Only perform if clinically indicated such as for worsening signs/symptoms of pneumonia and verification of progression is clinically needed for diagnosis.			X[f]	X	Only perform if clinically indicated (eg, in the setting of persistent signs and symptoms of pneumonia).	Screening: If chest x-ray performed, must still be performed in association with current infection and be within 48 hours of randomization. If performed at Screening Visit, do not perform at randomization. Randomization (Day 1): Perform prior to first dose of IV study medication; only perform if prior chest x-ray has not been performed in association with the current infection within 48 hours prior to randomization. A CT scan obtained within 48 hours of randomization can be used in place of the baseline chest x-ray if a scout view or similar view can be produced. Days 3, 6, 10 & 28: only perform if clinically indicated. Post-baseline, chest x-rays must be used at subsequent visits. If CT scans are performed at the time of study visits for diagnostic purposes other than for HABP/VABP, the scout view or similar view can be used in place of the chest x-ray.

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
PaO_2/FiO_2 Ratio or O_2 Saturation		Daily during IV study therapy				X	X	X	PaO_2 and FiO_2 measured via ABG (in ventilated subjects who have an existing arterial line) or oxygen saturation via pulse oximetry (in all other subjects) must all be measured on Day 1, Day 3 (OTX1), Day 6 (OTX2), and Day 10 (OTX3, if applicable) of IV study therapy, and at the EOT, EFU, and Day 28 post-randomization visits. On all other days of IV study therapy, oxygen saturation via pulse oximetry should be measured. See Section 8.2.6 for details
Infection Source Control Review		X	X	X	X				Source control includes the following: (a) details regarding intubation, extubation, reintubation, or replacement of the endotracheal tube, (b) details regarding lung procedures/surgeries performed to drain/remove a loculated pulmonary infection, or (c) details regarding a thoracentesis procedure to drain any accompanying pleural fluid. See Section 8.2.7 for details

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Laboratory Procedures/Assessments									
Blood for Hematology	X	X	X	X	X[f]	X[f]	X	X	Screening: Hematological parameters to support Inclusion/Exclusion Criteria assessment only. Local labs drawn within 24 hours prior to screening are permissible to use to assess I/E criteria. Local labs drawn specifically for the study should occur after informed consent is obtained. Visit 2: Perform prior to first dose and send to central safety lab (Table 16). Visits 3-8: Perform once on each visit day and send to central safety lab (Table 16). All findings must be recorded in the appropriate eCRFs.
Blood for Chemistry	X	X	X	X	X[f]	X[f]	X	X	Screening: Chemistry parameters to support I/E assessment only. Local labs drawn within 24 hours of screening are permissible to use to assess I/E criteria. Local labs drawn specifically for the study should occur after informed consent is obtained. Visit 2: Perform prior to first dose and send to central safety lab (Table 16). Visits 3-8: Perform once on each visit day and send to central safety lab (Table 16).

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
HIV/HBV/HCV (Per local guidance)	X								
Blood for Local Laboratory Assessment of Creatinine	X	X	X	X	X				Screening: Perform locally if creatinine assessment not already done as part of Blood for Chemistry Visit 2: Perform prior to first dose. Visits 3-5: Perform once on each visit day for the purpose of dose adjustments based on renal insufficiency by unblinded study staff (Table 2 and Table 3)
Urine for Urinalysis	X	X				X			Perform on Screening or Day 1 on a mid-stream clean catch urine or catheter urine specimen if possible; Table 16

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Serum/urine for β-human Chorionic Gonadotropin (β-hCG), in women of reproductive potential only	X							X	Screening: Documented, local lab-assessed, negative serum β-hCG within 48 hours prior to enrollment can replace the screening assessment. If documentation is not available, a rapid urine β-hCG test may be used for screening; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. To conduct urine testing, sites must have individuals certified in administration and interpretation of test and the urine test utilized must have sensitivity of <25 mIU/L. Day 28: Serum pregnancy testing must be performed by central safety laboratory. See Appendix 3 for details.

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Lower Respiratory Tract Specimen for Gram stain, Culture and Susceptibility[d]	X	X	X	X	X	X	X	X	On either Screening or Day 1: Collect prior to first dose of IV study medication. A culture obtained within 48 hours prior to the screening visit is acceptable. Microscopic examination of Gram-stained smears must be performed prior to randomization to ensure the adequacy of the specimen. The subject must be excluded from participating in the trial if the Gram stain shows the presence of Gram-positive cocci **only**. See Section 8.2.4.1 for details. Cultures are not required at EOT or EFU if considered clinically cured ('cure,' 'improved,' or 'sustained cure'). Days 3, 6, 10, & 28: only perform if clinically indicated. See Section 8.2.4.2 for details.

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	
Blood Specimen for Culture and Susceptibility[e]	X	X	As clinically indicated, or if Screening or Day 1 blood culture was positive, repeat as clinically indicated until negative on 2 consecutive cultures						On either Screening or Day 1: Collect 2 sets of blood cultures, from 2 separate venipunctures (or 1 venipuncture and 1 catheter) sites prior to first dose of IV study medication. A culture obtained within 48 hours prior to the randomization visit is acceptable, as long as the blood cultures collected meet the protocol requirement, ie, 2 sets of blood cultures, from 2 separate venipunctures (or 1 venipuncture and 1 catheter). See Section 8.2.4.3 for details.
Efficacy Evaluation									
Survival Assessment							X	X	
Clinical Response Assessment			X	X	X	X	X	X	See Section 8.2.2
Microbiological Assessment (By-Pathogen)						X	X		See Section 8.2.3

Trial Period	Screening	IV Study Treatment					Post-treatment		Notes
Visit Title	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3** (OTX_1)	**Visit 4** (OTX_2)	**Visit 5**[a] (OTX_3)	**Visit 6**[b] (EOT)	**Visit 7**[b] (EFU)	**Visit 8**[b] Day 28[c]	
Scheduled Day	≤2 days (48 hours) prior to randomization	Day 1	Day 3	Day 6	Day 10	Day 7 to Day 14	7 to 14 days post EOT	Day 28 Post-Randomization	
Scheduling Window	≤2 days (48 hours) prior to randomization	N/A	N/A	N/A	N/A	≤24 hours after EOT	+2 days	+3 days	

I/E = Inclusion/Exclusion; PaO_2 = partial pressure of oxygen in arterial blood; FiO_2 = Fraction of inspired oxygen

a OTX3 (Visit 5) is not performed if participants receive less than 10 days of IV study therapy.

b Register completion of EOT, EFU, and Day 28 visits in IRT.

c The Day 28 post-randomization visit may be combined with the EFU visit on a single day, as long as compliance with the visit windows is maintained for both visits. Specifically, if a participant receives 12 to 14 days of IV study therapy, the EFU visit may potentially be combined with the Day 28 post-randomization visit. For example, if 12 days of IV study therapy are provided, the EFU visit could be scheduled 16 days (14 days +2 day variance) following completion of IV study therapy, which would be 28 days (12 days of IV study therapy +16 days of follow-up) following randomization. It is required that for any case, the allowable visit window ranges are maintained.

d Obtain lower respiratory tract sample for Gram stain, culture, and susceptibility testing from infection site **prior to** initiation of IV study therapy for all subjects. A previously obtained culture is acceptable if it was obtained within 2 days (48 hours) of the screening visit. Microscopic examination of Gram-stained smears must be performed prior to randomization to ensure the adequacy of the specimen. The subject must be excluded from participating in the trial if the Gram stain shows the presence of Gram-positive cocci **only**. All culture and susceptibility should be performed at the local microbiology laboratory per local standards; in addition, any suspected causative bacterial pathogen must be collected and available for submission to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local microbiology laboratory if possible future testing is needed. In addition, the available data from the Gram stain and culture specimen, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRF forms.

e Two sets of blood cultures, from 2 separate venipunctures (or 1 venipuncture and 1 catheter) sites must be collected in **all** subjects **prior to** initiation of IV study therapy. Subjects with positive blood cultures at screening should have follow-up blood cultures collected as clinically indicated until 2 consecutive cultures demonstrate no growth. Blood culture and susceptibility will be performed at the local microbiology laboratory. Per local standards; in addition, any suspected causative bacterial pathogen must be collected and available for submission to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local microbiology laboratory if possible future testing is needed. Relevant culture data, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRF forms.

f If blood samples for chemistry and hematology safety evaluations, and Chest X-ray were performed within 24 hours prior to the EOT Visit, additional blood samples for chemistry and hematology and Chest x-ray are not required at EOT.

2. Introduction

2.1 Study Rationale

This regional study (PN016) is the second pivotal HABP/VABP study, to allow sufficient enrollment of Chinese participants and support MK-7655A registration in China. Details regarding specific benefits and risks for participants participating in this study may be found in the accompanying MK-7655 Investigators Brochure (IB) and Informed Consent documents.

HABP and VABP are important problems in the care of critically ill hospitalized patients despite advances in antimicrobial therapy, improvements in supportive care and the use of a wide range of preventative measures. In patients with HABP, mortality rates are significant and range from 12% to 22% globally [Kollef, M. H., et al 2012] [Freire, A. T., et al 2010] [Rubinstein, E., et al 2011]. The risk of mortality increases approximately 2-fold in patients with VABP and can be even higher when the lung infection is caused by multidrug-resistant (MDR) bacteria [Safdar, N., et al 2005]. These infections are among the most frequently occurring infections in intensive care units (ICUs) and account for the majority of the antibacterial utilization within ICUs [Freire, A. T., et al 2010]. Appropriate antibiotic therapy significantly improves survival for patients with HABP or VABP. In these vulnerable patients, additional increases in morbidity and mortality can be attributed to the empiric use of antimicrobial therapy that is not active against causative pathogens [Hyle, E. P., et al 2005]. New, well-tolerated drugs with more definitive and rigorously tested dosing schemes showing proven activity against both susceptible and MDR bacteria without need for combination therapy are urgently needed, especially in patients with HABP or VABP. IMI/REL has the potential to fulfill a significant and growing unmet medical need by providing a next-generation β-lactam (BL)/BLI with which to combat severe gram-negative bacterial infections.

A recent Asia prospective surveillance study (7 countries or regions were included: Korea, China, Hong Kong, Taiwan, Philippines, Thailand, Malaysia, Singapore, Indonesia) also showed a similar result and the most common bacterial isolates from HABP and VABP cases in Asian countries were *Acinetobacter* spp., *P. aeruginosa*, *S. aureus*, and *K. pneumoniae*. Imipenem resistance rates of *Acinetobacter* and *P. aeruginosa* were 67.3% and 27.2%, respectively. Multidrug-resistant (MDR) rates were 82% and 42.8%, and extensively drug-resistant rates were 51.1% and 4.9%, respectively. The multidrug-resistant rate of *K. pneumoniae* was 44.7%. The rate of oxacillin resistance among *S. aureus* was 82.1%. The all-cause mortality rate was 38.9%. All-cause mortality and pneumonia-related mortality rates were higher in VABP patients than those in HABP patients (52.5% in non-ICU and 41.6% in ICU VABP patients vs 34.5% in non-ICU and 34.1% in ICU HABP patients). Among all the isolates, *Acinetobacter* spp. (48.8% and 35.1%), followed by *K. pneumoniae* (37.7% and 22.7%), *P. aeruginosa* (31% and 22.4%), and *S. aureus* (30.7% and 18.9%) contributed the highest all-cause and pneumonia-related mortality rates, respectively [Chung, D. R., et al 2011].

In China, HABP/VABP are the most common infections in hospital-acquired infections (HAI) with high mortality rates between 15.7%-66.7% [An-hua, W., et al 2014] [Ning, L., et al 2011] [Yuncai, Y., et al 2011]. Compared to that of HABP, the mortality for VABP is

around 2 times higher [Liu, Y. N., et al 2012]. Based on a China local survey, the most common pathogens for HABP/VABP are gram-negative bacteria, and the top 3 most common gram-negative pathogens are *Acinetobacter baumannii, P. aeruginosa* and *K. pneumoniae.* In HABP/VABP patients, the antibiotic resistance of gram-negative bacteria is the toughest problem in China clinical practice. ESBL-producing *E.coli* (55.3%) and *K. pneumoniae* (33.9%), KPC-producing gram negatives (10.8%), and MDR *P. aeruginosa* (1.5%) are the most difficult to treat in HABP/VABP. Of note, the *P. aeruginosa* resistance rate to imipenem was 27.1% and to meropenem was 25.1%, according to the CHINET 2013 survey [Fupin, H., et al 2014].

The purpose of this study is to evaluate the efficacy and safety of IMI/REL with the intention of demonstrating that IMI/REL is non-inferior to PIP/TAZ in the treatment of adult participants diagnosed with HABP or VABP. If non-inferiority is established, then superiority of IMI/REL compared to PIP/TAZ will be evaluated. Among 270 participants, there will be approximately 200 Chinese participants enrolled; this is the general requirement per China regulations.

The primary endpoint for this study, all-cause mortality through Day 28 post-randomization, was selected based upon the expected large antibacterial treatment effect on survival. In this study, clinical response and microbiological response will be the secondary endpoints in an effort to provide additional information with regard to the effect of IMI/REL versus PIP/TAZ in HABP/VABP participants.

2.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on IMI/REL.

2.2.1 Pharmaceutical and Therapeutic Background

Relebactam (REL, MK-7655) is a parenteral (IV), small-molecule β-lactamase inhibitor (BLI) which is being developed as a fixed-dose combination in a single vial with imipenem/cilastatin (referred to as IMI) for the treatment of infections caused by gram-negative bacteria. Throughout this document the fixed-dose combination (MK-7655A) of imipenem/cilastatin (IMI) + REL will be referred to as IMI/REL.

β-lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) are among the most frequently used antimicrobial agents in clinical practice. The unrelenting development of resistance to β-lactam antibiotics by the production of β-lactamases is the most important resistance mechanism among gram-negative bacteria and poses an ongoing threat to the clinical utility of all β-lactams. Therefore, there is an urgent need for new BLIs that can be combined with existing β-lactam antibiotics to protect against hydrolysis by 1 or more of the 4 classes (A, B, C and D) of β-lactamase enzymes.

IMI, a potent broad spectrum β-lactam antibacterial agent from the carbapenem class, has been used clinically for the treatment of serious infections since 1985, and has been used widely in China and other Asian countries for moderate to severe infections. The bactericidal activity of imipenem results from inhibition of cell wall synthesis. Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I, resulting in relatively low levels in the urine. Cilastatin sodium is an inhibitor of this enzyme and effectively prevents renal metabolism of imipenem so that, when given together, adequate

antibacterial levels of imipenem are achieved. Imipenem is active against a broad range of gram-positive and gram-negative organisms and is approved for use globally in a variety of infections, including lower respiratory tract infections, urinary tract infections (complicated and uncomplicated), intra-abdominal infections, gynecologic infections, bacterial septicemia, bone and joint infections, skin and skin structure infections, endocarditis, and polymicrobial infections. The approved indications of IMI may be slightly different among approved countries. In China, it has been approved for the treatment of intra-abdominal infections, lower respiratory tract infections, gynecologic infections, septicemia, urogenital tract infections, bone and joint infections, skin and skin structure infections and endocarditis.

REL represents a new generation of BLIs to combat evolving clinical resistance and to maintain the usefulness of the β-lactam class of antibiotics. REL is an inhibitor of Ambler class A and class C β-lactamases and is highly potent against AmpC, a common class C β-lactamase encountered in many bacteria, most predominantly *P. aeruginosa*. REL is also active against the class A β-lactamases, including the *K. pneumoniae* carbapenemase (KPC) present in some Enterobacteriaceae, including Klebsiella strains. REL has no activity against the class B metallo-β-lactamases (including NDM-1, IMP, or VIM-containing strains) or class D β-lactamases (including OXA-producing strains).

2.2.2 Preclinical and Clinical Studies

Pre-clinical Studies

Preclinical data, including *in vitro* microbiological studies with imipenem-resistant clinical isolates of *P. aeruginosa* and KPC-producing organisms, as well as *in vivo* infection models with imipenem-resistant *P. aeruginosa* and *K. pneumoniae*, suggest that REL, in combination with IMI, has the potential to fulfill a significant and growing medical need by providing a next-generation BLI to combat severe gram-negative bacterial infections. Preclinical toxicity studies in rats and monkeys have demonstrated that REL is generally well-tolerated. There was no evidence of adverse effects of REL as a single agent on cardiovascular, central nervous system, and respiratory function in well-characterized preclinical safety pharmacology models. Toxicity of REL in combination with IMI has been evaluated for up to 1 month in monkeys with no adverse effects noted at 1.3 times the targeted human exposure of 344.4 μM.hr. Evidence of renal toxicity was observed in preclinical studies when MK-7655 was administered alone at levels 8 times the target human exposure. A 1-month intravenous toxicity study in monkeys with MK-7655 showed renal toxicity at the highest dose tested (225 mg/kg/day) by drug Week 4, including an increase in kidney weight and histomorphologic changes in the renal tubular epithelium (very slight to slight granular cytoplasm and very slight degeneration) that was reversible. At the mid dose (75 mg/kg/day), very slight to slight granular cytoplasm was observed in the renal tubular epithelium in 1 of 6 animals; however, no clinically relevant findings associated with renal function have been identified in the Phase 1 studies or in the completed Phase 2 studies in humans.

Clinical Trials

Phase 1

As of 01-Jan-2018, REL has been evaluated in approximately 265 individuals, 232 of whom have received at least 1 dose of REL, across 7 completed Phase 1 studies (PN001, PN002, PN005, PN007, PN009, PN012, and PN019). Healthy young and elderly male and female adults as well as patients with varying degrees of renal insufficiency have been studied, including patients with end-stage renal disease (ESRD) on hemodialysis.

Unblinded safety data from the Phase 1 studies have demonstrated that single and multiple intravenous doses of REL have been generally safe and well tolerated throughout the dose ranges tested. In PN001, generally mild elevations in hepatic transaminases above the upper limit of normal range (ULN) have been observed in the multiple-dose treatment arms in which REL was co-administered with IMI. Elevations were also seen in participants receiving IMI alone. None of the liver transaminase elevations in these participants were associated with clinical findings. The elevations were not dose related and were reversible after discontinuation of dosing. Elevations have not been observed in participants administered single or multiple doses in PN002, PN005, or PN007.

The pharmacokinetics of REL, imipenem, and cilastatin were evaluated following single and multiple doses of REL in combination with 500 mg IMI, administered every 6 hours for 7 to 14 days in PN001 and PN002. Data from these studies demonstrated that REL exposures increase proportionally with dose, doses at 125 mg and above exceeding the identified REL PK target of $AUC_{0-\infty}$ ≥37.5 μM.hr. The pharmacokinetics of REL, imipenem, and cilastatin were also evaluated in renally impaired participants (PN005). Pharmacokinetic data from PN005 were consistent with expectations given that REL, imipenem and cilastatin are cleared almost entirely renally in healthy participants. The plasma clearance (CL_{plasma}), terminal half-life ($t_{1/2}$) and area under the concentration-time curve ($AUC_{0-\infty}$) all were significantly and similarly altered for each of these 3 analytes when comparing participants with renal impairment to their healthy matched participants. These data are consistent with the expected change in magnitude of glomerular filtration rate (GFR). In addition, in participants with ESRD, REL, imipenem and cilastatin were efficiently removed by hemodialysis. The pharmacokinetics of REL was also studied in healthy volunteers in an intrapulmonary lung penetration study (PN007). In PN007, the intrapulmonary pharmacokinetic profiles of REL and imipenem were assessed after administration of REL and IMI administered every 6 hours over 5 doses. Data in these participants showed comparable penetration of REL and imipenem into the epithelial lung fluid (ELF), with relative exposures ($AUC_{0-\infty}$ in ELF compared to plasma) based on mean profiles of 43% for REL and 42% for IMI.

The effect of REL on the QTc interval was assessed in PN009, which was a single-dose, double-blind (with respect to REL only), randomized, placebo and positive-controlled, 3-period, balanced crossover study under fasting conditions. The pharmacokinetics of REL was assessed to confirm that supratherapeutic levels were achieved. Because there were no changes in QTcP, a relationship between REL exposure and cardiodynamic assessments was not performed. A single 1150-mg dose of REL in PN009 achieved $AUC_{0-\infty}$ and a C_{eoi} that were ~4-fold higher than those observed following a single dose of 250 mg and similar to exposures after an identical dose in PN001.

The PK and safety of REL was assessed in Japanese participants in PN012, which was a randomized, placebo-controlled, double-blind, single- and multiple-rising-dose trial of REL + IMI in healthy Japanese male participants. The objectives of the study were to evaluate the safety, tolerability, and pharmacokinetics of REL and IMI. The study results indicated that the single-dose pharmacokinetics of REL, imipenem and cilastatin appeared to be similar between Japanese (PN012) and non-Japanese (PN001) participants. Also, multiple-dose pharmacokinetics of MK-7655 at steady-state appears to be similar between Japanese (PN012) and non-Japanese (PN001) participants.

Phase 2

Two Phase 2 clinical trials of IMI + REL in participants with complicated urinary tract infections (cUTI, PN003) and complicated intra-abdominal infections (cIAI, PN004) have been completed. PN003 was a randomized, double-blind, multicenter, comparative study evaluating the safety, tolerability, and efficacy of IMI + REL versus IMI alone in adults ≥18 years of age with cUTI. A total of 302 participants with cUTI (including pyelonephritis) were randomized in a 1:1:1 ratio to 1 of 3 treatment groups (1) IMI (500 mg) + REL (250 mg), (2) IMI (500 mg) + REL (125 mg), or (3) IMI (500 mg) alone. The results show that at Discontinuation of IV Therapy (DCIV) in the ME population, the proportion of participants with a favorable microbiological response was 95.5 % (64/67) in the MK-7655 250 mg + IMI group, 98.6 % (70/71) in the MK-7655 125 mg + IMI group, and 98.7 % (74/75) in the Placebo + IMI group. Both of these comparisons indicate that treatment with either 250 mg or 125 mg of MK-7655 + IMI is at least as effective as IMI alone with respect to microbiological response rate at DCIV. The proportions of participants in the ME population achieving a favorable microbiological response at late follow-up (LFU) visit were 68.3% (43/63) in the MK-7655 250 mg + IMI group, 65.2% (45/69) in the MK-7655 125 mg + IMI group and 62.5% (45/72) in the Placebo + IMI group. The proportion was numerically higher for both active MK-7655 groups compared to that observed in the Placebo + IMI group. In general, the incidence rate of AEs observed in the active MK-7655 + IMI groups was similar to that observed in the Placebo + IMI group. Event of clinical interest (ECI) #1 was defined as a confirmed AST or ALT ≥5 X ULN. There were no statistically significant differences between either of the 2 MK-7655 groups versus Placebo + IMI group with respect to the percentage of participants meeting this definition (both $p>0.05$). ECI #2 was defined as an AST or ALT ≥3 X ULN, a total bilirubin ≥2 X ULN, and an alkaline phosphatase <2 X ULN. No participants experienced ECI #2. The results demonstrate that both active doses of MK-7655 + IMI are at least as effective as IMI alone with respect to microbiological response rate in the ME population at DCIV. Overall, both active doses of MK-7655 were generally well tolerated.

A Phase 2 comparator-controlled clinical trial of IMI + REL (PN004) has completed. PN004 was a randomized, double-blind, multicenter, comparative study evaluating the safety, tolerability, and efficacy of IMI + REL versus IMI alone in adults with cIAI. A total of 351 participants with cIAI were randomized in a 1:1:1 ratio to 1 of 3 treatment groups (1) IMI (500 mg) + REL (250 mg), (2) IMI (500 mg) + REL (125 mg), or (3) IMI (500 mg) alone in PN004. Data from PN004 demonstrated that both doses of IMI + REL were at least as effective as IMI alone with respect to clinical response rate at the discontinuation of IV study therapy (DCIV). Clinical response rates at DCIV were similar in participants who received 250 mg REL plus IMI (96.3%) or 125 mg REL plus IMI (98.8%), and both were noninferior

to IMI alone (95.2%). The treatment groups were also similar with respect to clinical response at early and late follow-up, and microbiological response at all visits. Results for the MITT population were consistent with those obtained for the ME population. Results at later time points (EFU and LFU) were consistent with those observed at the DCIV time point. Only 4.3% of participants in the MK-7655 250 mg + IMI group, 4.3% of participants in the MK-7655 125 mg + IMI group, and 3.5% of participants in the placebo + IMI group reported an AE of ALT increased; 4.3% of participants in the MK-7655 250 mg + IMI group, 4.3% of participants in the MK-7655 125 mg + IMI group, and 2.6% of participants in the placebo + IMI group reported an AE of AST increased; there were no statistically significant differences between either of the 2 MK-7655 + IMI groups versus the placebo + IMI group. Overall, both doses of REL (125 mg and 250 mg) were generally well tolerated.

Phase 3

A Phase 3 study to evaluate the safety and efficacy IMI/REL in the treatment of imipenem-resistant bacterial infection, including hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), cIAI, or cUTI (PN013) was initiated in 2015 and has been completed. PN013 was a double-blind, active-controlled, parallel-group, multi-site trial of IMI/REL compared with colistin (in the form of colistimethate sodium [CMS]) + IMI. Forty-seven participants were randomized in a 2:1 ratio to the 2 blinded, randomized arms of the study: (1) IMI/REL (500 mg/250 mg) and (2) CMS (150 mg CBA, ~360 mg CMS or ~4.5 million IU) + IMI (500 mg). In addition to the 47 randomized participants, 3 participants with documented imipenem- and colistin-resistant but IMI/REL-susceptible bacterial infections were enrolled into a third nonrandomized, unblinded/open-label treatment group (Treatment Group 3) to receive IMI/REL.

Results of efficacy demonstrated a 71.4% (15/21) favorable overall response for IMI/REL versus 70.0% (7/10) for CMS+IMI, supporting that IMI/REL is at least as effective as CMS+IMI for the treatment of imipenem-non-susceptible gram-negative bacterial infections. IMI/REL was well tolerated in this critically ill population, and has a more favorable renal safety profile than colistin.

A Phase 3 clinical trial of IMI/REL in HABP/VABP (PN014) was initiated in the beginning of 2016 and has been completed. PN014 was a multi-national (excluding China), multi-center, randomized, double-blind, active comparator-controlled clinical trial to study the safety, tolerability, and efficacy of IMI/REL (MK-7655A) versus PIP/TAZ in participants with HABP/VABP. A total of 537 participants were randomized in a 1:1 ratio to 1 of the 2 treatment groups: (1) IMI/REL (500 mg/250 mg) administered IV as a fixed-dose combination, or (2) PIP/TAZ (4000 mg/500 mg) administered IV as a fixed-dose combination. The study design of PN014 is similar to the current study (PN016), the second pivotal HABP/VABP study.

In adult participants with HABP (ventilated or nonventilated) or VABP in PN014, IMI/REL was non-inferior to PIP/TAZ, as assessed by the incidence rate of all-cause mortality through Day 28. As the non-inferiority criterion based on all-cause mortality was successfully met, noninferiority was also evaluated based on clinical response at the early follow-up (EFU) visit. IMI/REL was non-inferior to PIP/TAZ in participants with HABP/VABP, as assessed by the incidence rate of favorable clinical response at the EFU visit.

Additional details regarding the preclinical, Phase 1, Phase 2, and Phase 3 clinical studies completed to date are summarized in the MK-7655 IB.

2.2.3 Ongoing Clinical Studies

There are 2 ongoing intervention trials for IMI/REL, both of which are pediatric trials. PN020 is a Phase 1b, open label, single dose study to evaluate the pharmacokinetics, safety and tolerability of MK-7655A in pediatric subjects from birth to less than 18 years of age with confirmed or suspected gram-negative infections. Subjects are enrolled into 1 of 5 pediatric age cohorts:

• Cohort 1: Adolescents (age 12 to <18 years)

• Cohort 2: Older children (6 to <12 years)

• Cohort 3: Younger children (2 to <6 years)

• Cohort 4: Infants and toddlers (3 months to <2 years)

• Cohort 5: Neonates and young infants (birth to <3 months); are further divided into the following age sub-cohorts:

  o 4 weeks to <3 months of age

  o 1 to <4 weeks of age

  o <1 week of age

A single IV dose of IMI/REL is administered to subjects any time after initiating standard of care treatment for a confirmed or suspected gram-negative bacterial infection. Enrollment in this study has been completed, but the final summarized data are not yet available.

PN021 is a Phase 2/3 open label, randomized, active controlled clinical study to evaluate safety, tolerability, efficacy and pharmacokinetics of MK-7655A in pediatric participants with confirmed or suspected -gram-negative bacterial infections. Subjects are enrolled into 1 of 5 pediatric age cohorts:

• Cohort 1: Adolescents (age 12 to <18 years)

• Cohort 2: Older children (6 to <12 years)

• Cohort 3: Younger children (2 to <6 years)

• Cohort 4: Infants and toddlers (3 months to <2 years)

• Cohort 5: Neonates and young infants (birth to <3 months)

Subjects receive multiple doses of IV IMI/REL for a minimum of 5 days to a maximum of 14 days. The first subject was randomized in this study on 09-OCT-19.

2.2.4 Information on Other Study-related Therapy

2.2.4.1 Comparator Therapy

Participants in the comparator arm of this trial will receive intravenous (IV) infusions of piperacillin/tazobactam (PIP/TAZ).

PIP/TAZ is a combination product consisting of a penicillin-class antibacterial, piperacillin, and a β-lactamase inhibitor, tazobactam. It is indicated for the treatment of systemic and/or local bacterial infection caused by susceptible gram-negative and gram-positive bacterial isolates for conditions such as lower respiratory tract infections, urinary tract infections (complicated and uncomplicated), intra-abdominal infections, skin and skin structure infections, bacterial septicemia, gynecological infections, bacterial infection in patients with neutropenia combined with aminoglycosides antibiotics, bone and joint infections and polymicrobial infections in China [Chinese Package Insert 2016]. The approved indications of PIP/TAZ may be slightly different among other approved countries.

PIP/TAZ acts by inhibiting septum formation and cell wall synthesis of susceptible bacteria.

In the 2005 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) *Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia*, PIP/TAZ is a recommended agent for empiric therapy for HABP/VABP. In Asian countries, PIP/TAZ is also recommended for empiric therapy for HABP/VABP and is widely used. In China clinical practice, PIP/TAZ is one of the most commonly used drugs for HABP/VABP. In a China local guideline for HABP [Chinese Thoracic Society, Chinese Medical Association 2002], PIP/TAZ is recommended for severe HABP. In a China VABP guideline [Chinese Society of Critical Care Medicine, Chinese Medical Assoc 2013], PIP/TAZ is also recommended for empiric use, and first line use in VABP patients with *P. aeruginosa* and extended-spectrum beta-lactamase (ESBL)-producing isolates.

2.2.4.2 Co-administration of Open-label Therapy with Linezolid for MRSA

Beginning at randomization, all participants will receive initial empiric treatment with IV linezolid (600 mg q12h) for MRSA infection.

Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones. It is used for the treatment of infections caused by gram-positive bacteria. The *in vitro* spectrum of activity of linezolid also includes certain gram-negative bacteria and anaerobic bacteria. Linezolid is a bacterial protein synthesis inhibitor. Its mechanism of action is prevention of the formation of the ribosomal initiation complex thus affecting the translation process. Results from time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci.

Linezolid is indicated for the treatment of the following infections caused by susceptible gram-positive bacteria in most approved countries: nosocomial pneumonia; community-acquired pneumonia; complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; uncomplicated skin and skin structure infections; vancomycin-resistant *Enterococcus faecium* infections [Chinese Package Insert 2017].

Both linezolid or vancomycin are recommended for the treatment of MRSA infections when there is a proven or suspected infection due to MRSA, as per the IDSA/ATS guideline on the treatment of HABP/VABP and the IDSA guideline on treatment of MRSA infections. Of note, these guidelines recognize that linezolid might be preferred in certain situations, including (a) participants with evidence of renal insufficiency due to potential for vancomycin under-dosing in this patient population and the potential risk of nephrotoxicity

associated with vancomycin; and (b) institutions where vancomycin resistance (ie, MRSA isolates with vancomycin MIC ≥2 mcg/mL) is common [Kalil, A. C., et al 2016] [Liu, C., et al 2011].

Linezolid and vancomycin are also recommended for VABP patients with MRSA in the China VABP guideline [Chinese Society of Critical Care Medicine, Chinese Medical Assoc 2013], while in the HABP China guideline, vancomycin is recommended (linezolid was not available at that time in China clinical practice), which is similar to the guidelines in other Asian countries.

Linezolid was compared to vancomycin for the treatment of nosocomial pneumonia due to MRSA in a randomized double-blind trial. In this study, the efficacy responses were numerically higher with linezolid than vancomycin. Overall, 58% of linezolid-treated participants and 47% of vancomycin-treated participants had achieved clinical cure at end of study. Additionally, 83% of linezolid-treated participants and 70% of vancomycin-treated participants had achieved clinical cure at the end of treatment. The incidence of documented microbiological persistence was also lower in the linezolid group, with 17% of linezolid-treated participants and 46% of vancomycin-treated participants having a positive culture result for MRSA at the end of treatment. The incidence of all-cause mortality at Day 60 was similar between treatment groups. Although the overall incidence of adverse events was similar in the 2 treatment groups, nephrotoxicity occurred more commonly on vancomycin than linezolid (18% vs. 8%, respectively) [Wunderink, R. G., et al 2012].

2.3 Benefit/Risk Assessment

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

Participants enrolled in this trial are hospitalized patients with infections requiring treatment with IV therapy. If randomized to receive IMI/REL, participants will receive treatment, in part, with an agent, IMI, recommended and commonly used for the treatment of HABP/VABP, and in addition can potentially benefit from treatment with the investigational agent REL. The combination, IMI/REL, is specifically targeted for treatment of gram-negative imipenem-resistant infections. Participants randomized to the comparator arm will also receive a treatment regimen expected to be efficacious against HABP/VABP (see Section 4.2.2).

Although potentially more frequent than standard of care for some of the participants (ie, moderate infections, mainly in non-ventilated participants), the study procedures described in Section 1.3 – Schedule of Activities (SoA) are generally typical procedures performed for this hospitalized patient population. Additional burden may be incurred due to visits following release from the hospital. However, the procedures performed at these visits are generally not likely to lead to significant harm (eg, blood draws, urine collection, physical exam, vital signs). These procedures are necessary to support a robust evaluation of the safety and efficacy of the investigational drug.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and Informed Consent documents.

3. Objectives/Hypotheses and Endpoints

The following objectives and endpoints will be evaluated in adult participants diagnosed with HABP or VABP:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To determine the incidence rate of all-cause mortality through Day 28 post-randomization associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the modified intention-to-treat (MITT) population. Hypothesis (H1): IMI/REL is non-inferior to PIP/TAZ as measured by the incidence rate of all-cause mortality through Day 28 post-randomization in the MITT population. If non-inferiority is established, the following hypothesis will be tested: Hypothesis (H2): IMI/REL is superior to PIP/TAZ as measured by the incidence rate of all-cause mortality through Day 28 post-randomization in the MITT population.	• All-cause mortality
Secondary	
• Objective: To evaluate favorable clinical response (CR) rate associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the following visits and analysis populations: - At the early follow-up (EFU) visit in the MITT population - At the EFU visit in the clinically evaluable (CE) population - At the end of treatment (EOT) visit in the MITT population - At the EOT visit in the CE population	• Favorable CR at EFU requires "sustained cure" or "cure" (see Table 6) • Favorable CR at EOT requires "cure" or "improved" (see Table 5)

Objective/Hypothesis	Endpoint
• Objective: To evaluate favorable microbiological response (MR) rate associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the following visits and analysis populations: - At the EFU visit in the microbiologically evaluable (ME) population - At the EOT visit in the microbiologically modified intention-to-treat (mMITT) population - At the EOT visit in the ME population	• Favorable MR at EFU requires "eradication" or "presumed eradication" (see Table 9) • Favorable MR at EOT requires "eradication" or "presumed eradication" (see Table 8)
• Objective: To evaluate the safety and tolerability profile of IMI/REL compared with PIP/TAZ.	• Number of participants experiencing adverse events (AEs) • Number of participants discontinuing study drug due to adverse events
Tertiary/Exploratory	
• Objective: To determine the incidence rate of all-cause mortality associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the following visits and analysis populations: - Through Day 28 post-randomization in the mMITT population - At the EFU visit in the MITT population - At the EFU visit in the mMITT population	• All-cause mortality

Objective/Hypothesis	Endpoint
• Objective: To determine the incidence rate of all-cause mortality through Day 28 post-randomization associated with treatment with IMI/REL compared to treatment with PIP/TAZ based on pneumonia type (non-ventilated HABP, ventilated HABP/VABP) in the following analysis populations: - In the MITT population - In the mMITT population	• All-cause mortality
• Objective: To evaluate favorable clinical response rate associated with treatment with IMI/REL compared to treatment with PIP/TAZ in the following visits and analysis populations: - At Day 3 of IV study therapy (OTX1) in the MITT population and CE population -At Day 6 of IV study therapy (OTX2) in the MITT population and CE population - At Day 10 of IV study therapy (OTX3, if applicable) in the MITT population and CE population - At Day 28 post-randomization in the MITT population and CE population.	• Favorable CR at OTX1, OTX2, or OTX3 requires "improved"(see Table 4) • Favorable CR at Day 28 post-randomization requires "sustained cure" or "cure" (see Table 6)

4. Study Design

4.1 Overall Design

This is a randomized, active-controlled, parallel-group, multi-site, double-blind trial of imipenem/cilastatin/relebactam (also known as MK-7655A; hereafter referred to as IMI/REL) compared with piperacillin/tazobactam (PIP/TAZ) in participants with hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) to be conducted in conformance with Good Clinical Practices. Participants with HABP may either be ventilated (ventilated HABP) or non-ventilated (non-ventilated HABP).

Approximately 270 participants from around 10 countries (approximately 74% of total population [ie, approximately 200 participants] comes from China mainland) will be randomized in a 1:1 ratio to 1 of 2 treatment arms of the study: Treatment Group 1 (IMI/REL) or Treatment Group 2 (PIP/TAZ). Both treatments will be provided as fixed-dose combinations, administered intravenously (IV) every 6 hours. After a maximum 48-hour screening period, randomized participants in each treatment group will receive a minimum of 7 days to up to a maximum of 14 days of IV study therapy. Participants with evidence of concurrent bacteremia or with *P. aeruginosa* infection should receive 14 days of IV study therapy. While on IV study therapy, study visits will be performed on Day 1 (randomization), Day 3 (on-therapy visit #1, OTX1), Day 6 (on-therapy visit #2, OTX2), Day 10 (on-therapy visit #3, OTX3, if applicable) and at the end of therapy (EOT). Following the completion of IV study therapy, all participants will have a study visit 7 to 14 days following completion of therapy (at the early follow-up visit, EFU). In addition, a Day 28 (up to an additional 3 days) post-randomization visit will be performed in all participants (this visit may be performed on the same day as the EFU visit, depending on the duration of IV study therapy). All participants will remain in the study for a total of up to 33 days.

Since the study will enroll participants without confirmed microbiological (culture) evidence of the HABP/VABP pathogen from a lower respiratory tract specimen at study entry, the use of initial empiric treatment with open-label IV linezolid (600 mg every 12 hours [q12h]) for methicillin-resistant *S. aureus* (MRSA) infection is required. Participants with a confirmed MRSA lower respiratory tract culture should receive a minimum of 7 days of therapy. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA.

Randomization will be stratified based on pneumonia type (non-ventilated HABP vs ventilated HABP/VABP) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at baseline (<15 vs ≥15). A minimum of 25% of participants will have ventilated HABP or VABP.

Protocol amendment MK-7655A-016-02 extended the participants' age range from ≤75 years of age to ≤90 years of age due to the unmet medical need for treatment of HABP/VABP in the elderly population. In support of the age limit change, prior studies in the MK-7655A program enrolled all adults aged 18 years or older, and a comparable safety profile for IMI/REL was observed across all participants ≤90 years of age.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities (SoA), Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint in this study is all-cause mortality through Day 28 post-randomization in the MITT population. Given the severity of illness in hospitalized participants with HABP/VABP whom routinely require in-hospital treatment with IV antibiotics, evaluation of mortality is appropriate. A 1-month mortality endpoint has commonly been used for evaluation of efficacy of antibacterial therapy against HABP/VABP infections [Freire, A. T., et al 2010] [Chastre, J., et al 2008] [West, M., et al 2003] [U.S. Prescribing Information 2017]. Based on the results of recently conducted trials, approximately 15% of participants will die even though they receive antibacterial drug therapy for HABP/VABP [Chastre, J., et al 2008] [Joshi, M., et al 2006] [West, M., et al 2003] [Chastre, J., et al 2008]. The goal of this trial is to demonstrate that IMI/REL is non-inferior to piperacillin/tazobactam (PIP/TAZ) in participants with HABP/VABP, as measured by the incidence of all-cause mortality through Day 28 post-randomization. If non-inferiority is established, then superiority of IMI/REL compared to PIP/TAZ will be evaluated.

The secondary efficacy endpoints (including clinical response and microbiological response) are based on the Guidance of Antibacterial Development from NMPA.

4.2.1.2 Safety Endpoints

In support of the secondary objective to evaluate the safety and tolerability profile of IMI/REL, the safety and tolerability of IMI/REL (as well as the safety of the comparator, PIP/TAZ) will be assessed by clinical evaluation of adverse events and inspection of other study parameters including vital signs, physical examinations, and standard laboratory safety tests at time points specified in Section 1.3 - SoA. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

4.2.2 Rationale for the Use of Comparator

PIP/TAZ is one of several empiric regimens for HABP and VABP recommended by the IDSA and ATS in their current treatment guidelines. It is approved for use in nosocomial pneumonia in the United States, EU, and other countries. Significant clinical experience, from both clinical trials and post-marketing data, exists for the use of PIP/TAZ in the treatment of HABP and VABP. It is the optimal choice for use as a comparator for IMI/REL as both regimens are routinely administered at an every-6-hour interval.

The chosen dose for PIP/TAZ in this study is 4500 mg (4000 mg piperacillin/500 mg tazobactam), administered IV once every 6 hours. This represents the currently recommended dose in the current IDSA/ATS treatment guidelines [Kalil, A. C., et al 2016]

for nosocomial pneumonia. The chosen dose is routinely administered to participants in clinical practice for this indication.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

Based on data from *in vivo* animal models of imipenem-resistant gram-negative infections, the target pharmacokinetic (PK) parameter for REL has been defined as a plasma $AUC_{0\text{-}24hr}$ following 4-times daily dosing of 150 μM*hr (or an $AUC_{0\text{-}\infty} \geq 37.5$ μM*hr following single-dose administration). Extensive PK/PD *in vitro* and *in vivo* modeling work, together with multiple-dose safety data for REL from the Phase 1 program, supports doses of REL administered IV at or above 125 mg every 6 hours. However, preclinical microbiology data indicate that there are some highly resistant strains of *P. aeruginosa* that may require higher concentrations of REL. To this end, it is appropriate to target a safe dose of REL that exceeds the anticipated PK target for common pathogens in order to appropriately cover a broader range of resistant bacteria. This is particularly important in HABP/VABP infections as MDR gram-negative organisms are more common in these infections. REL doses that are associated with plasma exposures exceeding the PK target of REL for common pathogens, such as 250 mg administered IV once every 6 hours, would support this evaluation.

A dosing regimen of IMI/REL 500mg/250 mg every 6 hours was selected for PN016 based on results from Phase 1 and Phase 2 trials. There were 7 Asian males enrolled in PN001; analysis showed that the PK parameters and safety profile of these Asian participants are similar to non-Asian participants in PN001. Also, preliminary data from a Japanese PK study (PN012) show that the pharmacokinetic profiles of REL, imipenem and cilastatin in healthy Japanese participants are similar with historical data obtained from non-Japanese in PN001.

Per the IDSA/ATS treatment guidelines for nosocomial pneumonia, a recommended IMI dose for HABP/VABP is 500 mg every 6 hours [Kalil, A. C., et al 2016]. The recommended dose is well accepted in most countries.

Based on the China local label for TIENAM® (imipenem/cilastatin), the recommended dose for severe infection is 2 to 4g of imipenem per day. In China, in clinical practice, 0.5 g (0.5 g imipenem/0.5 g cilastatin) every 6 hours is commonly used.

In order to assess drug penetration at the site of action (pulmonary penetration), an open-label study was conducted to evaluate the PK of REL and imipenem in the pulmonary epithelial lining fluid (ELF) and alveolar cells (AC) after administration of multiple doses of REL and IMI in 16 healthy young male or female participants. The intrapulmonary pharmacokinetic profiles of REL and imipenem were assessed after participants received multiple administrations of REL (250 mg) and IMI (500 mg) IV every 6 hours (q6h) over 5 doses. Penetration of both REL and imipenem into the ELF was similar, with relative exposures ($AUC_{0\text{-}\infty}$ in ELF compared to plasma) based on mean profiles of 43% for REL and 42% for imipenem. Thus, given the PK target based on plasma PK was exceeded at the 125 mg dose, this target is also projected to be met in the ELF at the selected 250 mg clinical dose, accounting for differences in ELF versus plasma exposure.

Both 125-mg and 250-mg doses of REL have been evaluated in the Phase 2 clinical studies (PN003 and PN004). In order to inform the choice of dose for the current proposed study, results of an interim analysis of combined safety data from PN003 and PN004 were reviewed by a standing internal Data Management Committee (siDMC). The interim analysis included an evaluation of the safety and tolerability of the 250-mg dose of REL given in combination with IMI in comparison to the control regimen (IMI alone) and in comparison to the 125-mg dose of REL + IMI. The analysis was performed after 50% of planned participants across PN003 and PN004 (N=331) were followed through the early follow-up visit (5 to 9 days following completion of study therapy). The data from the interim analysis supported the use of a 250-mg dose of REL with IMI. The safety profile of the 250-mg dose is further supported by unblinded data from PN004 which showed that the safety and tolerability profile of the 250-mg dose was similar to the 125-mg dose of REL as well as to IMI alone (See Section 2.2.2 and the MK-7655 IB for further details). The 250-mg dose was selected for this study to achieve exposures above the PK target for common pathogens that may be required for the treatment of highly resistant organisms.

The total daily dose in PN016 is adjusted based on renal function. Relebactam, imipenem, and cilastatin are primarily renally excreted. In a Phase 1 renal insufficiency trial (PN005), changes in renal clearance and exposures with changing renal function were similar for both IMI and REL, supporting their coadministration across all the spectrum of renally impaired population, with dose adjustments made in the same proportion for both IMI and REL. IMI and REL will be provided together in a single vial as a fixed-dose combination product in this study. Dose adjustment is required in participants with renal impairment. Depending on the individual participant's renal function (as determined by actual or estimated creatinine clearance), the total daily dose of IMI/REL may be adjusted. Unlike the Phase 2 trials (PN003 and PN004) but similar to the other Phase 3 trials (PN013 and PN014), the total daily dose in this study (PN016) is not adjusted based on weight. Population PK-based simulations were conducted to evaluate the impact of removal of weight-based adjustments for IMI, and the results were supportive of dose adjustments based solely on renal function. This approach is consistent with the current TIENAM® and PRIMAXIN® (imipenem/cilastatin) labels (updated in January 2016 and December 2016, respectively), as well as with general clinical practice and other recent clinical trials using IMI as a comparator. For example, clinical trials for HABP/VABP published since 2006 have administered IMI at standard dosages without an adjustment for weight. Efficacy rates in these trials have ranged from ~60% to 80% without significant toxicity [Kollef, M. H., et al 2012] [Ramirez, J., et al 2013] [Joshi, M., et al 2006] [Schmitt, D. V., et al 2006]. The few published clinical trials in which IMI dosage was adjusted for weight describe similar efficacy and safety [Freire, A. T., et al 2010] [Chastre, J., et al 2008]. Furthermore, weight is already a component of calculated creatinine clearance, used for determination of renal function and need for dose adjustment, thus raising the theoretical concern of under-dosing in participants with low body weight. Population PK-based simulations were conducted to evaluate the impact of removal of weight-based adjustments for IMI. Results of these simulations indicate that in individuals of lower weight, exposures of IMI/REL are significantly lower than those in higher weight ranges when doses are adjusted based on weight, and are supportive of dose adjustments based solely on renal function, as has been described above in clinical practice. Specifically, simulation results indicate that in

participants with normal renal function, the dose of 250-mg REL and 500-mg IMI given every 6 hours IV is appropriate. For participants with mild renal insufficiency, the dose should be reduced to 200-mg REL and 400-mg IMI given every 6 hours IV; for moderate renal insufficiency, 150-mg REL and 300-mg IMI given every 6 hours IV; and for severe renal insufficiency, 100-mg REL and 200-mg IMI given every 6 hours IV. These doses result in a consistent percentage of participants achieving the PK targets for both REL and IMI across the range of weights and creatinine clearances, and maintain exposures in a range demonstrated to be safe and well-tolerated for both IMI and REL. The specific dosing guidelines are included in Section 6.

4.3.2 Maximum Dose/Exposure for This Study

No dose modifications are planned for this study aside from dose reductions for renal insufficiency. Therefore, the maximum dose for this study will be 500 mg IMI/250 mg REL every 6 hours.

4.3.3 Rationale for Dose Interval and Study Design

Blinded IV study therapy will be administered for a minimum of 7 days up to a maximum of 14 days. Of note, participants with evidence of concurrent bacteremia or with *P. aeruginosa* infection should receive 14 days of treatment. The duration of therapy is consistent with practice guidelines and data from clinical trials.

Guidelines published by IDSA/ATS recommend treatment of HABP/VABP for as few as 7 days, provided that the patient has a good clinical response and the infection is not caused by *P. aeruginosa* [Kalil, A. C., et al 2016]. If deemed clinically appropriate, participants may receive up to 14 days of treatment for non-*Pseudomonas* infections. In the setting of *Pseudomonas* infection, a treatment duration of 14 days is predicated on data from several studies and meta-analyses which show a lesser incidence of persistence or recurrence with ~2 weeks versus ~1 week of therapy [Pugh, R., et al 2011] [Chastre, J., et al 2003]. Lower responses and higher mortality were also recently seen following treatment with a shorter course of therapy (1 week of doripenem) versus a longer course of therapy (10 days of IMI) in *P. aeruginosa* VABP cases [Kollef, M. H., et al 2012]. Treatment duration of 14 days for concurrent bacteremia is supported by current IDSA guidelines on the treatment of bloodstream infections and by standard clinical practice.

Based on the most recent China data, the new China VABP guideline (published in 2013) recommended shorter treatment durations for VABP overall (7 to 10 days for most of the cases, and a longer duration for immunocompromised patients or those with infections caused by MDR pathogens) compared with the recommended duration of therapy in an older HABP guideline published in 2002 (recommended 14 to 28 days for *E.coli*, *K. pneumonia, P. aeruginosa*).

Preclinical toxicology data for REL support administration of study therapy for up to 14 days in this study. Refer to the MK-7655 IB for more detailed information on preclinical toxicity studies of REL.

Open-label treatment with linezolid for a confirmed MRSA infection is recommended for a minimum of 7days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

5. Study Population

Male/Female participants with HABP/VABP between the ages of 18 and 90 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Require treatment with IV antibiotic therapy for HABP or VABP.

   NOTE: HABP is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms accompanied by presence of new or progressive infiltrate on chest radiograph *occurring in a participant after being hospitalized for more than 2 days (48 hours) or within 7 days after discharge from a hospital stay of at least 2 days (48 hours) duration (includes patients institutionalized in a skilled nursing or other long-term care facility)*. Of note, such participants may or may not require mechanical ventilation (ventilated HABP and non-ventilated HABP). VABP is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms accompanied by presence of new or progressive infiltrate on chest radiograph *occurring in a participant already receiving mechanical ventilation via an endotracheal tube for a minimum of 2 days (48 hours)*.

2. Fulfill the clinical and radiographic criteria described below within 48 hours prior to randomization, with onset of criteria occurring after more than 2 days (48 hours) of hospitalization or within 7 days after discharge from a hospital (for HABP) or at least 2 days (48 hours) after mechanical ventilation (for VABP):

   (a) Participant has at least one of the following clinical features:

   - New onset or worsening pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (eg, respiratory rate greater than 25 breaths per minute), expectorated sputum production, or requirement for mechanical ventilation
   - Hypoxemia (eg, a partial pressure of oxygen less than 60 millimeters of mercury while the participant is breathing room air at standard atmosphere pressure, as determined by arterial blood gas [ABG] or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen [PaO_2/FiO_2])
   - Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure
   - New onset of suctioned respiratory secretions

   AND

   (b) Participant has at least one of the following signs:

   - Documented fever (body temperature ≥38 degrees Celsius)
   - Hypothermia (body temperature ≤35 degrees Celsius)
   - Total peripheral white blood cell (WBC) count ≥10,000 cells/cubic millimeter (mm^3)
   - Leukopenia with total WBC ≤4,000 cells/mm^3
   - Greater than 15 percent immature neutrophils (bands) noted on peripheral blood smear

   AND

   (c) Participant has a chest radiograph showing the presence of a new or progressive infiltrate(s) suggestive of pneumonia.

3. Have an adequate baseline (at or within 2 days [48 hours] of screening) lower respiratory tract specimen obtained for Gram stain and culture.

   NOTE: Microscopic examination of Gram-stained smears must be performed prior to randomization to ensure the adequacy of the specimen. The low-power microscopic view of the Gram stain can be used to ascertain the quality of the respiratory specimen which helps to ensure that the respiratory specimen sent for culture does not represent oropharyngeal contamination. For specimens obtained by direct sampling of the lower respiratory tract (ie, sampling via bronchoalveolar lavage [BAL], mini BAL or protected brush specimen [PBS]), no predefined requirements are required to ascertain the quality of the respiratory specimen. However, for specimens not

obtained by direct sampling of the lower respiratory tract, such as those obtained by expectorated sputum, an adequate lower respiratory tract specimen is defined as having fewer than 10 squamous epithelial cells and greater than 25 neutrophils per low power field of Gram stains (white blood cell [WBC] counts of greater than 25 per low power field of Gram stains are acceptable in place of neutrophils). In addition, a high-power microscopic view of the Gram stain can be used to characterize the general type of bacteria causing the pneumonia. Specimens should be processed for culture according to recognized methods.

4. Have an infection known or thought to be, in the opinion of the investigator, caused by microorganisms susceptible to the IV study therapy.
5. Agree to allow any bacterial isolates obtained from protocol-required specimens related to the current infection to be provided to the Central Microbiology Reference Laboratory for study-related microbiological testing and long-term storage.

Demographics

6. Be between 18 to 90 (inclusive) years of age on the day of signing informed consent.

   NOTE: Adults are the intended study population for this protocol. Participants under the age of legal consent per a specific country's regulation should be excluded from participation in this study.

Male participants:

7. A male participant must agree to use contraception as detailed in Appendix 3 of this protocol from the time of providing informed consent through completion of the study and refrain from donating sperm during this period.

Female participants:

8. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 from the time of providing informed consent through completion of the study.

Informed Consent

9. The participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study.

   Note: As allowable by local regulations in Russia, the consent may be provided by a council of healthcare professionals for deciding on the possibility of inclusion of a patient in the clinical study or 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. In these circumstances, special care must be taken to ensure consent is consistent with all local laws and regulations and that patients (if/when they are able to provide consent for themselves) or their Legally Acceptable Representative (when available) are reconsented.

Additional Criteria

10. If a penicillin skin test is required by local clinical practice, the participant must have a negative skin test result for allergy to penicillin before receipt of first dose of IV study therapy.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has a baseline lower respiratory tract specimen Gram stain that shows the presence of gram-positive cocci **only**.
   - NOTE: For example, the following Gram stain patterns are acceptable:
     - only gram-negative organisms;
     - only gram-positive rods;
     - a mixture of gram-positive and gram-negative organisms;
     - a mixture of gram-positive cocci and gram-positive rods; or
     - no organisms seen on Gram stain
2. Has confirmed or suspected community-acquired bacterial pneumonia (CABP).
3. Has confirmed or suspected pneumonia caused by *Mycoplasma*, *Chlamydia*, or *Legionella*, or of viral, fungal, or parasitic etiology.
4. Has HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.
5. Has a carcinoid tumor or carcinoid syndrome.
6. Has active immunosuppression, defined as either receiving immunosuppressive medications or having a medical condition associated with immunodeficiency. Including but not limited to: (1) HIV (AIDS or CD4 <200 cell/mm^3), (2) Chemotherapy was performed within 6 weeks before randomization, (3) Immunosuppressive therapy, including maintenance glucocorticoid therapy (>40 mg/d prednisolone equivalent dose continuously administered for ≥7 days), (4) Neutrophilic granulocyte absolute count <500/mm^3.

   NOTE: Short-term treatment with systemic (IV or oral) steroids of <1 week duration (eg, treatment for an acute asthma exacerbation or acute skin condition) is allowed. Topical steroids for the treatment of skin conditions are also allowed.
7. The participant is expected to die during the 7- to 14-day treatment period, despite adequate antibiotic therapy.
8. Has a concurrent condition or infection that, in the investigator's judgment, would preclude evaluation of therapeutic response (eg, active tuberculosis, cystic fibrosis,

granulomatous disease, a disseminated fungal infection, invasive fungal pulmonary infection or endocarditis).

9. Has a history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to any of the following:

   - any β-lactams (including PIP/TAZ, carbapenems, cephalosporins, or other β-lactam agents)
   - β-lactamase inhibitors (eg, tazobactam, sulbactam, clavulanic acid, avibactam)

   NOTE: Participants with a history of mild rash to penicillins or other β-lactams may be enrolled and closely monitored, and this should be judged by investigators.

10. Has a history of a seizure disorder which has required ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years.
11. Is currently undergoing hemodialysis or peritoneal dialysis.
12. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the investigator, might confound the results of the study, interfere with the participant's participation for the full duration of the study, or pose additional risk in administering the study drugs to the participant.

    Note: patients with a history of allergy to linezolid or any oxazolidinones are required to be assessed under this exclusion criterion for severity of the allergy or potential hypersensitivity that would require exclusion from the study as judged by the investigator.

13. A WOCBP who has a positive urine pregnancy test at screening.

    If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required; a WOCBP who has a positive serum pregnancy test will be excluded.

Prior/Concomitant Therapy

14. Has received effective antibacterial drug therapy with known coverage of pathogens that cause HABP/VABP for a continuous duration of more than 48 hours during the previous 72 hours.

    Exceptions:

    - Participants who have failed prior antibiotic therapy for the current episode of HABP/VABP (ie, have persistent/worsening signs and/or symptoms of HABP/VABP at screening which are still present despite at least 48 hours on the prior antibacterial regimen), provided the prior respiratory or blood culture did not grow only *S. aureus* (methicillin-susceptible *S. aureus* [MSSA] or methicillin-resistant *S. aureus* [MRSA]).
    - Prior therapy with a non-absorbed antibiotic therapy used for gut decontamination (eg, low dose erythromycin or polymyxin) or to eradicate *Clostridium difficile* (oral vancomycin or fidaxomicin).

15. Is anticipated to be treated with any of the following medications during the course of study therapy:

    - valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening)
      NOTE: The exclusion of participants with valproic acid or divalproex sodium use in the 2 weeks prior to screening is only applicable to participants with a history of a seizure disorder. This criterion does not apply to participants who do not have a history of a seizure disorder and had previously received valproic acid or divalproex sodium for prophylactic purposes.
    - serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans) (during treatment with linezolid)
    - monoamine oxidase inhibitors (MAOIs) (during treatment with linezolid or has used MAOIs during the 2 weeks prior to screening)
    - meperidine (during treatment with linezolid)
    - buspirone (during treatment with linezolid)
    - dopaminergic agents (during treatment with linezolid)
    - concomitant systemic (IV or oral), inhaled, or intrapleural antibacterial agents in addition to those designated in the study treatment groups

      NOTE: As the study will enroll participants without confirmed microbiological (culture) evidence of the HABP/VABP pathogen on a lower respiratory tract specimen at study entry, the use of initial empiric treatment with open-label IV linezolid for MRSA infection is required. The recommended treatment duration for a confirmed MRSA infection is a minimum of 7 days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA.
    - concomitant systemic (IV or oral) antifungal or antiviral therapy for the index infection of HABP/VABP
    - traditional Chinese medicine or herbal medicine

Prior/Concurrent Clinical Study Experience

16. Is currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of the presentation or during the previous 90 days prior to screening or is anticipated to participate in such a clinical study during the course of this trial.
17. Has previously participated in this study at any time.

Diagnostic Assessments

18. Has an estimated or actual creatinine clearance of <15 mL/min at screening, based on the findings of local laboratory values. Creatinine clearance in mL/min may be calculated from serum creatinine concentration by the Cockcroft-Gault (C-G) equation:

    Creatinine clearance (Males) = $\frac{\text{(weight in kg) X (140 minus age)}}{\text{(72) X (creatinine in mg/dL)}}$

    Creatinine clearance (Females) = 0.85 X the value obtained using the formula above

19. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

There are no dietary or activity restrictions in this study, except as medically indicated.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events (AEs) or serious adverse events (SAEs) meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws from the study will not be replaced.

6. Treatments

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

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

The study treatments to be used in this study are outlined below in Table 1 Study Treatments.

Table 1 Study Treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Treatment Period	Use	IMP/ NIMP	Sourcing
Imipenem/ cilastatin/relebactam (IMI/REL)[a]	Powder for Constitution	MK-7655A (REL) 250 mg Imipenem 500mg Cilastatin 500mg	Imipenem /cilastatin 500 mg/ relebactam 250 mg[b] once every 6 hours	IV infusion	Visits 2 through 6 (7 to 14 days)[c,d]	Experimental	IMP	Provided centrally by the Sponsor
Piperacillin/ tazobactam (PIP/TAZ)[a]	Powder for Reconstitution	Piperacillin / Tazobactam 4g / 0.5g	4000 mg piperacillin/ 500 mg tazobactam[b] once every 6 hours	IV infusion	Visits 2 through 6 (minimum of 7 days, maximum of 14 days)[c,d]	Active comparator	IMP	Provided centrally by the Sponsor
Linezolid	Single-use, ready-to-use infusion bag	Linezolid 600 mg	600 mg every 12 hours	IV infusion	Visits 2 through 6 (minimum of 7 days if MRSA in lower respiratory tract, minimum of 14 days if MRSA in blood)[e]	Open-label therapy for MRSA	NIMP	Provided centrally by the Sponsor. May be sourced locally by trial site, subsidiary or designee with Sponsor approval

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Treatment Period	Use	IMP/ NIMP	Sourcing
Definition Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. [a] IMI/REL and PIP/TAZ are each provided as a fixed-dose combination (FDC) in a single vial. IMI/REL also includes 500 mg of cilastatin within the FDC. [b] Adjustments to dosage of IMI/REL or PIP/TAZ are required for participants with renal insufficiency (Please reference Table 2 and Table 3 in Section 6.2.1). [c] IV study therapy should be administered for a minimum of 168 hours (7 full days). Seven full days of therapy corresponds to 28 doses of IMI/REL (Treatment Group 1) and PIP/TAZ (Treatment Group 2) for every 6 hours (q6h). The total duration of IV study therapy should not exceed 14 days. [d] Participants with evidence of concurrent bacteremia or with *P. aeruginosa* should receive 14 days of IV study therapy. [e] Treatment duration for a confirmed MRSA infection is a minimum of 7 days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood samples do not demonstrate the presence of MRSA.								

All supplies indicated in Table 1 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study etc.).

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

Co-administration of Open-label Therapy with Linezolid

As the study may enroll participants without confirmed microbiological (culture) evidence of the HABP/VABP pathogen on a lower respiratory tract specimen at study entry, the use of initial empiric treatment with IV linezolid for MRSA infection is required. The recommended treatment duration for a confirmed MRSA infection is a minimum of 7 days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA. Linezolid will be given open-label in both treatment groups. Linezolid will be provided by the Sponsor, or locally by the trial site, subsidiary or designee if approved by the Sponsor.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

All IV study therapy will be reconstituted and administered according to the details provided in a separate Pharmacy Manual. An unblinded study staff (eg, pharmacist or qualified designee) at the study site will be responsible for preparing the IV study therapy for this study; this individual(s) must not be involved in any of the safety and efficacy evaluations of the study participants. Due to a visual difference in the appearance of study treatment solutions, the infusion bags will be covered with an opaque sleeve by the unblinded study staff (eg, pharmacist or qualified designee) to ensure that other study personnel and all participants remain blinded to clinical material assignments.

6.2.1.1 IMI/REL

The chosen dose for IMI/REL in participants with normal renal function is IMI/REL 500 mg/250 mg administered IV as an FDC once every 6 hours. **For participants with renal insufficiency or whose creatinine clearance changes during treatment with study therapy, the dose must be adjusted by the unblinded study staff (eg, pharmacist or qualified designee) based upon the degree of renal function impairment, as determined by the estimated or actual creatinine clearance.** Participants should be carefully monitored for renal function during IV treatment. Dose adjustments are included in Table 2.

Table 2 Administration Dosage of IMI/REL According to Renal Function

Creatinine Clearance (mL/min)	IMI/REL[a]
≥90	500/250 mg q6h
<90 to ≥60	400/200 mg q6h
<60 to ≥30	300/150 mg q6h
<30 to ≥15	200/100 mg q6h

[a] IMI/REL is provided as a single vial in a fixed-dose combination; therefore, the dose for each component will be adjusted equally during preparation. For example, a participant who has a creatinine clearance of 50 mL/min should receive a 300/150 mg q6h dose of IMI/REL according to the table.

6.2.1.2 PIP/TAZ

Participants in Treatment Group 2 will receive piperacillin/tazobactam (PIP/TAZ) as an FDC at a dosage of 4500 mg (4000 mg PIP/500 mg TAZ) every 6 hours, resulting in a daily total of 18.0 g (16.0 g PIP/2.0 g TAZ). **For participants with renal insufficiency or whose creatinine clearance changes during treatment with study therapy, the dose must be adjusted by the unblinded study staff (eg, pharmacist or qualified designee) based upon the degree of renal function impairment, as determined by the estimated or actual creatinine clearance.** Participants should be carefully monitored for renal function during IV treatment. The recommended daily doses for participants with renal impairment per the US product label are included in Table 3.

NOTE: Dose adjustment for renal impairment may be different in labels from different countries, eg in the China local label, the dose adjustment for renal impairment is a little bit different from that in the US label for nosocomial pneumonia patients, while the recommended total daily dose is identical. In China clinical practice, for renal impairment nosocomial pneumonia patients, the dose adjustment is either to decrease the dose frequency (China label) or to decrease the single dose (US label) [U.S. Prescribing Information 2017]. Based on the PK/PD profile description of PIP/TAZ in the China label, there are no significant differences in steady-state serum concentration between the 2 different dose regimens, ie, 2.25 g q6h and 4.5 g q6h. The $t_{1/2}$ in renal impairment patients will increase with the decrease of creatinine clearance. Also based on the compound profile, for PIP/TAZ, as with other beta-lactam antibiotics, T >MIC is the PK parameter associated with efficacy, which should still be achieved by the more frequent dosing interval with lower dose in the renal dose adjustment in the US label. As a result, to get the best product profile of PIP/TAZ and keep double-blind fashion, the dosing regimen in this study will be based on the US label in renal impairment nosocomial pneumonia patients.

Table 3 Recommended Dosage of PIP/TAZ in Participants According to Renal Function in the US Label

Creatinine clearance (mL/min)	PIP/TAZ dose[a] for nosocomial pneumonia patients recommended in US label[b]
>40	4500 mg (4000 mg PIP/500 mg TAZ) q6h
40 to ≥20	3375 mg (3000 mg PIP/375 mg TAZ) q6h
<20 to ≥15	2250 mg (2000 mg PIP/250 mg TAZ) q6h

[a] PIP/TAZ is provided as a single vial in a fixed-dose combination; therefore, the dose for each component will be adjusted equally during preparation. For example, a participant who has a creatinine clearance of 30 mL/min should receive a 3375 mg dose (3000 mg PIP/375 mg TAZ) according to the table.

[b] The dosing regimen will be based on the US label in renally impaired participants in this study.

6.2.2 Handling, Storage and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to IMI/REL (Treatment Group 1; N=135) or PIP/TAZ (Treatment Group 2; N= 135), respectively.

6.3.1.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Pneumonia type at baseline: non-ventilated HABP vs ventilated HABP/VABP
2. APACHE II score at baseline: <15 vs ≥15

Participants will be stratified by factors (as noted above) that are most likely to impact mortality outcomes. This will be done in order to balance treatment assignment within each stratum level and for increased efficiency of the statistical analysis.

In addition, the randomization will be controlled by quotas built into the IRT such that a minimum of 25% of randomized participants are in the ventilated HABP/VABP stratum.

6.3.2 Blinding

A double-blinding technique will be used. IMI/REL and PIP/TAZ will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site personnel. The participant and the investigator who is involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.

Study therapy supplies will be provided in an open-label fashion to the sites; hence an unblinded study staff (eg, pharmacist or qualified designee) at the study site will be responsible for preparing the IV study therapy for this study; this individual(s) must not be involved in any safety or efficacy evaluations of the study participants and needs to consult the most current renal function prior to dispensing each dose. Due to a visual difference in the appearance of study treatment solutions, the infusion bags will be covered with an opaque sleeve by the unblinded study staff (eg, pharmacist or qualified designee) to ensure that other study personnel and all participants remain blinded to clinical material assignments. The intravenous line (through which the infusion is administered) does not require opaque covering since the differences between the clinical materials are not visually distinguishable within the tubing. Once each infusion bag is properly prepared and masked with an opaque sleeve, the study therapy will be administered by qualified trial site personnel. The personnel involved in the administration of the study infusion treatment should be unaware of the treatment group assignments. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the participants are unaware of the group assignments.

As the study may enroll participants without confirmed microbiological (culture) evidence of the HABP/VABP pathogen on a lower respiratory tract specimen at study entry, participants

will receive treatment with open-label IV linezolid for MRSA infection beginning at randomization.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Treatment Compliance

Administration of trial medication will be performed by the blinded qualified trial site personnel.

Interruptions from the protocol specified treatment totaling ≥4 doses of IV study therapy during the first 7 days of therapy OR ≥4 doses of IV study therapy during Days 8 to 14 of therapy require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

The following concomitant medications/therapies are not permitted during IV study therapy:

1. Immunosuppressive agents (>40 mg/d prednisolone equivalent dose continuously administered for ≥7 days) (including chemotherapy

   NOTE: Short-term treatment with systemic (IV or oral) steroids of ≤7 days duration (eg, treatment for an acute asthma exacerbation or acute skin condition) is allowed. Topical steroids for the treatment of skin conditions are also allowed.
2. Valproic acid or divalproex sodium
3. Serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans)(during treatment with linezolid)
4. MAOIs (during treatment with linezolid and the 2 weeks prior to screening)
5. Meperidine (during treatment with linezolid)
6. Buspirone (during treatment with linezolid)
7. Dopaminergic agents (during treatment with linezolid)
8. Non-study systemic (IV or oral), inhaled, or intrapleural antibacterial treatments

   NOTE: As noted in Section 6.1, the use of initial empiric treatment with IV linezolid for MRSA infection is required. The recommended treatment duration for a confirmed

MRSA infection is a minimum of 7 days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA.

9. Systemic (IV or oral) antifungal or antiviral therapy for the index infection of HABP/VABP
10. Traditional Chinese Medicine or herbal medicine

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

6.6 Dose Modification

No dose modifications are planned for this study.

6.7 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified study site personnel will be used to blind supplies. Study treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

For studies using Controlled Substances, all Federal, State, Province, Country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the study is being conducted.

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

Participants may discontinue study treatment at any time for any reason or be discontinued from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary or through the emergency unblinding call center.
- Any of the following post-baseline elevations in liver transaminase levels:
  - In participants without baseline transaminase elevations:
    - ALT or AST ≥8 X ULN.
    - ALT or AST ≥3 X ULN, accompanied by total bilirubin >2 X ULN OR INR >1.5.
    - ALT or AST ≥3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (defined as body temperature ≥38.0°C), rash, and/or eosinophilia (>5%).
  - In participants with baseline transaminase elevations:
    - Further increase in transaminases to ≥8 X ULN **(with at least 50% increase from transaminase values collected at randomization [Day 1])** that is not anticipated from their underlying medical condition.
    - ALT or AST ≥3 X ULN (**with at least 50% increase from transaminase values collected at randomization [Day 1**]) and new onset of clinical signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (defined as body temperature ≥38.0°C), rash, and/or eosinophilia (>5%).

  - Clinically significant worsening of liver function associated with further transaminase elevations in a participant with abnormal transaminase levels already meeting the above criteria (ie, ≥8X ULN [**with at least 50% increase from transaminase values collected at randomization (Day 1)**]; ALT or AST ≥3 X ULN [**with at least 50% increase from transaminase values collected at randomization (Day 1)**] and new onset of clinical signs and symptoms listed) at baseline

- A post-baseline decline in estimated or actual creatinine clearance to a value of less than 15 mL/min.
- The participant requires initiation of hemodialysis or peritoneal dialysis.
- The participant has a confirmed positive serum pregnancy test.
- A physician investigator feels it is in best interest of the participant to discontinue for any reason, including, but not limited to, the need for alternative non-study antibacterial therapy. If while on study medication isolates are found to be resistant to piperacillin/tazobactam and the patient is not improving clinically, the patient should be discontinued from study medication in order to initiate appropriate alternative treatment. Consultation with the Sponsor physician is encouraged.

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

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

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

8. Study Assessments and Procedures

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 100 mL.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

investigator or qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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

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

As allowable by local regulations in Russia, the consent may be provided by a council of healthcare professionals for deciding on the possibility of inclusion of a patient in the clinical study or 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. In these circumstances, special care must be taken to ensure consent is consistent with all local laws and regulations and that patients (if/when they are able to provide consent for themselves) or their Legally Acceptable Representative (when available) are reconsented.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification

Card immediately after the participant provides documented informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. In addition to the evaluation of a participant's medical history in terms of study eligibility, all medical conditions present during the 12 months prior to study entry will be documented at the screening visit on the appropriate eCRF.

Any history of prior HABP or VABP episodes or conditions that may predispose a participant to the development of a pulmonary infection will also be documented on the appropriate eCRF, even if the prior episode or predisposing condition was diagnosed more than 12 months prior to study entry.

A full evaluation of the current primary diagnosis (HABP/VABP) will also be performed. The details of the HABP/VABP diagnosis will be documented separately on the appropriate eCRF(s).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 14 days before starting the trial.

Following a diagnosis of HABP/VABP and prior to the receipt of first dose of IV study therapy, participants may receive no more than 48 hours' worth (for example, >2 dose of a once-daily antibiotic, >4 doses of a twice-daily antibiotic) of active non-study antibiotic therapy in the 72 hours preceding the first dose of IV study therapy for treatment of the current index infection.

Participants who have failed prior antibiotic therapy for the current episode of HABP/VABP (ie, have persistent/worsening signs and symptoms at the time of screening) may be considered for enrollment provided the prior antibiotic was given for at least 48 hours before a diagnosis of clinical failure was made and the prior respiratory or blood culture did not grow only *S. aureus* (methicillin-susceptible *S. aureus* [MSSA] or methicillin-resistant *S. aureus* [MRSA]). For such participants, the baseline lower respiratory tract culture must be obtained while the participant is on the failing antibiotic therapy and before the participant receives the first dose of IV study therapy. Following collection of the baseline lower respiratory tract culture, only IV study therapy is permitted in these participants.

Participants receiving prior therapy with a non-absorbed antibiotic used for gut decontamination (ie, low dose erythromycin or polymyxin) or to eradicate *C. difficile* (oral

vancomycin or fidaxomicin) are eligible for enrollment, irrespective of duration of prior antibacterial therapy.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

Since the study will enroll participants without confirmed microbiological (culture) evidence of the HABP/VABP pathogen from a lower respiratory tract specimen at study entry, the use of initial empiric treatment with open-label IV linezolid (600 mg q12h) for MRSA infection is required. The recommended treatment duration for a confirmed MRSA infection is a minimum of 7 days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization or treatment allocation. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Rescreening of an individual participant for enrollment is not expected to occur commonly. However, any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening visit requirements (screening/rescreening) are provided in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Treatment Administration

Administration of study medication will be witnessed by the investigator and/or study staff.

The first dose of prescribed study therapy should be administered at the Day 1 visit (detailed procedures please refer to Section 1.3 – SoA). The unblinded study staff (eg, pharmacist or qualified designee) will contact the IRT for assignment of the study therapy to be

administered. Sites should not call the IRT for drug administration until the participant has met all entry criteria for the study and is ready to be randomized.

8.1.8.1 Timing of Dose Administration

The frequency of administration will be every 6 hours, regardless of dose adjustments for renal insufficiency (Table 2 and Table 3). Each infusion should be administered within 60 minutes of the scheduled dose.

IMI/REL (Treatment Group 1) and PIP/TAZ (Treatment Group 2) should be administered by the blinded investigator and/or blinded trial staff over 30 minutes ±10 minutes. The study therapy must NOT be administered simultaneously through the same infusion line/lumen with any other drugs (including IV non-study drugs). If another IV drug is required either prior to or after study drug and only 1 line/lumen is available, an appropriate volume of saline flush must be used between IV infusions.

IV study therapy should be administered for a minimum of 7 full days to up to a maximum of 14 days. Participants with evidence of concurrent bacteremia or with *P. aeruginosa* infection should receive 14 days of IV study therapy.

Additional details for preparation and administration of study drug are provided in a separate Pharmacy Manual.

8.1.8.1.1 Linezolid Therapy Administration

Since the study will enroll participants without confirmed microbiological (culture) evidence of the HABP/VABP pathogen from a lower respiratory tract specimen at study entry, the use of initial empiric treatment with open-label IV linezolid (600 mg q12h) for MRSA infection is required. The recommended treatment duration for a confirmed MRSA infection is a minimum of 7 days. Participants with MRSA bacteremia should receive 14 days of therapy. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract and/or blood sample do not demonstrate the presence of MRSA.

Each infusion should be administered within 60 minutes of the scheduled dose. Linezolid should be administered by the blinded investigator and/or blinded trial staff over 30 to 120 minutes ±10 minutes. Linezolid therapy can be administered concomitantly with IV study therapy, at those time points where there is administration overlap; however, the IV study therapy and IV linezolid therapy must NOT be administered simultaneously through the same infusion line/lumen.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Day 28 visit should be performed (at the time of withdrawal). Any AEs

which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

Overall survival status at Day 28 post-randomization or later will be assessed among all participants according to procedures outlined in the ICF.

8.1.10 Participant Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE PARTICIPANT UNLESS NECESSARY.

For emergency situations where the investigator or delegate needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or delegate should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or nonstudy treating physician must be discontinued from study drug, but should continue to be monitored in the study.

Additionally, the investigator must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible.

Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Survival Assessment

For each participant, survival status (ie, whether the participant is alive or dead) will be assessed at Day 28 post-randomization to support the primary endpoint of all-cause mortality at Day 28. Results of the assessment, including date and cause of death if relevant, will be recorded on the appropriate eCRF.

8.2.2 Clinical Response

Clinical signs and symptoms of infection (eg, cough, dyspnea, fever, etc.) will be assessed at visits specified in Section 1.3 - SoA in support of determination of a clinical response rating for each participant. A detailed list of disease-specific signs and symptoms in support of evaluation of the clinical response rating are included in Section 8.2.2.1, Table 7.

Based on comparison to baseline clinical signs and symptoms of the participant's infection, the investigator will determine and record the clinical response rating at each visit as described in Table 4 (for OTX1, OTX2, and OTX3 visits), Table 5 (for EOT visit), and Table 6 (for EFU and Day 28 post-randomization visits).

The clinical response rating determined by the investigator at each visit will be categorized as "favorable" or "unfavorable," as described in the footnote of each table describing clinical response.

Table 4 Definitions of the Clinical Response Rating at the OTX Visits (Day 3, Day 6 and Day 10 of IV Study Therapy)

Clinical Response[a]	Response Definition
Improved	The majority of pre-therapy signs and symptoms[b] of the index infection have improved or resolved (or returned to "pre-infection status")
Persistence	Little apparent response to IV study therapy in pre-study signs and symptoms[b] of the index infection(s): persistence of the majority of or all pre-therapy signs and symptoms.
Progression	Worsening of response while on IV study therapy in pre-study signs and symptoms[b] of the index infection(s): progression of the majority of or all pre-therapy signs and symptoms.
Indeterminate	Study data are not available for evaluation of clinical response for any reasons at the OTX1, OTX2 or OTX3 visit, including: a) Complication related to underlying medical condition; **OR** b) Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation for any reason; **OR** c) Extenuating circumstances (eg, a major protocol violation) preclude classification as "improved," "persistence," or "progression;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.
[a] A favorable clinical response at OTX1, OTX2, or OTX3 requires an assessment of "improved". [b] Refer to Inclusion Criterion #2 for a description of relevant clinical signs and symptoms.	

Table 5 Definitions of the Clinical Response Rating at the EOT Visit

Clinical Response[a]	Response Definition
Cure	All pre-therapy signs and symptoms[b] of the index infection have resolved (or returned to "pre-infection status") **AND** no additional antibiotic therapy is required for the index infection.
Improved	The majority of pre-therapy signs and symptoms[b] of the index infection have improved or resolved (or returned to "pre-infection status") **AND** no additional antibiotic therapy is required.
Failure	No apparent response to IV study therapy in pre-study signs and symptoms[b] of the index infection: persistence or progression of the majority of or all pre-therapy signs and symptoms.
Indeterminate	Study data are not available for evaluation of clinical response for any reasons at the EOT visit, including: a) Complication related to underlying medical condition; **OR** b) Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation for any reason; **OR** c) Extenuating circumstances (eg, a protocol violation) preclude classification as "cure," "improved," or "failure;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

[a] A favorable clinical response at EOT requires an assessment of “cure” or “improved”.
[b] Refer to Inclusion Criterion #2 for a description of relevant clinical signs and symptoms.

Table 6 Definitions of the Clinical Response Rating at the EFU Visit and Day 28 Post-Randomization Visit

Clinical Response[a,]	Response Definition
Sustained Cure	All pre-therapy signs and symptoms[b] of the index infection have resolved (or returned to "pre-infection status") with no evidence of resurgence **AND** no additional antibiotic therapy was required for the index infection.
Cure	All pre-therapy signs and symptoms[b] of the index infection have resolved (or returned to "pre-infection status") **AND** no additional antibiotic therapy is required for the index infection.
Failure	No apparent or insufficient response to IV study therapy in pre-study signs and symptoms of the index infection: persistence, progression, or improvement (without full resolution) of all pre-therapy signs and symptoms[b]
Relapse	Participants with a favorable clinical response (cure or improved) at the EOT visit have worsening signs and symptoms[b] of the index infection by the EFU or Day 28 post-randomization visit.
Indeterminate	Study data are not available for evaluation of efficacy for any reasons, including: a) Complication related to underlying medical condition; **OR** b) Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical response; **OR** c) Extenuating circumstances (eg, a major protocol violation) preclude classification as "sustained cure," "failure," or "relapse;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

[a] A favorable clinical response at EFU or Day 28 post-randomization requires an assessment of “cure” or “sustained cure.” To be considered “sustained cure,” the clinical response for the prior visit (EOT or EFU) must have been considered “cure.”
[b] Refer to Inclusion Criterion #2 for a description of clinical signs and symptoms.

8.2.2.1 Clinical Signs and Symptoms

A detailed diagnosis as well as relevant clinical information associated with the HABP/VABP diagnosis including clinical signs and symptoms, radiographic and laboratory characteristics related to the participant's infection will be reviewed and documented on the appropriate eCRFs at time points specified in Section 1.3 – SoA.

In particular, clinical signs and symptoms specific to the index infection for this study are based predominantly on criteria outlined in Inclusion Criterion #2 (Section 5.1) and are summarized in Table 7 below. Presence or absence of these symptoms will be recorded daily while on IV study therapy and at visits as specified in Section 1.3 – SoA. Intensity of signs and symptoms will also be graded by the investigator as mild, moderate, or severe (see Appendix 4). Collection at randomization (Visit 2) should be performed **prior to** initiation of IV study therapy.

Table 7 Infection-Site Clinical Signs and Symptoms

Infection Site	Clinical Signs and Symptoms
HABP/VABP	• Cough • Dyspnea • Tachypnea (eg, respiratory rate greater than 25 breaths per minute) • Expectorated sputum production • Requirement for mechanical ventilation • New onset of suctioned respiratory secretions • Chills/rigors • Chest pain or chest tenderness • Fever (body temperature ≥38 degrees Celsius) • Hypothermia (body temperature ≤35 degrees Celsius)

8.2.3 Microbiological Response

Microbiological response will be evaluated separately for each lower respiratory tract pathogen isolated in the baseline culture (ie, by-pathogen). The by-pathogen response rating determined by the investigator will be assessed based on local laboratory results.

A by-pathogen microbiological response rating will be determined by the investigator at EOT, and EFU visits based on the results of lower respiratory tract cultures collected for participants at each of these visits relative to the pathogen(s) isolated at baseline/admission as described in Table 8 (for EOT visit) and Table 9 (for EFU visit). As described in Section 8.2.4, lower respiratory tract cultures would preferentially include samples collected from a tracheostomy or endotracheal aspirates, or bronchoscopy specimens. Expectorated or induced sputum samples are also accepted provided the sample does not represent oropharyngeal contamination (ie, sample contains fewer than 10 squamous epithelial cells on low power microscopy review of the Gram stain).

The overall microbiological response (ie, overall microbiological response for the participant based on the response of all pathogens present in the baseline lower respiratory tract culture) will be assessed as "favorable" or "unfavorable," as described in the tables describing microbiological response. For participants from whom only 1 pathogen is isolated in the baseline lower respiratory tract culture, the overall microbiological response assessment will be based on the microbiological response rating for that pathogen. For randomized participants from whom more than 1 baseline pathogen is isolated in the baseline lower respiratory tract culture, the overall microbiological response outcome will be based on microbiological culture results for all pathogens (ie, a "favorable" overall microbiological response requires eradication of all baseline pathogens).

Antibiotic susceptibility results from the Central Microbiology Lab, as well as microbiological response, will be summarized by pathogen. The by-pathogen microbiological response rating determined by the investigator at each EOT and EFU visits will be utilized to categorize the overall microbiological response.

Table 8 Definitions of the By-Pathogen Microbiological Response Rating at the EOT Visit

Microbiological Response[a,b]	**Response Definition**
Eradication	A lower respiratory tract culture taken at the EOT visit[c] shows eradication of the pathogen found at study entry.
Presumed Eradication	No specimen taken because subject is deemed clinically cured or improved.
Persistence[d]	A lower respiratory tract culture taken at the EOT visit[c] grows the pathogen found at study entry.
Superinfection	A lower respiratory tract culture grows a pathogen other than a baseline pathogen at the EOT visit.[c]
Indeterminate	a) Follow-up culture is not available at the EOT visit[c] due to participant death or withdrawal from study; **OR** b) Available microbiological data are incomplete; **OR** c) Extenuating circumstances (eg, a major protocol violation) preclude microbiological assessment; **OR** d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating must be completed separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit that was not identified at baseline, the microbiological response rating should be recorded as "superinfection."

[b] A favorable by-pathogen microbiological response at EOT requires "eradication" or "presumed eradication" of the baseline pathogen.

[c] If a culture is not available at EOT, an assessment at this visit can be made from the last available culture which was collected after at least 72 hours of IV study therapy.

[d] If a participant is discontinued from IV study therapy due to clinical failure (ie, unfavorable clinical response), but persistence of the baseline pathogen is not confirmed by culture results or no culture is obtained at the time of clinical failure, the baseline pathogen will be presumed to have persisted.

Table 9 Definitions of the By-Pathogen Microbiological Response Rating at the EFU Visit

Microbiological Response[a,b]	Response Definition
Eradication	A lower respiratory tract culture taken at the EFU[c] visit shows eradication of the pathogen found at study entry.
Presumed Eradication	No specimen taken because subject is deemed clinically cured or improved.
Persistence	A lower respiratory tract culture taken at the EFU visit grows the pathogen found at study entry.
New Infection	A lower respiratory tract culture grows a pathogen other than a baseline pathogen at the EFU visit.[d]
Recurrence	A lower respiratory tract specimen grows the baseline pathogen taken at EFU visit after documented eradication.
Indeterminate	a) Follow-up culture is not available at the EFU visit due to participant death or withdrawal from study; **OR** b) Available microbiological data are incomplete; **OR** c) Extenuating circumstances (eg, a major protocol violation) preclude microbiological assessment; **OR** d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating must be completed separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit that was not identified at baseline, the microbiological response rating should be recorded as "new infection."

[b] A favorable by-pathogen microbiological response at EFU visit requires "eradication" or "presumed eradication" of the baseline pathogen.

[c] If a culture is not available at EFU, an assessment at this visit can be made based on the culture collected at EOT as long as it was collected at least 24 hours after the end of IV therapy and before the EFU visit and provided the participant had fully resolved clinical symptoms/signs of the index infection at the EFU visit.

[d] If a culture is not available at EFU, an assessment can be made based on a culture collected at the EOT visit as long as it was collected at least 24 hours after the end of IV therapy and before the EFU visit.

8.2.4 Culture and Susceptibility Testing

8.2.4.1 Lower Respiratory Tract Sample Collected at Baseline

A lower respiratory tract sample will be obtained at baseline for Gram stain, culture and susceptibility testing from infection site **prior to** initiation of IV study therapy for all participants. A previously obtained culture is acceptable if it was obtained within 2 days (48 hours) of the screening visit. Culture and susceptibility should be performed at the local microbiology laboratory.

Microscopic examination of Gram-stained smears must be performed prior to randomization to ensure the adequacy of the specimen and to exclude participants with gram-positive cocci only detected. For specimens obtained by direct sampling of the lower respiratory tract (ie, sampling via BAL, mini BAL or PBS), no predefined requirements are required to ascertain the quality of the respiratory specimen. However, for specimens not obtained by direct sampling of the lower respiratory tract, such as those obtained by expectorated sputum, the

low-power microscopic view of the Gram stain can be used to ascertain the quality of the respiratory specimen which helps to ensure that the respiratory specimen sent for culture does not represent oropharyngeal contamination (eg, fewer than 10 squamous epithelial cells and greater than 25 neutrophils per low power field of Gram stains is an example of an adequate expectorated/suctioned sputum specimen; white blood cell [WBC] counts of greater than 25 per low power field of Gram stains are acceptable in place neutrophils). In addition, a high-power microscopic view of the Gram stain can be used to characterize the general type of bacteria causing the pneumonia.

Specimens should be processed for Gram stain and culture at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures. **In addition to local laboratory testing, a pure isolate of any suspected causative bacterial pathogen(s) must be submitted to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local laboratory for possible future testing.**

The available data from the Gram stain and culture specimen, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRF forms.

Additional details regarding bacterial specimen collection, processing, handling, and shipment will be provided by the Sponsor in a separate microbiology laboratory manual.

8.2.4.2 Other Lower Respiratory Tract Samples Following Randomization

Culture from the lower respiratory tract site, including susceptibility testing of any identified pathogens on culture, should also be performed at the EOT and EFU visits as outlined in Section 1.3 – SoA; cultures are not required at EOT or EFU if subjects is considered clinically cured (‘cure,’ ‘improved’ or ‘sustained cure).’ Lower respiratory tract cultures would preferentially include samples collected from a tracheostomy or endotracheal aspirates, or bronchoscopy specimens. Expectorated or induced sputum samples are also accepted provided the sample does not represent oropharyngeal contamination (ie, sample contains fewer than 10 squamous epithelial cells).

In addition, at other times during the study, lower respiratory tract samples may also be collected if there is clinical or laboratory evidence of persistence or progression of the infectious process (including persistent fever, elevated white blood cell count, or significant changes in the participant’s clinical condition). Of note, specimens should also be collected at any time of surgical or drainage procedure (if required).

All culture and susceptibility should be performed at the local microbiology laboratory following the same standard procedures as used for the baseline lower respiratory tract sample. **In addition, a pure isolate of any suspected causative bacterial pathogen(s) must be submitted to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local laboratory for possible future testing, if needed.**

The available data from the Gram stain and culture specimen, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRF forms.

Additional details regarding bacterial specimen collection, processing, handling, and shipment will be provided by the Sponsor in a separate microbiology laboratory manual.

8.2.4.3 Blood Cultures

On either Screening or Day 1, two sets of blood cultures, from 2 separate venipunctures (or 1 venipuncture and 1 catheter) sites must be collected in all participants prior to initiation of IV study therapy. A culture obtained within 48 hours prior to the randomization visit is acceptable, as long as the blood cultures collected meet the protocol requirement, ie, 2 sets of blood cultures, from 2 separate venipunctures (or 1 venipuncture and 1 catheter). Participants with positive blood cultures at screening should have follow-up blood cultures collected as clinically indicated until 2 consecutive cultures demonstrate no growth. Follow-up blood cultures in participants with no evidence of bacteremia (ie, positive blood cultures) at study entry should also be performed, at the investigator discretion, as clinically indicated.

Blood culture and susceptibility will be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures. In addition, any suspected causative bacterial pathogen must be collected and available for submission to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local microbiology laboratory if possible future testing is needed.

Relevant culture data, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRF forms.

8.2.4.4 Other Relevant Culture Samples

During the study, other pulmonary samples, including pleural fluid or direct lung samples, or samples from other distant sites of infection may also be collected if there is clinical or laboratory evidence of persistence or progression of the infectious process (including persistent fever, elevated white blood cell count, or significant changes in the participant's clinical condition). In general, for any pulmonary procedure, specimens should also be collected at any time of surgical or drainage procedure (if required).

In these situations, relevant culture data, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRFs.

8.2.5 Chest X-Ray

A baseline chest x-ray should be performed in all participants prior to initiation of IV study therapy on the Day 1 (Randomization) visit and at other visits as specified in Section 1.3 - SoA. A baseline chest x-ray at randomization is not required if a prior chest x-ray was performed in association with the current infection within 2 days (48 hours) of

randomization. CT scans obtained within 48 hours of randomization can be used in place of the baseline chest x-ray if a scout view or similar view can be produced. A CT scan obtained at the Screening Visit is acceptable for entry if local clinical practice requires a CT scan for HABP/VABP diagnosis. Post-baseline, chest x-rays must be performed at subsequent visits, as indicated in the SoA. Scout view data from CT scans performed for non-study purposes can be used in place of chest x-ray assessments post-baseline.

Chest x-ray results at baseline (prior to initiation of IV study therapy) and at indicated follow-up visits including a description, location, and extent of infiltrates or consolidation must be documented on the appropriate eCRF(s). The presence of a pleural effusion and other abnormalities associated with disease-related complications should also be noted on the appropriate eCRF(s).

8.2.6 PaO_2/FiO_2 or O_2 Saturation

PaO_2 and FiO_2 should be measured by arterial blood gas (ABG) determination and oxygen saturation should be determined by pulse oximetry or by ABG.

For ventilated participants who have an existing arterial line in place, PaO_2 and FiO_2 should be measured by ABG on Day 1, Day 3 (OTX1), Day 6 (OTX2), and Day 10 (OTX3, if applicable) of IV study therapy, and at the EOT, EFU, and Day 28 post-randomization visits. On all other days while on IV study therapy, oxygen saturation via pulse oximetry should be measured daily.

For non-ventilated participants or ventilated participants who do not have an existing arterial line in place, oxygen saturation via pulse oximetry should be measured daily while on IV study therapy and at the EOT, EFU, and Day 28 post-randomization visits.

All measured values for PaO_2, FiO_2, or oxygen saturation should be documented on the appropriate eCRFs.

8.2.7 Infection Source Control Review

Information related to infection source control must be collected for all participants at the visits specified in Section 1.3 – SoA.

Source control includes the following: (a) details regarding intubation, extubation, reintubation, or replacement of the endotracheal tube, (b) details regarding lung procedures/surgeries performed to drain/remove a loculated pulmonary infection, or (c) details regarding a thoracentesis procedure to drain any accompanying pleural fluid. Relevant information regarding infection source control should be documented on the appropriate eCRF.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of

the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Section 8.

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

8.3.1 Physical Examinations

All physical examinations must be performed by the principal investigator or sub-investigator (physician, physician assistant or nurse practitioner).

A full physical examination, performed at randomization, includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. If a physical examination was performed within 72 hours prior to screening, those results can be recorded and a repeat physical examination is not required. Any abnormal or clinically significant findings from the physical examinations must be recorded on the appropriate eCRF.

After the initial full physical examination, a physical examination targeted to the participant's illness and complaints will be performed at subsequent visits as specified in Section 1.3 –SoA.

8.3.2 Height and Weight

The participant's height and weight should be measured prior to initiation of IV study therapy at the randomization (Day 1) visit. Collection at randomization (Visit 2) should be performed **prior to** initiation of IV treatment.

8.3.3 Vital Signs

Vital signs should be collected daily while on IV study therapy and at other time points/visits as specified in Section 1.3 – SoA. Collection at randomization (Visit 2) should be performed **prior to** initiation of IV therapy.

For this study, vital signs include heart rate (HR), blood pressure (BP), respiratory rate (RR), and oral temperature. Participants should be resting in a seated or semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. For participants who are intubated and cannot sit up, HR, BP, and RR may be taken in a supine or semi-recumbent position. Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary methods are acceptable.

Any abnormal or clinically significant vital signs findings must be recorded on the appropriate eCRF.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 5 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 1 day after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Laboratory Monitoring for Liver Function

Participants' liver function should be closely monitored during the study execution, please refer to Section 7.1 (Discontinuation of Study Treatment) for details regarding liver function monitoring.

Local Laboratory Monitoring for Renal Function

Safety laboratory results from the central laboratory will likely not be available in a timely fashion to impact on an individual participant's medical management. Therefore, additional laboratory tests required for adequate medical management of individual study participants should be obtained as indicated by the primary physician and submitted to the local laboratory for testing in the medically appropriate timeframe.

Specifically, for the purpose of monitoring an individual participant's renal function in "real time," a creatinine assessment should be performed at the local laboratory on Days 1, 3, 6, and 10 (if applicable) during IV study therapy in addition to the chemistry safety panel performed at the central laboratory. **For participants with renal insufficiency or whose creatinine clearance changes during treatment with study therapy (refer to** Table 2 **and** Table 3 **in Section 6.2.1), the dose of study drug must be adjusted based upon the degree of renal function impairment as determined by the estimated or actual creatinine clearance.**

Results of these local laboratory tests must be documented in the appropriate eCRF. Laboratory abnormalities resulting in an adverse event or dose adjustment should also be collected on the appropriate eCRF. Any laboratory test abnormality that emerged during study therapy and was considered by the investigator to be an adverse event or event of clinical interest should be repeated until the abnormal value has normalized, stabilized, or returned to baseline.

8.3.5 APACHE II Score

Severity of illness in this study will be determined by APACHE II score at screening [Knaus, W. A., et al 1985]. See Appendix 6 for details regarding the calculation of this score. Results of APACHE II score calculations must be entered on the appropriate eCRF(s).

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 4.

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

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

From the time of treatment allocation/randomization through the Day 28 post-randomization visit, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she

considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Time Period			Time Frame to Report Event and Follow-up Information to SPONSOR:
	Consent to Randomization/ Allocation	**Randomization/ Allocation through Protocol-Specified Follow-up Period**	**After the Protocol Specified Follow-up Period**	
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event		Time Period				Time Frame to Report Event and Follow-up Information to SPONSOR:
		Consent to Randomization/ Allocation	Randomization/ Allocation through Protocol-Specified Follow-up Period	After the Protocol Specified Follow-up Period		
Cancer		Report if: - due to intervention - causes exclusion	Report all	Not required		Within 5 calendar days of learning of event
Overdose		Not applicable	Report all	Not required		Within 5 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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

Not applicable.

8.4.6 Pregnancy and Exposure During Breastfeeding

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. a confirmed (ie, verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5 X ULN as a result of within-protocol-specific testing or unscheduled testing.

NOTE: In participants with pre-existing elevations in transaminase values, only a further elevation that is not anticipated from an underlying medical condition will be considered an ECI. These events may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder.

3. An overdose of Sponsor's product, as defined in Section 8.5 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

8.4.8 Local Infusion Site Tolerability Monitoring

Local infusion site tolerability will be evaluated daily during IV study therapy. The tolerability of all study therapy at the local IV infusion site will be based on investigator inspection and participant comments regarding signs and symptoms of intolerance. The IV infusion site should be observed daily during IV therapy to determine the presence/absence of erythema, induration, pain, tenderness, warmth, swelling, ulceration, local phlebitis, rash, or other reactions. All events should be documented on the appropriate eCRF.

8.5 Treatment of Overdose

In this study, an overdose in IV study therapy is defined as (1) administration of a total daily dose of IMI/REL in excess of 4 g (IMI) or 2 g (REL) OR (2) administration of a total daily dose of PIP/TAZ greater than 16 g (PIP) and 2 g (TAZ).

In this study, an overdose in linezolid is defined as administration of a total daily dose of linezolid in excess of 1200mg.

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met. This must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event using the terminology "accidental or intentional overdose without adverse effect." This must be reported by the investigator within 5 calendar days of learning of event to the Sponsor either by electronic media or paper.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

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

8.9 Future Biomedical Research Sample Collection

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

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 2 days (48 hours) prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

Rescreening of an individual participant for enrollment is not expected to occur commonly. Screening procedures may be repeated in some circumstances but only after consultation with the Sponsor.

8.10.2 Treatment Period

IV study therapy should be administered for a minimum of 7 full days to up to a maximum of 14 days. Participants with evidence of concurrent bacteremia or with *P. aeruginosa* infections should receive 14 days of IV study therapy.

For participants who receive 7 to 9 days of IV study therapy, Day 10 (OTX3 [Visit 5]) will not be completed. Assessments and procedures while on IV study therapy will be completed at the indicated times and intervals as per Section 1.3 – SoA. The EOT visit for participants who receive 7 to 9 days of therapy will be completed within 24 hours after the last dose of IV study therapy on Day 7, Day 8, or Day 9 followed by the subsequent post-treatment visits as indicated in Section 1.3 – SoA.

Participants receiving IV study therapy through Day 10 and up to Day 14 will complete all OTX visits (OTX1 on Day 3, OTX2 on Day 6, and OTX3 on Day 10). Assessments and procedures while on IV study therapy will be completed at the indicated times and intervals as per Section 1.3 – SoA. The EOT visit will be completed within 24 hours after the last dose of IV study therapy on Day 10, 11, 12, 13, or 14 followed by the subsequent post-treatment visits as indicated in Section 1.3 – SoA. Participants who end treatment on Day 10 will have a combined OTX3 and EOT visit. All procedures required for each visit must be completed for the combined visit. Procedures that are common to both visits would only be assessed once.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

8.10.4 Poststudy

An EFU visit (7 to 14 days after the cessation of IV study therapy [ie, 7 to 14 days after EOT]) and a Day 28 post-randomization visit must be completed for each participant. Depending on the total duration of IV study therapy, the EFU and Day 28 post-randomization visit may be combined into a single visit. These visits may only be combined as long as compliance with the protocol-specified visit windows is maintained for both visits.

Specifically, if a participant receives 12 to 14 days of IV study therapy, the EFU visit may potentially be combined with the Day 28 post-randomization visit. For example, if 12 days of IV study therapy are provided, the EFU visit could be scheduled 16 days (14+2) following completion of therapy which would be 28 days (12 days of IV therapy +16 days of follow-up) following randomization. It is required that for any case, the allowable visit window ranges are maintained and all procedures required for each visit must be completed for the combined visit.

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A randomized, double-blind (with in-house blinding), active-controlled, parallel-group, multi-site, trial of IMI/REL compared with PIP/TAZ in participants with HABP or VABP.
Treatment Assignment	This study will randomize participants in a 1:1 ratio to the 2 treatment arms of the study (Group 1: IMI/REL and Group 2: PIP/TAZ). Randomization will be stratified by: 1) pneumonia type at baseline (non-ventilated HABP vs. ventilated HABP/VABP) and 2) APACHE II score at baseline (<15 vs. ≥15). In addition, randomization will be controlled such that a minimum of 25% of randomized participants are in the VABP or ventilated HABP strata. A double-blind/masking technique will be used. IMI/REL and PIP/TAZ will be dispensed in a blinded fashion by an unblinded study staff (eg, pharmacist or qualified designee). Due to a visual difference in the appearance of study treatment solutions, the infusion bags will be covered with an opaque sleeve by the unblinded study staff (eg, pharmacist or qualified designee) to ensure that other study personnel and all participants remain blinded to clinical material assignments. The personnel involved in the administration of the study infusion treatment should be unaware of the treatment group assignments. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the participants are unaware of the group assignments.
Analysis Populations	Primary Efficacy Analysis: modified intention-to-treat (MITT) population (defined as all randomized participants who receive at least 1 dose of IV study therapy and do not have the presence of gram-positive cocci **only** on baseline Gram stain). Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Incidence of all-cause mortality through Day 28 post-randomization
Statistical Methods for Key Efficacy Analyses	For the primary hypothesis (mortality), IMI/REL will be compared to PIP/TAZ using the stratified Miettinen and Nurminen method with the Cochran-Mantel-Haenszel (CMH) weighting. IMI/REL will be considered non-inferior (NI) to PIP/TAZ if the upper bound of the 2-sided 95% confidence interval for the difference in incidence between the treatment groups (IMI/REL minus PIP/TAZ) is less than 12.5%. If non-inferiority is established, then superiority of IMI/REL compared to PIP/TAZ will be evaluated at the α=0.025 (1-sided) level. For secondary endpoints, point estimates and 2-sided 95% confidence intervals will be calculated using the same stratified Miettinen and Nurminen method as described above.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method.

Interim Analyses	A blinded review of the aggregate mortality rate will be ongoing during the study. The impact of the blinded aggregate rate on the assumptions underlying the power/sample size calculation will be formally assessed by the Sponsor when approximately 75% of the planned sample size (N=202) have completed 28 days of follow-up or sooner if enrollment or event rates are occurring faster than anticipated. If Day 28 all-cause mortality is higher than the 15% assumed in the power calculation, consideration will be given to increasing the sample size. There are no plans to conduct a formal interim analysis of unblinded efficacy data in the study.
Multiplicity	A sequential testing approach will be employed on the primary efficacy endpoint.
Sample Size and Power	The planned sample size of 135 participants per group will provide 80% power to reject the null hypothesis that the true difference in all-cause mortality exceeds the NI margin of 12.5% assuming true rates for both the control and experimental regimens of 15% (1-tailed alpha of 2.5%).

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in IRT.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

For the primary hypothesis, IMI/REL will be considered non-inferior (NI) to PIP/TAZ if the upper bound of the 2-sided 95% confidence interval (CI) for the difference in incidence between the treatment groups (IMI/REL minus PIP/TAZ) is less than 12.5%. The 12.5% NI margin is selected based on the estimated treatment effect from the random effect meta-analysis of all-cause mortality by the FDA. Specifically, the all-cause mortality rate with effective treatment is 20% with a 95% upper confidence bound of 23%, and the lower bound of the all-cause mortality of inadequate/delayed treatment is 52%; therefore, the treatment effect is almost 29% (52%-23%=29%). Based on this estimate, the treatment effect has been conservatively set to be 25%, and the NI margin is set to be its half, ie, 12.5%. If non-inferiority is established, then a subsequent test will be performed to determine whether or not IMI/REL is superior to PIP/TAZ (ie, the upper bound of the 2-sided 95% CI for the difference in incidence between the treatment groups is less than 0%).

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Efficacy Endpoints

A full description of the efficacy measures is provided in Section 8.2, and primary and secondary efficacy endpoints are summarized in Table 11.

IV study therapy will be administered for a minimum of 7 days up to a maximum of 14 days (see Section 4.3.3). The duration of therapy will be summarized by treatment group for the overall population. In addition, the impact of any difference in duration of therapy on the treatment group comparisons will be assessed.

Table 11 Summary of Primary and Secondary Efficacy Endpoints and Components of a Favorable Response

Objective	Endpoint	Timing	Favorable Response	Analysis Population	References (Section/Table)
Primary Endpoint	All-Cause Mortality	Day 28	Survival	MITT	Section 8.2.1
Secondary Endpoint	Clinical Response	EOT, EFU	• EOT (Cure or Improved) • EFU (Cure or Sustained Cure)	MITT and CE	Section 8.2.2 Table 5 and Table 6
	Microbiological Response	EOT, EFU	• EOT (Eradication or Presumed Eradication) • EFU (Eradication or Presumed Eradication)	mMITT and ME	Section 8.2.3 Table 8 and Table 9

Abbreviations: CE=clinically evaluable population; Day 28=Day 28 post-randomization; EFU=early follow-up visit; EOT=end of therapy visit; MITT=modified intention to treat population; mMITT=microbiological modified intention to treat population; NA=not applicable

9.4.2 Safety Endpoints

A description of safety measures is provided in Section 8.3. The analysis of safety endpoints will follow a tiered approach. For this protocol, the following are pre-specified events of interest (Tier 1 events).

1. An elevated AST or ALT laboratory value that is greater than or equal to 3 X ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 X ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 X ULN, as a result of within-protocol-specific testing or unscheduled testing.

It will not be counted as a Tier 1 event if the preceding conditions were present at randomization (Day 1).

2. A confirmed (ie, verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5 X ULN as a result of within-protocol-specific testing or unscheduled testing. It will not be counted as a Tier 1 event if the preceding conditions were present at randomization (Day 1).

The broad clinical and laboratory adverse event (AE) categories, consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug related and serious, who discontinued IV study therapy due to an AE, and who discontinued IV study therapy due to a drug-related AE, will be considered Tier 2 endpoints.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The modified intention-to-treat (MITT) population will serve as the primary population for efficacy analyses in this study. The MITT population is defined as all randomized participants who receive at least 1 dose of IV study therapy and do not have the presence of -positive cocci **only** on baseline Gram stain.

The microbiological modified intention-to-treat (mMITT) population is the secondary population for efficacy analyses. The mMITT population is defined as all randomized participants who receive at least 1 dose of IV study therapy and do not have gram-positive cocci **only** on baseline Gram stain and who have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity.

The clinical-evaluable (CE) and microbiological-evaluable (ME) populations will serve as additional analysis populations for the some of the secondary and exploratory efficacy endpoints. The CE population is a subset of the MITT population who also meet the following criteria:

- Meet important diagnostic criteria for entry into the study,
- Have no significant deviation from the protocol that could impact the assessment of efficacy,
- Receive the minimum duration of IV study therapy, ie, 7 days, and
- Have an efficacy assessment at the time point of interest.

The CE population does not require a positive baseline culture for a bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity.

The ME population is a subset of the CE population who also meet the following criteria:

- Have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity, and
- Have results from a lower respiratory tract culture obtained at the indicated time point.

The final determination on major protocol deviations, and thereby the composition of the CE and ME populations, will be made prior to the final unblinding of the database and will be documented in a separate memo.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the MITT and mMITT populations. Details on the approach to handling missing data are provided in Section 9.6 – Statistical Methods.

9.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized participants who received at least 1 dose of IV study therapy. Participants will be included in the treatment group corresponding to the IV study therapy they actually received for the analysis of safety data using the ASaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study therapy for the entire treatment period will be included in the treatment group corresponding to the study therapy actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of IV study therapy is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

For the analysis of pre-specified events of interest (Tier 1 events) described above in Section 9.4.2, participants will be excluded from specific analyses if the conditions defining the event were present at randomization (Day 1).

9.6 Statistical Methods

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error rate control strategy are described in Section 9.8 - Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests of efficacy endpoints will be conducted at the α=0.025 (1-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

The analysis of between-treatment differences in the incidence (or percentage of participants) with binary events will be performed using the stratified Miettinen and Nurminen method (1985) [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. The analyses will be stratified by: 1) pneumonia type at baseline (non-ventilated HABP vs. ventilated HABP/VABP), and 2) APACHE II score at baseline (<15 vs. ≥15), with the Cochran-Mantel-Haenszel (CMH) weighting.

Missing Values

Any participant missing an evaluation for a specific endpoint (clinical or microbiological) at any particular visit will be generally considered as being "indeterminate" for that endpoint in the MITT and mMITT populations. The following are exceptions to this rule:

- Participants discontinuing IV study therapy due to lack of efficacy (ie, withdrawals with subsequent non-study antibiotic therapy) will be considered as "failures" with respect to clinical response at the time of discontinuation and all subsequent time points.

- Participants discontinuing IV study therapy due to lack of efficacy will be presumed to have persistence for the microbiological response at the time of discontinuation and all subsequent time points.

The primary and secondary endpoints, primary and secondary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 12. Since a favorable clinical response at EOT requires an assessment of "cure" or "improved", an assessment of "indeterminate" would be considered a failure to achieve a favorable clinical response. Since a favorable clinical response at EFU requires an assessment of "cure" or "sustained cure", an assessment of "indeterminate" would be considered a failure to achieve a favorable clinical response. Since a favorable microbiological response at EOT and EFU requires an assessment of "eradication" or "presumed eradication", an assessment of "indeterminate" would be considered a failure to achieve a favorable microbiological response.

Table 12 Summary of Analysis Strategy for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Incidence of all-cause mortality through Day 28 post-randomization. NI comparison of IMI/REL to PIP/TAZ using 12.5% margin	Stratified M&N[a]	MITT[b]	M=F[c]
Secondary:			
Percentage of participants achieving a favorable clinical response at EFU.	Stratified M&N[a]	MITT[b]	M=F[c]
Percentage of participants achieving a favorable clinical response at EOT.	Stratified M&N[a]	MITT[b]	M=F[c]

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
Percentage of participants achieving a favorable clinical response at EFU.	Stratified M&N[a]	CE[e]	DAO[d]
Percentage of participants achieving a favorable clinical response at EOT.	Stratified M&N[a]	CE[e]	DAO[d]
Percentage of participants achieving a favorable microbiological response at EOT.	Stratified M&N[a]	mMITT[f]	M=F[c]
Percentage of participants achieving a favorable microbiological response at EFU.	Stratified M&N[a]	ME[g]	DAO[d]
Percentage of participants achieving a favorable microbiological response at EOT.	Stratified M&N[a]	ME[g]	DAO[d]

[a] M&N is Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] stratified by pneumonia type at baseline (non-ventilated HABP vs. ventilated HABP/VABP) and APACHE II score (<15 vs. ≥15).
[b] MITT population includes all randomized participants who receive at least 1 dose of IV study therapy and do not have the presence of gram-positive cocci **only** on baseline Gram stain.
[c] M=F is missing=failure.
[d] DAO=data as observed.
[e] CE population is a subpopulation of MITT population who also meet the following criteria: 1) Meet important diagnostic criteria for entry into the study; 2) Have no significant deviation from the protocol that could impact the assessment of efficacy; 3) Receive the minimum duration of IV study therapy; and 4) Have an efficacy assessment at the time point of interest.
[f] mMITT population includes all randomized participants who receive at least 1 dose of IV study therapy and do not have gram-positive cocci only on baseline Gram stain and who have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity.
[g] ME population is a subpopulation of CE population who also meet the following criteria: 1) have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity, and 2) Have results from a lower respiratory tract culture obtained at the indicated time point.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

The analysis of safety results will follow a tiered approach Table 13. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. p-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method. Since the stratification factors (pneumonia type at baseline and APACHE II score at baseline) are not considered to be related to safety endpoints, they will not be included as stratification factors in the safety analyses.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs parameters that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3," based on the number of events observed. Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event; all other adverse events and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

Continuous measures such as changes from baseline in laboratory and vital signs parameters that are not pre-specified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Elevated AST or ALT ≥3 X ULN and elevated total bilirubin ≥2 X ULN and alkaline phosphatase <2 X ULN	X	X	X
	A confirmed elevated AST or ALT ≥5 X ULN	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Discontinuation due to Drug-Related AE		X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 participants in 1 of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

† Adverse Event references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
Abbreviations: PDLC=Pre-Defined Limit of Change; SOC=System Organ Class; X=results will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

There are no plans to conduct a formal interim analysis of unblinded efficacy data in the study.

An internal blinded sample size re-estimation will be conducted as described in the following paragraph.

Blinded review of the aggregate Day 28 all-cause mortality rate (referred to as the mortality rate for the remainder of this section) will be ongoing during the study. The impact of the mortality rate on the assumptions underlying the power/sample size calculation will be formally assessed when approximately 75% (N=202) of the planned sample size (N=270) have completed 28 days of follow-up or sooner if enrollment or event rates are occurring faster than anticipated. If the observed overall mortality rate is higher than the 15% assumed in the power calculation, consideration will be given to increasing the overall sample size as outlined in Table 14. If the observed mortality rate is less than 15%, the overall sample size will be maintained at the planned N=270 and power for this endpoint/hypothesis will exceed 80%. The maximum sample size will not exceed N=380 (190 per group) regardless of the observed overall mortality rate. The accruing database will not be officially locked for this blinded sample size re-estimation; however, all data relating to the assessment of mortality will be cleaned and all queries resolved before the formal assessment of the mortality rate. As this sample size re-estimation will be done in a blinded fashion, there is no impact on type 1 error rates.

Table 14 Sample Size Adjustments Based on Interim Blinded Review of Day 28 All-Cause Mortality

Observed Mortality Rate (%) †	Power Based on Original Sample Size (N=270)	Revised Sample Size ‡	Percent Increase from Original Sample Size
16%	78.3%	282	4.4%
17%	76.6%	294	8.9%
18%	74.9%	306	13.3%
19%	73.3%	318	17.8%
20%	71.9%	328	21.5%
21%	70.5%	340	25.9%
22%	69.2%	350	29.6%
23%	67.9%	360	33.3%

Observed Mortality Rate (%) †	Power Based on Original Sample Size (N=270)	Revised Sample Size ‡	Percent Increase from Original Sample Size
24%	66.8%	370	37.0%
25%	65.7%	380	40.7%

† This is the aggregate Day 28 all-cause mortality rate expressed as a percent and rounded to the nearest integer value.
‡ Calculated to provide 80% power based on the observed mortality rate

9.8 Multiplicity

A sequential testing approach will be employed on the primary efficacy endpoint (incidence of Day 28 all-cause mortality). The non-inferiority will be evaluated first using 1-sided α=0.025 level. If non-inferiority is met, the superiority will be evaluated using α=0.025, 1-sided.

9.9 Sample Size and Power Calculations

This study will randomize participants in a 1:1 ratio to the 2 treatment arms of the study (Group 1: IMI/REL and Group 2: PIP/TAZ), in order to obtain approximately 270 participants who meet the criteria for inclusion in the modified intention-to-treat (MITT) population. A sample size of 135 participants per group will provide 80% power to reject the null hypothesis that the true difference in all-cause mortality exceeds the NI margin of 12.5%, assuming true rates for both the control and experimental regimens of 15% (1-tailed alpha of 2.5%).

Another way to assess the precision of a non-inferiority trial is to consider the maximum observed difference that would just meet the criterion for non-inferiority (in this case, an upper bound of the 2-sided 95% CI for the difference in all-cause mortality [IMI/REL minus PIP/TAZ] that is just less than 12.5%). This maximum observed difference will increase as the observed mortality in the control group decreases. For example, an observed difference of 2.3 percentage points will just meet the criterion for non-inferiority given an observed mortality of 20.7% (28/135) in the control group and 23% (31/135) in the experimental group. An observed difference of 3.7 percentage points will just meet the criterion for non-inferiority given an observed mortality of 10.4% (14/135) in the control group and 14.1% (19/135) in the experimental group.

9.10 Subgroup Analyses

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the Day 28 all-cause mortality (MITT population) will be estimated within each category of the following classification variables (assessed prior to or at the point of randomization) if there are at least 25 participants in each subgroup in each treatment group:

- Age category (<65, ≥65 years)
- Gender (female, male)
- Country (China, other countries/regions)

- Stratification variable: Pneumonia type at baseline (non-ventilated HABP, ventilated HABP/VABP)
- Stratification variable: APACHE II score at baseline (<15, ≥15)
- Concurrent bacteremia (Y, N)

9.11 Compliance (Medication Adherence)

Considering this is an IV study on hospitalized participants conducted by investigators/nurses, it is expected to follow the protocol strictly without compliance issues. Any non-compliance dosage will be monitored and recorded for discussion.

9.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (e.g., International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and

conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

Financial Disclosure

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

Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

Data Protection

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

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

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

Confidentiality of Data

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

Confidentiality of Participant Records

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

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

Confidentiality of IRB/IEC Information

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

Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Study 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 study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

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

Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other

generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

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

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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

Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
    - The following are not acceptable methods of contraception:
        - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
        - Male and female condom cannot be used together.
    - A combination of male condom with either cap, diaphragm or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 15 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 15 Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b, c] • Intrauterine hormone-releasing system (IUS)[b] • Intrauterine device (IUD) • Bilateral tubal occlusion • Azoospermic partner (vasectomized or secondary to medical cause). This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[b, c] o Oral o Intravaginal o Transdermal o Injectable • Progestogen-only hormonal contraception[b, c] o Oral o Injectable • Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods With a Failure Rate of >1% per Year When Used Consistently and Correctly:
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[d]

Notes:
- Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.
- The following are not acceptable methods of contraception:
  - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
  - Male and female condom should not be used together (due to risk of failure with friction).

[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).

[b] If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period. IUS is a progestin-releasing IUD.

[c] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

[d] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.

Pregnancy Testing

WOCBP should only be included after a negative pregnancy test has been confirmed at screening. Prior documentation of a negative serum β-hCG within 2 days (48 hours) of enrollment is acceptable for women of reproductive potential. If documentation is not available, a rapid urine β-hCG test may be used for screening; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. To conduct urine testing, sites must have individuals certified in administration and interpretation of test and the urine test utilized must have sensitivity of <25 mIU/L.

Additional serum pregnancy testing will be performed at the Day 28 post-randomization visit.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to Section 8.4.5 for protocol specific exceptions

Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events Reported

Additional events which require reporting

- In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.
- Is a cancer;
- Is associated with an overdose.

Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric studies, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. (for pediatric studies, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?
  - The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental

factors

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

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

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE

onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

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

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

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

● If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section). ● Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).
SAE reporting to the Sponsor via paper CRF
● If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor. ● In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. ● Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. ● Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the central laboratory, with the exception of the rapid urine β-hCG test and HIV/HBV/HCV assessment (if HIV/HBV/HCV testing is required per local policy).
- As described in Section 8.3.4, for the purpose of monitoring an individual participant's renal function in "real time," a creatinine assessment should be performed at the local laboratory on Days 1, 3, 6, and 10 (if applicable) during IV study therapy in addition to the chemistry safety panel performed at the central laboratory. The local laboratory results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 16 Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	Rapid urine β-hCG
Platelet count	Alanine aminotransferase (ALT)	Protein	HIV/HBV/HCV (Per local guidance)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	
		Microscopic exam, if abnormal results are noted	
	Bicarbonate		
	Calcium		
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

Investigators must document their review of each laboratory safety report.

Table 17 Approximate Blood Volumes Drawn by Trial Visit and Sample Types

	Screening	IV Study Treatment					Post-Treatment	
Trial Visit	V1 Screening	V2 Randomization	V3 OTX1	V4 OTX2	V5 OTX3	V6 EOT	V7 EFU	V8 Day 28
Blood Parameter	Approximate Blood Volume (mL)							
Hematology	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Serum/ Plasma Chemistry	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Serum ß-hCG[a]	3.5							3.5
Local Laboratory Assessment of Creatinine[b]	2.0	2.0	2.0	2.0	2.0			
Culture and Susceptibility		40	As clinically indicated (40 mL per assessment)					
Expected Total (mL)[c,d]	**11.0**	**47.5**	**7.5 or 47.5 if culture and susceptibility testing clinically indicated**	**7.5 or 47.5 if culture and susceptibility testing clinically indicated**	**7.5 or 47.5 if culture and susceptibility testing clinically indicated**	**5.5 or 45.5 if culture and susceptibility testing clinically indicated**	**5.5 or 45.5 if culture and susceptibility testing clinically indicated**	**9.0**

[a] For female subjects of childbearing potential only; to be conducted only if prior documentation (within 48 hours of enrollment) of a negative β-hCG unavailable and if rapid urine β-hCG test result is positive or cannot be confirmed as negative. Further guidance can be found in appendix 3 of the protocol.

[b] Not needed at screening visit if performed at screening Blood for Chemistry assessment.

[c] Additional blood samples may be collected in support of evaluation for an underlying etiology throughout the study. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder. Depending on the results of initial testing, additional blood volumes could range from approximately 8.5 mL up to approximately 92.0 mL and could include HIV and/or Hepatitis testing.

[d] Blood cultures will be collected in all subjects prior to initiation of IV study therapy. Subjects with positive blood cultures at screening should have follow-up blood cultures collected daily until 2 consecutive blood cultures demonstrate no growth. Blood cultures will be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures and isolates sent to the central microbiology laboratory.

10.6 Appendix 6: APACHE II Severity of Disease Classification System – APACHE II Score Form

A. Acute Physiology Score[a]:

		HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature rectal (°C)[b]	□ ≥41	□ 39-40.9		□ 38.5-38.9	□ 36.0-38.4	□ 34-35.9	□ 32-33.9	□ 30-31.9	□ ≤29.9
2	Mean arterial pressure (mmHg)= (2 x diastolic + systolic)/3	□ ≥160	□ 130-159	□ 110-129		□ 70-109		□ 50-69		□ ≤49
3	Heart rate (ventricular response)	□ ≥180	□ 140-179	□ 110-139		□ 70-109		□ 55-69	□ 40-54	□ ≤39
4	Respiratory rate (nonventilated or ventilated)	□ ≥50	□ 35-49		□ 25-34	□ 12-24	□ 10-11	□ 6-9		□ ≤5
5	Oxygenation[c] A-aDO_2 or PaO_2 (mm Hg) a)FiO_2≥0.5:record A-aDO_2	□ ≥500	□ 350-499	□ 200-349		□ <200				
	b)FiO_2<0.5:record only PaO_2					□ >70	□ 61-70		□ 55-60	□ <55
6	Arterial pH (*If no ABGs record Serum HCO3 below)	□ ≥7.7	□ 7.6-7.69		□ 7.5-7.59	□ 7.33-7.49		□ 7.25-7.32	□ 7.15-7.24	□ <7.15
7	Serum sodium (mMol/L)	□ ≥180	□ 160-179	□ 155-159	□ 150-154	□ 130-149		□ 120-129	□ 111-119	□ ≤110
8	Serum potassium (mMol/L)	□ ≥7	□ 6-6.9		□ 5.5-5.9	□ 3.5-5.4	□ 3-3.4	□ 2.5-2.9		□ <2.5
9	Serum creatinine (mg/dL) Double point for acute renal failure	□ ≥3.5	□ 2-3.4	□ 1.5-1.9		□ 0.6-1.4		□ <0.6		
10	Hematocrit (%)	□ ≥60		□ 50-59.9	□ 46-49.9	□ 30-45.9		□ 20-29.9		□ <20
11	White blood count (total/mm^3) (in 1000's)	□ ≥40		□ 20-39.9	□ 15-19.9	□ 3-14.9		□ 1-2.9		□ <1
12	Glasgow Coma Scale Enter 15 minus actual GCS –see calculations in table below	15-GCS =								
A	Total Acute Physiology Score (APS)	Sum of the 12 individual variable points =								
*	Serum HCO3(venous-mMol/L) (Not preferred, use if no ABGs)	□ ≥52	□ 41-51.9		□ 32-40.9	□ 22-31.9		□ 18-21.9	□ 15-17.9	□ <15

APACHE II Severity of Disease Classification System

Glasgow Coma Score (GCS) (circle appropriate response)		
Eyes open (E)	Motor response (M)	Verbal - Response (V)[e]
4 - spontaneously	6 - to verbal command	5-oriented and controversed
3 - to verbal command	5 - localizes to pain	4-confused and disoriented
2 - to painful stimul	4 - withdraws to pain	3-inappropriate words
1 - no response	3 - decorticate[d]	2-incomprehensible sounds
	2 - decerebrate[d]	1-no response
	1 - no response	
GLASGOW COMA SCORE[†] = E + M + V		
† Participants scoring 3 or 4 have an 85% chance of dying or remaining vegetative, while scores above 11 indicate 5 to 10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of participants recovering.		
B. Age Points		
Age Points ≤44 0 45-54 2 55-64 3 65-74 5 ≥75 6 Age points = _____		
C. Chronic Health Points (CHE)[f]		
If any of the 5 CHE categories is answered with yes give +5 points for nonoperative or emergency postoperative participants, or +2 points for elective postoperative participants Liver - Cirrhosis with Portal Hypertension (PHT) or encephalopathy Cardiovascular –NYHA Class IV angina or at rest or with minimal self-care activities Pulmonary -chronic hypoxemia or hypercapnia or polycythemia or pulmonary hypertension >40 mm Hg Kidney -chronic peritoneal or hemodialysis Immune -immune compromised host Chronic Health Points=_____		
APACHE-II Score is sum of A+B+C APS points A _____ Age points +B _____ Chronic Health Points+C _____ Total APACHE-II Score=_____		

Adapted From: [Knaus, W. A., et al 1985]

a. The most severe value in the last 48 hours prior to a participant's randomization into the study should be used for each variable of the APACHE II score calculation. The calculation of the APACHE II score should be captured in the patient's medical chart or in a copy of the APACHE II Score form.

b. The sponsor recommendation is to use rectal temperature measurement whenever possible. If rectal temperature is not possible, it is acceptable to use non-rectal temperature with no conversion as a substitute.

c. It is recommended that when assessing the Oxygenation variable for the APACHE II calculation, ABG measurements should be used. If ABG has not been performed for a participant, then the APACHE II score calculation should be recorded as 0 for Oxygenation variable.

d. Decerebrate for +2 points means extension to pain. Decorticate for +3 points means flexion to pain.

e. Verbal response for participants that are intubated and/or sedated/paralyzed: If there is a reliable pre-sedation GCS score or all of the elements of the GCS score were documented in the medical record - then just use the pre-sedation GCS score (not just the verbal response piece, but the whole GCS score). But if there is no reliable pre-sedation GCS score, then the GCS section of the Acute Physiology Score would just be null overall. Investigators should note on the source documents and then commenting out on the APC2 eCRF that the GCS was not assessed.

f. The CHE score can only be +5, +2 or 0. These additional points are to be given only once and not multiple times for each separate condition that has been observed.

10.7 Appendix 7: Clinical Pulmonary Infection Score (CPIS)

PARAMETER	SCORE
Temperature (°C)	
≥36.5 and ≤38.4	0
≥38.5 and ≤38.9	1
≥39.0 or <36.5	2
White Blood Cell (WBC) Count (X 10^9/L)	
≥4,000 and ≤11,000	0
<4,000 or >11,000	1
<4,000 or >11,000 & band forms ≥50%	2
Lower Respiratory Tract Sample/Tracheal Secretions	
No or minimal sputum/secretions	0
Non-purulent sputum/secretions	1
Purulent sputum/secretions	2
PaO_2/FiO_2*	
Not ventilated to allow assessment	0
>240 or evidence of ARDS**/pulmonary contusion	0
≤240 and no evidence of ARDS**/pulmonary contusion	2
Chest Radiograph at Study Entry	
No infiltrate	0
Diffuse (or patchy) infiltrate	1
Localized infiltrate	2

* Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.
** ARDS is defined as a PaO_2/FiO_2 ≤200, PAOP ≤18mmHg, and acute bilateral infiltrates
Source: Modified from[Zilberberg, M. D. 2010]

10.8 Appendix 8: Abbreviations

Abbreviation	Definition
ABG	arterial blood gas
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-24hr}	area under the concentration-time curve from time zero to 24 hours
BAL	bronchoalveolar lavage
β-hCG	β-human chorionic gonadotropin
BL	β-lactam
BLI	β-lactamase inhibitor
BP	blood pressure
CABP	community-acquired bacterial pneumonia
CD4	cluster of differentiation 4
CE	clinically evaluable
C_{eoi}	concentration at the end of infusion
CFR	Code of Federal Regulations
C-G	Cockcroft-Gault
CI	confidence interval
cIAI	complicated intra-abdominal infection
CL_{plasma}	plasma clearance
CMS	colistimethate sodium
CPT	Common Protocol Template
CSR	clinical study report
cUTI	complicated urinary tract infection
DCIV	discontinuation of iv therapy
DNA	deoxyribonucleic acid
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EFU	early follow-up
ELF	epithelial lung fluid
EOT	end of therapy; end of treatment
ESBL	extended-spectrum beta-lactamase
ESRD	end-stage renal disease
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed-dose combination
FiO_2	fraction of inspired oxygen
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
GFR	glomerular filtration rate

Abbreviation	Definition
HABP	hospital-acquired bacterial pneumonia
HAI	hospital-acquired infections
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IMI	imipenem/cilastatin
IMI/REL	fixed-dose combination of imipenem/cilastatin/relebactam
IMI + REL	imipenem/cilastatin co-administered with relebactam (ie, from separate vials)
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Boards
IRT	Interactive Response Technology
IUD	intrauterine device
IV	intravenous (parental)
KPC	*Klebsiella pneumoniae* carbapenemase
LAM	lactational amenorrhea method
LFU	late follow-up
MAOI	monoamine oxidase inhibitors
MDR	multi-drug resistant
ME	Microbiologically evaluable
mg	milligram
MIC	minimum inhibitory concentration
MITT	modified intention-to-treat
mMITT	microbiological modified intention-to-treat
MRSA	methicillin-resistant *S. aureus*
MSD	Merck & Co, Inc. (Merck Sharp & Dohme outside the US)
MSSA	methicillin-susceptible *S. aureus*
NI	non-inferior
NIMP	non-investigational medicinal product
NMPA	National Medical Products Administration (China)
OTX	on-therapy
PaO_2	partial pressure of oxygen
PaO_2/FiO_2	ratio of partial pressure of oxygen to the fraction of inspired oxygen
PBS	protected brush specimen
PD	pharmacodynamic
PDLC	pre-defined limit of change
PIP	piperacillin
PK	pharmacokinetic
q6h	every 6 hours
q12h	every 12 hours
QTc	corrected QT interval

Abbreviation	Definition
QTcP	population-specific corrected QTc
REL	relebactam
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
siDMC	standing internal Data Management Committee
SoA	Schedule of Activities
SOC	system organ class
TAZ	tazobactam
$t_{1/2}$	terminal half-life
ULN	upper limit of normal
US	United States
VABP	ventilator-associated bacterial pneumonia
WBC	white blood cell
WOCBP	women of childbearing potential

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