Statistical Analysis Plan

(SAP)

Interim Analysis

A Phase 3, Multi-Center, Randomized, Open-Label Study of Carbavance (Meropenem/RPX7009) Versus Best Available Therapy in Subjects with Selected Serious Infections Due to Carbapenem-Resistant *Enterobacteriaceae*

Protocol Number: REMPEX-506

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SAP APPROVAL FORM

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AP	Acute Pyelonephritis
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAT	Best Available Therapy
BMI	Body Mass Index
CDAD	Clostridium difficile–Associated Diarrhea
CE	Clinical Evaluable
CFU	Colony-forming Unit
cIAI	Complicated Intra-abdominal Infection
CRE	Carbapenem-resistant *Enterobacteriaceae*
CRE-ME	Carbapenem-resistant *Enterobacteriaceae* Microbiological Evaluable
CT	Computed Tomography
cUTI	Complicated Urinary Tract Infection
ECG	Electrocardiogram
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of Treatment
FDA	Food and Drug Administration
HABP	Hospital-acquired Bacterial Pneumonia
ICU	Intensive Care Unit
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
KPC	*Klebsiella pneumoniae* Carbapenemase
LCE	Leukocyte Esterase
LFU	Late Follow-up
LLN	Lower Limit of Normal
LTAC	Long-term Acute Care

mCRE-MITT	Microbiological Carbapenem-resistant *Enterobacteriaceae* Modified Intent-to-Treat
ME	Microbiological Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MITT	Modified Intent-to-Treat
m-MITT	Microbiological Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDM	New Delhi Metallo Beta-lactamase
OXA	Oxacillinase
PCS	Potentially Clinically Significant
PI	Principal Investigator
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TOC	Test of Cure
ULN	Upper Limit of Normal
VABP	Ventilator-associated Bacterial Pneumonia
VIM	Verona Integron-encoded Metallo Beta-lactamase
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on the Study Protocol for REMPEX Study 506 (Version 3.0, April 24, 2015) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol.

2. STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the safety, tolerability, and efficacy of Carbavance (henceforth referred to as meropenem-vaborbactam) in treatment of subjects with selected serious infections, suspected or known to be due to carbapenem-resistant *Enterobacteriaceae* (CRE); and
- To assess the pharmacokinetics (PK) of meropenem and vaborbactam in subjects with selected serious infections, suspected or known to be due to CRE.

3. STUDY DESIGN

3.1. General Study Design and Plan

This is a Phase 3, multi-center, randomized, open-label study of meropenem-vaborbactam versus Best Available Therapy (BAT) in the treatment of subjects with selected serious infections, specifically cUTI or AP, HABP, VABP, and bacteremia, suspected or known to be caused by CRE.

For this study, the specific serious infections selected for study will be defined as the following:

- Complicated UTI (cUTI) is a urinary infection occurring in a subject with a structural or functional abnormality of the genitourinary tract associated with clinical signs and symptoms.
- Acute pyelonephritis (AP) is an acute infection of the renal pelvis or parenchyma associated with clinical signs and symptoms.
- Complicated Intra-abdominal Infection (cIAI) is an infection in the abdominal cavity which extends beyond the hollow viscus of origin (bowel, stomach, gallbladder, etc.) into the peritoneal space and is associated with either abscess formation or peritonitis associated with clinical signs and symptoms.
- Hospital-acquired bacterial pneumonia (HABP) is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms in a subject hospitalized for more than 48 hours, or in a subject admitted from a long-term acute care or rehabilitation center, or admitted from home $\leq$7 days after discharge from a hospital or health care facility.
- Ventilator-associated bacterial pneumonia (VABP) is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms beginning

more than 48 hours after a subject receives ventilatory support via an endotracheal (or nasotracheal) tube.

- Bacteremia is defined by the presence of a bacterial pathogen in a blood culture that is not thought to be a contaminant. Subjects enrolled with the indication of bacteremia will not have concurrent HABP, VABP, cIAI, or cUTI/AP infections. However, subjects enrolled with HABP, VABP, cIAI, or cUTI/AP may also have concurrent secondary bacteremia.

Approximately 150 subjects who are expected to need at least 7 days of treatment with IV antibiotics will be enrolled in a 2:1 ratio of meropenem-vaborbactam to BAT, respectively.

The Treatment Arms in the study are as follows:

- Treatment Arm A: Subjects (n = 100) will receive meropenem 2 g plus vaborbactam 2 g IV q8h, with each dose infused for 3 hours for up to 14 days.

  NOTE: Dose adjustments will be required for subjects with renal insufficiency.

- Treatment Arm B: Subjects (n = 50) will receive BAT with IV antibiotics chosen from the following list, either in combination or alone, for up to 14 days: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin or gentamicin), polymyxin B, and ceftazidime-avibactam.

Subjects (or subject's legal representative) providing informed consent, meeting all study eligibility criteria including those criteria for their particular site of infection (e.g., cUTI or AP, cIAI, HABP, VABP, and bacteremia), and who have either a known CRE infection or a suspected CRE infection (based on colonization with a KPC-producing *Enterobacteriaceae* organism [which may be determined through rapid diagnostic tests, active surveillance cultures, or other documentation of CRE colonization] in the past 90 days or prior infection due to a CRE pathogen that was treated within the past 90 days) will be randomized to receive meropenem-vaborbactam or BAT.

Any isolated bacterial pathogen will be identified by genus and species. The local laboratory will culture each subject's sample for pathogen identification, quantification, and susceptibility testing. Isolated pathogens collected at the time points listed in Table 1 and cultured at the local laboratory will be sent to the central laboratory for confirmation of identification and testing results.

Day 1 is defined as the first day of study drug administration (meropenem-vaborbactam or BAT). Subsequent study days are defined by the number of calendar days thereafter. The planned total duration of IV study drug therapy is up to 14 days. A subject assessed as a clinical cure must receive ≥5 days of study drug therapy, and a subject assessed as a clinical failure must receive ≥3 days of study drug therapy.

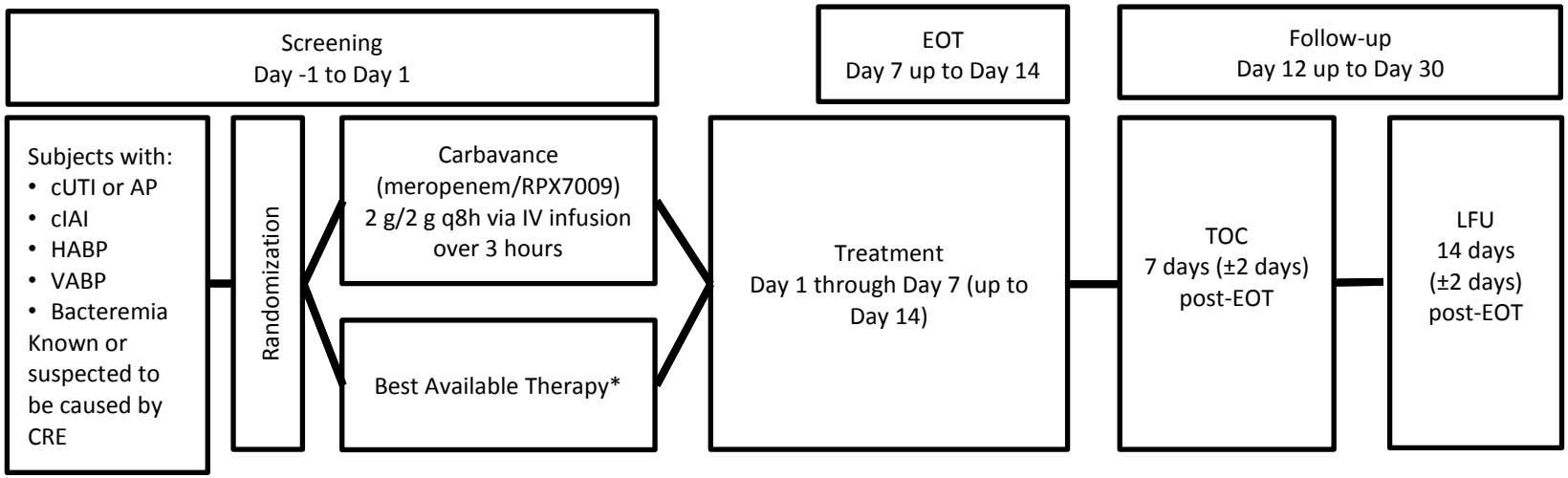
End of Treatment (EOT) will be the day on which the final dose of study drug is administered (+1 day). The Test of Cure (TOC) visit and Late Follow-up (LFU) visit will occur at time points as defined in the Schedule of Procedures (Table 1).

Figure 1 presents the flow diagram of the study.

Figure 1: Study Schema

REMPEX 506 Carbavance (Meropenem-Vaborbactam)

A Phase 3, Multi-center, Randomized, Open-Label Study of Carbavance (Meropenem/RPX7009) Versus Best Available Therapy in Subjects with Selected Serious Infections Due to Carbapenem-Resistant *Enterobacteriaceae*



* Best Available Therapy is treatment with any of the following antibiotics, alone or in combination: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycoside (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam.

AP = acute pyelonephritis; cIAI = complicated intra-abdominal infection; CRE = carbapenem-resistant *Enterobacteriaceae;* cUTI = complicated urinary tract infection; EOT = End of Treatment; HABP = Hospital-acquired bacterial pneumonia; IV = intravenous; LFU = Late Follow-up; PK = pharmacokinetics; q8h = Every 8 hours; TOC = Test of Cure; VABP = Ventilator-associated bacterial pneumonia.

3.2. Treatment Bias

This is an open label study and the Principal Investigator, study coordinators, and pharmacy staff will not be blinded. However, measures were implemented to optimize unbiased assessments of outcomes between treatment arms at the investigational sites. For example, subjects will not be informed which treatment arm they are assigned to and each site will designate a Blinded Investigator who will be blinded to study drug treatment and will evaluate criteria for Clinical Outcomes during designated study visits. Details regarding minimizing subject treatment bias can be referenced in the Rempex-506 Protocol.

In an effort to ensure unbiased assessment of outcomes between treatment arms, subjects will not be informed what treatment arm they are assigned. Efforts should be made to keep subjects naïve to their treatment throughout the course of the study.

3.3. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review accumulated safety data for this study and Rempex-505 when the total combined enrollment in both trials is approximately 25% and 50%. They will also review serious adverse events on an ongoing basis. They will make recommendations to the Sponsor based on this safety data. Further details regarding the data safety monitoring guidelines will be included in the DSMB Charter, which is the governing document of the DSMB.

3.4. Blinded Adjudication Committee

A blinded adjudication committee will also be formed to independently evaluate clinical outcome data in cases where the Investigator's and Blinded Investigator's assessment of outcome differ. In these instances the decision made by the blinded adjudication committee will factor into the final clinical outcome data as described in Section 15.1.2 of the protocol. Further details regarding the blinded adjudication committee, will be included in a Blinded Adjudication Committee Charter, which is the governing document of the committee.

3.5. Source Control Assessment

An independent assessor will review adequacy of source control in all cIAI patients.

3.6. Study Population

The study will enroll approximately 150 subjects with serious infections, of whom a proportion will have CRE infections across the following indications: cUTI or AP, cIAI, HABP, VABP, and bacteremia.

3.7. Randomization

Subjects will be randomized to receive either meropenem-vaborbactam or BAT through a centralized Interactive Web Response System (IWRS). The time and date of randomization will be recorded on the IWRS confirmation, which will be the reference time point for screening procedures and diagnostic time windows. The subject will only be randomized after the inclusion and exclusion criteria are verified. The detailed randomization algorithm is documented in the IWRS specification Appendix C.

To ensure balance among treatment arms, the randomization will be stratified by presenting indication (cUTI or AP, cIAI, HABP, VABP, and bacteremia) and by region (North America vs. Europe vs. Rest of World).

Enrollment will continue until at least 45 subjects (30 meropenem-vaborbactam, 15 BAT) with cUTI or AP are documented to have a CRE organism at baseline and until at least 30 subjects with cIAI with a documented CRE organism at baseline (20 meropenem-vaborbactam, 10 BAT) are enrolled. Once the specified number of subjects are enrolled in the cUTI and/or cIAI indications, data from these subjects may be submitted to regulatory agencies in support of a marketing application, and the enrollment of additional subjects into the specific indication(s) where enrollment was met may be stopped.

Subjects will be randomized in a 2:1 ratio. A randomization notification will be sent to the appropriate site personnel; it will contain subject identification information and the treatment assignment for entry onto the electronic Case Report Form (eCRF).

3.8. Unblinding

This is an open label study and the Principal Investigator (PI), study coordinators, and pharmacy staff will not be blinded. However, the measures outlined in the protocol will be implemented in order to optimize unbiased assessments of outcomes between treatment arms at the investigational site (See Section 3.2 Treatment Bias).

3.9. Study Assessments

Table 1 presents the visit schedule and procedures of the study to be conducted at each visit.

Table 1. Schedule of Procedures

	Screening	Treatment									Follow-Up		Early Termination[c]
Day	**-1 or 1[a]**	**1[a]**		**2**	**3**	**4**	**5**	**6**	**7**	**8-14**	**EOT[b] (+1 day)**	**TOC[c] EOT + 7 (±2) days**	**LFU[d] EOT + 14 (±2) days**	
Assessment/Procedure		**Pre Dose**	**Post Dose**											
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Medical history	X													
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X
Demographics[f]	X													
Height and weight[g]	X													
Complete physical examination[g]	X				X		X		X		X			X
Limited physical examination[g]				X		X		X		X		X	X	
Chest x-ray, MRI, or CT scan[p]	X											X		
Assessment of signs & symptoms (Unblinded)[h]	X	X		X	X	X	X	X	X	X	X	X	X	X
Assessment of signs & symptoms (Blinded)[q]		X									X	X		
Assessment of clinical outcome (Unblinded)					X				X		X	X	X	X
Assessment of clinical outcome (Blinded)[q]											X	X		
Vital signs[i]	X	X			X				X		X	X	X	X
Randomization to treatment arm		X												
Pregnancy test[j]	X	X									X[j]			X[j]
Screening laboratories[k] (Local laboratory)	X													
Hematology[l] (Central laboratory)		X			X				X		X	X	X	X
Serum chemistry[l] (Central laboratory)		X			X				X		X	X	X	X
Urinalysis[l] (Central laboratory)		X			X				X		X	X	X	X
Pharmacokinetic sampling[m]			X		X		X							
12-lead electrocardiogram	X										X			X
Blood culture[n]		X		X	X	X	X	X	X	X	X			
Infection-site specific sample for culture[o]		X			X				X		X	X	X	X
Study drug administration			X	X	X	X	X	X	X	X	X			
Assessment of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes appear on the following page.

a. Screening/baseline procedures may be performed up to 24 hours prior to the first dose of study drug. All screening procedures must be completed PRIOR to randomization and the first dose of study drug (Day 1). The date of the first dose of study drug will be considered Day 1, and subsequent study days are defined by calendar days thereafter.
b. All subjects will be assessed on their last day of treatment (any time from Day 7 to Day 14). The EOT visit activities should occur within 24 hours of last dose of study drug. If EOT is on Day 7, visit activities will be combined. If a subject's treatment is changed after 72-hours post-randomization, EOT procedures will be performed and the subject will complete further visits as planned.
c. The TOC visit will occur 7 days (±2 days) after EOT, between Day 12 and Day 23. Any subject receiving treatment for less than 7 days should have a TOC visit on Day 12 (+2 days).
d. The LFU visit will occur 14 days (±2 days) after EOT, between Day 19 to Day 30. The LFU visit should be performed in-house (with limited physical examination) if at all possible. If not possible, a phone call to assess the subject's wellbeing may be substituted. Any subject receiving treatment for less than 7 days should receive an LFU visit on Day 19 (+2 days). For outpatient subjects with an LFU visit occurring before Day 28, a phone call to assess survival will be made on Day 28.
e. Subjects are expected to complete all study visits. In circumstances where a subject discontinues the study early, early termination visit procedures are required.
f. Demographic data will be collected, including name, sex, age, race, weight, and alcohol use.
g. Height will be taken at screening only. A limited, symptom-based, physical examination will be performed at indicated visits. If a subject does not display symptoms, no limited physical examination needs to be performed.
h. Assessment of signs and symptoms will include assessments to classify as new onset, continuing (increased, decreased, no change), or resolved (returned to pre-infection state) indication-based symptoms as outlined in the protocol.
i. Vital signs include blood pressure, heart rate, respiratory rate, and temperature. Vital signs should be captured at approximately the same time as the Signs and Symptoms assessment.
j. A urine and serum pregnancy test will be performed before the first dose of study drug in women of childbearing potential, however, only urine results are required to initiate treatment. A urine and serum pregnancy test will be performed as part of EOT/early termination procedures.
k. Screening laboratories will be processed/analyzed by the local laboratory within 48 hours of randomization and include AST, ALT, total bilirubin, creatinine, WBC count with differentials, platelet count, and LCE in urine.
l. Laboratory samples will be collected, processed, and sent to the central laboratory for analysis. Hematology includes complete blood count (with red blood cell count, total WBC count with differential counts, platelet count, hemoglobin, and hematocrit). Serum chemistry includes creatinine, estimated creatinine clearance, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, lipase, amylase, albumin, total protein, glucose, sodium, potassium, chloride, carbon dioxide, calcium, and phosphorus. Urinalysis includes dipstick analysis of protein, glucose, ketones, bilirubin, blood, nitrites, LCE, and urobilinogen; microscopic evaluation for red blood cells, WBCs, bacteria, and casts; specific gravity; and pH.
m. For subjects randomized to Carbavance (meropenem/RPX7009vaborbactam only: Day 1 plasma PK samples will be collected within 30 minutes and 2 to 3 hours after the end of the first infusion. Day 3 and Day 5 plasma PK samples will be collected within 30 minutes after the end of one of that day's infusions.
n. Blood cultures are required from all study participants at baseline. All subjects with bacteremia will have daily blood cultures collected until the first negative blood culture (culture reading at 24 hours or more). Subsequent blood cultures may be collected at the Investigator's discretion, but are not required. Isolates from each positive culture will be sent to the central laboratory.
o. An adequate and appropriate infection site-specific specimen based upon diagnosis (e.g., cUTI or AP, cIAI, HABP, or VABP) should be obtained immediately prior to the first dose of study drug (or for cIAI, 96 hours before or 24 hours after the first dose of study drug) and submitted to the local microbiology laboratory for culture and susceptibility testing. If the screening sample for culture is taken per standard of care before the subject or the subject's legal representative signs informed consent, that isolate may be used for baseline and sent to the central laboratory once consent is obtained as long as the sample was collected within72 hours (96 hours for cIAI) of the first dose of study drug. Additional samples for culture should also be collected at the specified time points. If at any point in the study a subject fails while on therapy, an adequate and appropriate specimen should be obtained prior to the initiation of a new treatment. When bacteremia is a subject's primary index infection, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). When cIAI is the subject's baseline infection, post-baseline samples should be collected as clinically indicated.
p. A chest x-ray, MRI, or CT scan done within 48 hours of enrollment is acceptable.
q. The Blinded Investigator will be responsible for establishing a baseline level of health and performing outcome assessments independent of the unblinded staff per the Blinded Adjudication Charter.

ALT = alanine aminotransferase; AP = acute pyelonephritis; AST = aspartate aminotransferase; CT = computed tomography; cUTI = complicated urinary tract infection; cIAI = complicated intra-abdominal infection; EOT = End of Treatment; HABP = hospital-acquired bacterial pneumonia; LCE = leukocyte esterase; LFU = Late Follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; TOC = Test of Cure; VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.

4. SAMPLE SIZE JUSTIFICATION

Due to the infeasibility of recruiting a large number of subjects infected with CRE pathogens, no formal power calculations have been performed for this study. The sample size is based on practical considerations.

The study will enroll approximately 150 subjects with serious infections, of whom a proportion will have CRE infections across the following indications: cUTI or AP, cIAI, HABP, VABP, and bacteremia. Subjects will be stratified at randomization based on their presenting indication and by region (North America vs. Europe vs. Rest of World).

Enrollment will continue until at least 45 subjects (30 meropenem-vaborbactam, 15 BAT) with cUTI or AP are documented to have a CRE organism at baseline and until at least 30 subjects with cIAI (20 meropenem-vaborbactam, 10 BAT) are enrolled. Once the specified number of subjects are enrolled in the cUTI and/or cIAI indications, data from these subjects may be submitted to regulatory agencies in support of a marketing application, and the enrollment of additional subjects into the specific indication(s) where enrollment was met may be stopped.

5. STUDY ASSESSMENT

5.1. Efficacy Assessments

5.1.1. Efficacy Assessments for cUTI or AP

Primary Endpoint

The primary endpoint for cUTI or AP is defined differently by the EMA and FDA. The primary endpoint for the EMA is proportion of subjects in the mCRE-MITT Population that demonstrate microbiological eradication (See Table 2). The primary endpoint for the FDA is the proportion of subjects in the mCRE-MITT Population who demonstrate a response of overall success at the TOC visit (See Table 2).

To meet primary endpoints for either EMA or FDA definitions, a subject's gram-negative antimicrobial therapy to treat the baseline infection cannot be altered (other than dose adjustment or modification of BAT based on susceptibility of baseline pathogen within the first 72 hours after first dose of study drug) after randomization due to concerns of microbiological failure, clinical failure, or tolerability AND must meet the criteria in Table 2.

Table 2. Primary Endpoint Definitions By Regulatory Agency – cUTI and AP

Parameter	Analysis for EMA	Analysis for FDA
Outcome measure	Microbiological eradication[a)]	Overall Success (Clinical cure[b)] and microbiological eradication[a)])
Efficacy time point(s)	TOC[c)]	TOC[c)]

a. Microbiological eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^3$ CFU/mL of urine for EMA and $<10^4$ CFU/mL of urine for FDA.

b. Clinical cure is defined as complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy is warranted.
c. The TOC visit occurs 7 days (±2 days) post-EOT (Day 12 to Day 23).

CFU = colony-forming unit; EMA = European Medicines Agency; EOT = End of Treatment; FDA = Food and Drug Administration; TOC = Test of Cure.

Secondary Endpoints

- The all-cause mortality rate in the mCRE-MITT and m-MITT Populations at Day 28;
- Proportion of subjects in the m-MITT and ME Populations who demonstrate a response of overall success at the TOC visit;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at Day 3, EOT, TOC, and LFU;
- Proportion of subjects in the mCRE-MITT, m-MITT, CRE-ME, and ME Populations with a microbiological outcome of eradication at Day 3, EOT, TOC, and LFU;
- Relapse/recurrence rates of baseline cUTI or AP at the LFU visit; and
- Per-pathogen outcome in the mCRE-MITT, m-MITT, CRE-ME, and ME Populations at Day 3, EOT, TOC, and LFU.

5.1.2. Efficacy Assessments for *cIAI*

Primary Endpoint

The primary endpoint for cIAI for both the EMA and the FDA is the proportion of patients with a clinical outcome of cure in the mCRE-MITT population at TOC visit, approximately Day 28.

To meet the primary endpoint, a subjects' gram-negative antimicrobial therapy to treat the baseline infection cannot be altered (other than dose adjustment or modification of BAT based on susceptibility of baseline pathogen within the first 72 hours after first dose of study drug) after randomization due to concerns of microbiologic failure, clinical failure, or tolerability. In addition, subjects cannot require any further unplanned surgical or radiologic intervention after randomization until TOC due to concerns of microbiologic failure or clinical failure.

Secondary Endpoints

- The all-cause mortality rate in the mCRE-MITT and m-MITT Populations at Day 28;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at Day 3, EOT, TOC, and LFU;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at TOC, where the use of an aminoglycoside beyond 72 hours in subjects with a pathogen susceptible to meropenem-vaborbactam is assigned to failure;
- Relapse/recurrence rates of baseline cIAI at the LFU visit; and
- Per-pathogen outcome in the mCRE-MITT, m-MITT, CRE-ME, and ME Populations at Day 3, EOT, TOC, and LFU.

5.1.3. Efficacy Assessments for HABP and VABP

Primary Endpoint (Combined for HABP/VABP and Bacteremia)

The primary endpoint for HABP and VABP is the all-cause mortality rate in the mCRE-MITT Population at Day 28 for all subjects with HABP and VABP, combined with all subjects with bacteremia (not related to cUTI/AP, cIAI or HABP/VABP).

Secondary Endpoints

- The all-cause mortality rate in the mCRE-MITT and m-MITT Populations at Day 28;
- The proportion of subjects in the mCRE-MITT Population who demonstrate a clinical outcome of cure at the TOC visit.

  A clinical outcome of cure is defined as:

  - A subject whose gram-negative antimicrobial therapy to treat the baseline infection is not altered (other than dose adjustment or modification of BAT based on susceptibility of baseline pathogen within the first 72 hours after first dose of study drug) after randomization due to concerns of microbiological failure, clinical failure, or tolerability AND
  - Complete resolution or significant improvement of the baseline signs and symptoms of HABP or VABP such that no further antimicrobial therapy is warranted;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at Day 3, EOT, TOC, and LFU;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at TOC, where the use of an aminoglycoside beyond 72 hours in subjects with a pathogen susceptible to meropenem-vaborbactam is assigned to failure;
- Per-pathogen outcome in the mCRE-MITT, m-MITT, CRE-ME, and ME Populations at Day 3, EOT, TOC, and LFU;
- Relapse/recurrence rates of baseline bacterial pneumonia at the LFU visit;
- Total ventilator days measured from time of randomization;
- Change in the partial pressure arterial oxygen to fraction of inspired oxygen (PaO2:FiO2) ratio from baseline to Day 3, Day 7, and EOT; and
- Time (days) to extubation in subjects who are on the ventilator at baseline (i.e., Day 1).

5.1.4. Efficacy Assessments for Bacteremia

Primary Endpoint

The primary endpoint for bacteremia is the all-cause mortality rate in the mCRE-MITT Population at Day 28 for all subjects with HABP and VABP, combined with all subjects with bacteremia (not related to cUTI/AP, cIAI or HABP/VABP).

Secondary Endpoints

- The all-cause mortality rate in the mCRE-MITT and m-MITT Populations at Day 28;
- The proportion of subjects in the mCRE-MITT Population who demonstrate a response of overall success at the TOC visit.

  For subjects whose gram-negative antimicrobial therapy to treat the baseline infection is not altered (other than dose adjustment or modification of BAT based on susceptibility of baseline pathogen within the first 72 hours after first dose of study drug) after randomization due to concerns of microbiological failure, clinical failure, or tolerability, a response of success is defined by clearance of bacteremia (microbiological eradication) and a clinical assessment of cure.

  Clearance of bacteremia (microbiological eradication) is defined as the demonstration that bacterial pathogen(s) found at baseline is absent with repeat culture.

  Clinical cure is defined as complete resolution or significant improvement of the baseline signs and symptoms of bacteremia, such that no further antimicrobial therapy is warranted.
- Proportion of subjects in the m-MITT, CRE-ME, and ME Populations who demonstrate a response of overall success at the TOC visit;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at Day 3, EOT, TOC, and LFU;
- Proportion of subjects in the mCRE-MITT, m-MITT, CE, CRE-ME, and ME Populations with a clinical outcome of cure at TOC, where the use of an aminoglycoside beyond 72 hours in subjects with a pathogen susceptible to meropenem-vaborbactam is assigned to failure;
- Proportion of subjects in the mCRE-MITT, m-MITT, CRE-ME, and ME Populations with a microbiological outcome of eradication at Day 3, EOT, TOC, and LFU;
- Relapse/recurrence rates of baseline bacteremia at the LFU visit;
- Per-pathogen outcome in the mCRE-MITT, m-MITT, CRE-ME, and ME Populations at Day 3, EOT, TOC, and LFU; and
- Time to bacterial clearance in mCRE-MITT, m-MITT, CRE-ME, and ME Populations.

Exploratory analyses will be conducted based on subject evaluability and may include clinical and microbiological responses in various analysis populations at EOT, TOC, and LFU.

[redacted]

[redacted]

[redacted]

[redacted]

5.1.6. Clinical Outcome

Clinical outcome will be used to determine a response of success for subjects with cIAI, HABP or VABP. Clinical outcome, as a component of an assessment of overall response, will also be used to determine a response of success for subjects with cUTI or AP (FDA only), or bacteremia. The Investigator will be provided with a choice of clinical outcomes based on definitions to make a clinical assessment of the subject at the Day 3, Day 7, EOT, TOC, and LFU visits. The Investigator will assign a clinical outcome as defined in Table 3.

If all symptoms present at baseline are classified as mostly resolved or continuing (decreased), with no new onset symptoms, such that no further surgical intervention (cIAI only) or antimicrobial therapy is warranted, the subject will have a clinical outcome of cure at Day 7, EOT, TOC, and LFU visits. Subjects with lessening, incomplete resolution, or no worsening of these symptoms (i.e., continuing [decreased or no change] and resolved), who still warrant antimicrobial therapy, will have a clinical outcome of improvement at Day 3 and Day 7. Subjects with worsening of symptoms or the development of new onset symptoms sufficient to require initiation of non-study antimicrobials (and/or for cIAI subjects unplanned surgical procedures/percutaneous drainage), in addition to the criteria in Table 3 will have a clinical outcome of failure. In addition to the above components of clinical outcome, subjects with HABP or VABP will be monitored for oxygen requirements and ventilator settings per site standard of care to evaluate clinical outcome.

Table 3. Criteria for Clinical Outcome

Category	Criteria
Cure	Complete resolution or significant improvement of the baseline signs and symptoms, such that no further surgical intervention (cIAI only) or antimicrobial therapy is warranted. **This outcome category will only be used at Day 7, EOT, TOC, and LFU visits.**
Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms, but continued therapy is warranted. **This outcome category will only be used at Day 3 and Day 7 visits.**
Failure	Subjects who experience any **one** of the following: • At any study visit, worsening of baseline clinical signs and symptoms or the development of new clinical signs and symptoms of infection, sufficient to stop study medication and initiate non-study antimicrobial or for cIAI require unplanned surgical procedures or percutaneous drainage; • Surgical site wound infection (cIAI only); • At TOC and LFU visits, persistence, incomplete resolution of baseline clinical signs and symptoms of infection; • Withdrawal from the study due to an adverse event or due to lack of clinical improvement; or • Death of the subject during the study.
Indeterminate	Clinical outcome cannot be determined.

EOT = End of Treatment; LFU = Late Follow-up; TOC = Test of Cure.

If the Principal Investigator's and Blinded Investigator's assessments of clinical outcome are different, the adjudicated results from the blinded adjudication committee (BAC) are used. However, since BAC only adjudicate the clinical outcome at TOC visit per the Charter, if there are discrepancies between blinded and unblinded assessments at the visits other than TOC, the assessments from the unblinded investigator will be used.

5.1.7. Microbiologic Outcome

The microbiologic outcome will be used, as a component of an assessment of overall response, to determine a response of success for subjects with cUTI or AP (FDA only), or bacteremia. The microbiologic outcome will be used to determine a response of success for subjects with cUTI or AP for the EMA. The criteria for microbiological outcome for subjects with cUTI or AP are defined in Table 4, and the sponsor's algorithm for microbiologic assessment is included in Appendix 1.

Table 4. Criteria for Microbiologic Outcome for cUTI or AP

Category	Criteria
Eradication	• Eradication is the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^4$ CFU/mL on urine culture for FDA or $<10^3$ CFU/mL for EMA • AND a negative blood culture (after positive blood culture at baseline).
Persistence	• Persistence is the demonstration at EOT that 1 or more of the bacterial pathogen(s) found at baseline remains $\geq 10^4$ CFU/mL of urine culture for FDA or $\geq 10^3$ CFU/mL for EMA • OR a positive blood culture.
Recurrence	• Recurrence is the isolation of the same baseline bacterial pathogen(s) from culture after a response of eradication • OR a positive blood culture with the same baseline organism that was identified as a uropathogen after a response of eradication.
Indeterminate	• An indeterminate outcome will occur if there is no culture or the culture cannot be interpreted for any reason.

AP = acute pyelonephritis; CFU = colony-forming unit; cUTI = complicated urinary tract infection; EMA = European Medicines Agency; EOT = End of Treatment; FDA = Food and Drug Administration.

The criteria for microbiological outcome for subjects with bacteremia are presented in Table 5.

Table 5. Criteria for Microbiologic Outcome for Bacteremia

Category	Criteria
Eradication	• Eradication is the demonstration that the bacterial pathogen(s) found at baseline is absent with repeat blood culture.
Persistence	• Persistence is the demonstration at EOT that the bacterial pathogen(s) found at baseline is present with repeat blood culture.
Recurrence	• Recurrence is the isolation of the same baseline bacterial pathogen(s) from blood culture after a response of eradication.
Indeterminate	• An indeterminate outcome will occur if there is no blood culture or the blood culture cannot be interpreted for any reason.

EOT = End of Treatment.

5.1.8. Overall Response

Overall response will be used to determine a response of success for subjects with cUTI or AP (FDA only or bacteremia. This efficacy measure is derived from a composite of the clinical outcome and the microbiological outcome.

The algorithm for overall response at the TOC visit is summarized in Table 6.

Table 6. Overall Response at Test of Cure (TOC) Visit

Clinical Outcome	Microbiologic Outcome			
	Eradication	**Persistence**	**Recurrence**[a]	**Indeterminate**
Cured	Success	Failure	Failure	Success based on presumed eradication[b]
Failure	Failure	Failure	Failure	Failure based on presumed persistence[c]
Indeterminate	Failed if clinical outcome for any previous visit = failed; otherwise = indeterminate	Failure	Failure	Failed if clinical outcome for any previous visit = failed; otherwise = indeterminate

a. For an outcome of recurrence, subjects must have documented prior eradication at any prior time point.
b. Presumed eradication occurs when there is no material available for culture, and the subject has an investigator assessment of clinical outcome of cure.
c. Presumed persistence occurs when there is no material available for culture, or no culture was obtained, and the subject has an investigator assessment of clinical outcome of failure.

5.1.9. Overall Mortality Rate

The overall all-cause mortality rate across all indications will also be evaluated.

5.2. Safety Assessments

Safety assessments will include adverse events, clinical laboratory evaluations (including analysis of changes in renal function), vital signs, physical examinations, and electrocardiograms (ECGs).

5.2.1. Adverse Events

An adverse event is defined as any untoward medical occurrence deemed clinically relevant by the Investigator in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded and entered on the appropriate eCRF. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 17.0). The severity of all adverse events will be graded according to the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

5.2.2. Clinical Laboratory Evaluations

Blood samples for serum chemistry and hematology analyses will be collected as specified by the Schedule of Procedures (Table 1).

Eligibility criteria related to laboratory assessments (i.e., screening laboratory assessments) will be processed/analyzed by a local laboratory within 48 hours of randomization and must include, at a minimum, AST, ALT, total bilirubin, creatinine, white blood cell (WBC) count with differentials, platelet count, and leukocyte esterase (LCE) in urine.

All other study-related analyses will be performed by the central laboratory.

The chemistry, hematology, and urinalysis parameters assessed in this study include the following:

- Chemistry: creatinine, estimated creatinine clearance, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, lipase, amylase, albumin, total protein, glucose, sodium, potassium, chloride, carbon dioxide, calcium, and phosphorus.
- Hematology: complete blood count (red blood cell count, and white blood cell (WBC) count with differentials.
- Urinalysis: dipstick analysis of protein, glucose, ketones, bilirubin, blood, nitrites, LCE, and urobilinogen; microscopic evaluation for red blood cells, WBCs, bacteria, and casts; specific gravity; and pH.

For women of childbearing potential, a serum and urine pregnancy test will be performed before the first dose of study drug, however, only urine results are required to initiate treatment. A urine and serum pregnancy test will be performed at EOT or early termination.

5.2.3. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, will be measured at the indicated visits.

5.2.4. Electrocardiograms (ECGs)

Twelve-lead ECGs will be performed per the Schedule of Procedures (Table 1) in triplicate, at least 1 minute apart, after the subject has been in the supine position for at least 10 minutes. The ECG will include all 12 standard leads and should be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be recorded:

- PR interval,
- QRS interval,
- Heart rate,
- RR interval,
- QT interval, and
- QTc interval.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities. If clinically indicated per the Investigator for a safety event, a 12-lead ECG will be performed according to site standards and recorded in the electronic data capture (EDC) database according to the EDC guidelines.

5.2.5. Acute Kidney Injury Evaluations

Analysis of the changes in serum creatinine as a marker of changes in renal function will be performed using the Risk, Injury, Failure, Loss, or End-Stage (RIFLE) criteria for serum creatinine, as follows:

- Class 1: Risk – increase in serum creatinine $\geq$ 1.5 times baseline value
- Class 2: Injury – increase in serum creatinine $\geq$ 2 times baseline value
- Class 3: Failure – increase in serum creatinine $\geq$ 3 times baseline value, OR an acute increase in serum creatinine $\geq$44 umol/L from baseline $\geq$354 umol/L
- Class 4: Complete loss of kidney function for over 4 weeks
- Class 5: End-stage – complete loss kidney function for over 3 months

Note that as the duration of this study is approximately 4 weeks, Class 4 and 5 are not applicable in this study. Only the first three categories will be analyzed.

5.2.6. Physical Examination

A complete physical examination must include source documentation of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral angle tenderness, and neuromuscular assessments. Height and weight will be included at screening. Demographic data including name, sex, age, race, weight, and alcohol use will be recorded at screening. A limited, symptom-based, physical examination will be performed at other indicated visits. If a subject does not display symptoms, no limited physical examination needs to be performed.

Clinically significant physical examination findings (as determined by the Investigator) noted during a preceding physical examination (complete or limited) should be followed until resolution.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

5.3. Medical History

Relevant medical history, surgical history, and allergies will be collected at screening. Medical/surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 17.0).

5.4. Prior and Concomitant Medications

All relevant medications used in the 14 days prior to first dose of study drug and any medications used for standard subject care during the study are to be recorded. Concomitant treatments (non-pharmacological treatments) which include any surgical or diagnostic procedures will be captured in the source documents. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (June 2014).

5.5. Pharmacokinetic Assessments

Pharmacokinetic sampling will be completed in subjects randomized to meropenem-vaborbactam only. Samples will be collected for PK analysis on Day 1 within 30 minutes and 2 to 3 hours after the end of the first infusion. On Day 3 and Day 5, PK samples will be collected within 30 minutes after the end of one of that day's infusions. Samples will be taken as close to the 30-minute mark as possible and within the 1-hour window 2 to 3 hours after the end of

the selected infusion.

If subject is on a ventilator at the time of PK sampling, ventilator settings should be noted at the time of the blood draw.

6. ANALYSIS POPULATIONS

The following analysis populations will be included in the analyses. A schematic summary of the analysis populations is provide in Figure 2.

6.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population for efficacy will include all subjects screened and randomized to study drug (meropenem-vaborbactam or BAT).

6.2. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (MITT) Population will include subjects who meet the ITT criteria and receive at least 1 dose of study drug as randomized.

6.3. Safety Population

The Safety Population will include subjects who meet the ITT criteria and receive at least one dose of study drug, based on the actual treatment received.

6.4. Microbiological Modified Intent-to-Treat Population

The Microbiological Modified Intent-to-Treat (m-MITT) Population will include subjects who meet the MITT criteria and have a baseline gram negative bacterial pathogen(s).

6.5. Microbiological Carbapenem-resistant *Enterobacteriaceae* Modified Intent-to-Treat Population

The Microbiological Carbapenem-resistant *Enterobacteriaceae* Modified Intent-to-Treat (mCRE-MITT) Population will include subjects who meet the m-MITT criteria and who have a baseline *Enterobacteriaceae* that is confirmed to be meropenem-resistant. The mCRE-MITT is the primary efficacy population.

6.6. Clinical Evaluable Population

The Clinical Evaluable (CE) Population will include subjects who meet the MITT criteria, as well as the following criteria:

- Have no key inclusion or exclusion violations;
- Obtain a clinical outcome (cure, improvement, or failure) at EOT and a clinical outcome of cure or failure at TOC, unless criteria for failure on clinical outcome were met at an earlier time point;
- Receive ≥80% of expected IV doses for the completed treatment duration, miss no more than 1 IV dose in the first 48 hours of treatment, and miss no more than 2 consecutive IV doses overall; and

- Receive ≥3 days of study drug (and for cIAI adequate source control) if classified as a failure on clinical outcome, or receive ≥5 days of study drug (and for cIAI adequate source control) if classified as a cure on clinical outcome.

6.7. Microbiological Evaluable Population

The Microbiological Evaluable (ME) Population will include subjects who meet the m-MITT criteria, as well as the following criteria:

- Have no key inclusion or exclusion violations;
- Obtain a clinical outcome (cure, improvement, or failure) and a microbiological outcome (eradication or persistence) at EOT and an overall outcome of cure or failure at TOC, unless criteria for failure on clinical outcome were met at an earlier time point;
- Receive ≥80% of expected IV doses for the completed treatment duration, miss no more than 1 IV dose in the first 48 hours of treatment, and miss no more than 2 consecutive IV doses overall; and
- Receive ≥3 days of study drug (and for cIAI adequate source control) if classified as a failure on overall outcome, or receive ≥5 days of study drug (and for cIAI adequate source control) if classified as a cure on overall outcome.

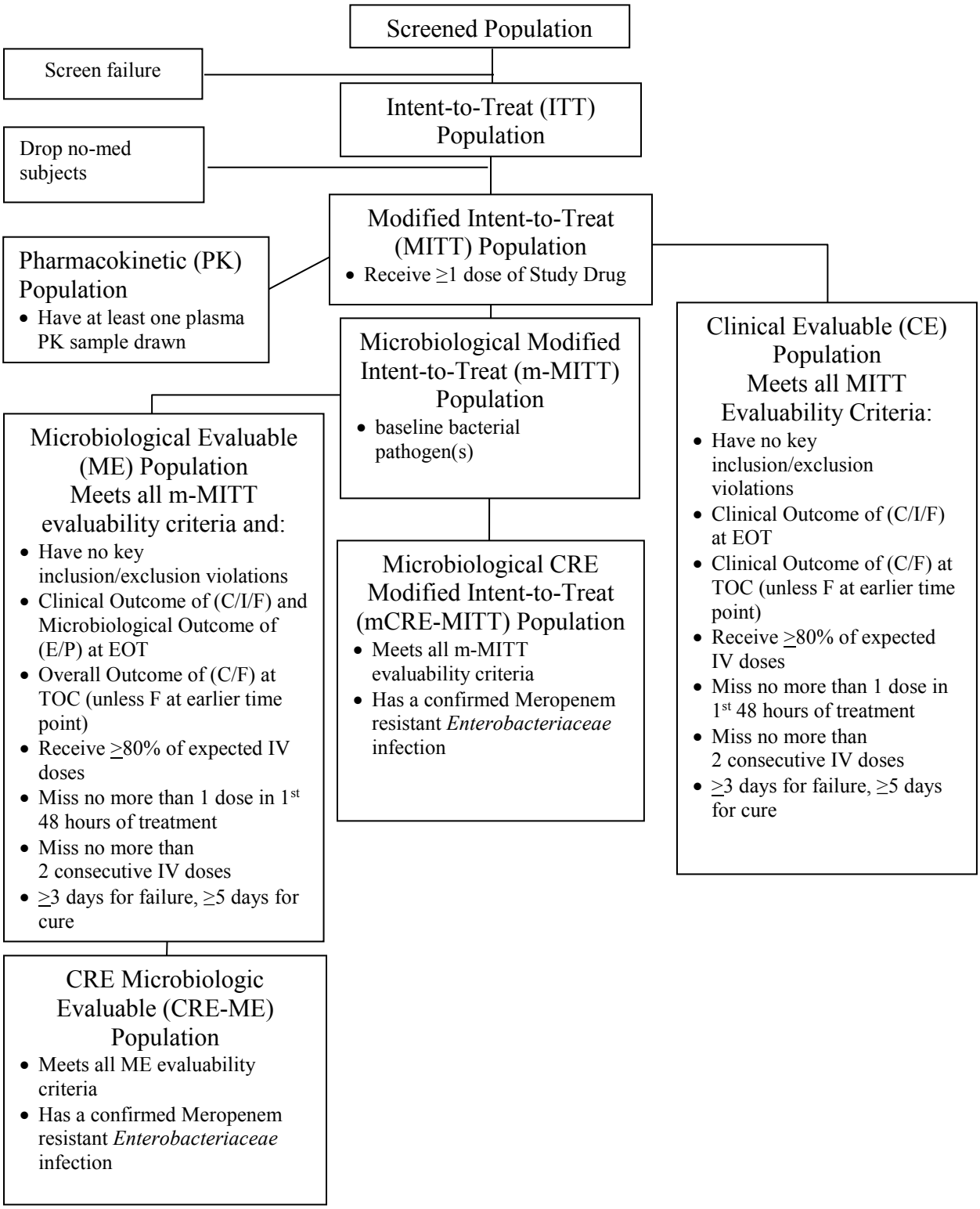
6.8. Carbapenem-resistant *Enterobacteriaceae* Microbiological Evaluable Population

The Carbapenem-resistant *Enterobacteriaceae* Microbiological Evaluable Population (CRE-ME) Population will include subjects who meet the ME criteria and who have a baseline *Enterobacteriaceae* that is confirmed to be meropenem-resistant.

6.9. Pharmacokinetics Population

The Pharmacokinetics (PK) Population will include subjects who meet the MITT criteria and have at least one plasma PK sample drawn.

Figure 2: Statistical Analysis Populations



C = Cure; E = Eradication; EOT = End of Treatment; F = Failure; I = Improvement; IV = intravenous; P = Persistence; PK = pharmacokinetic; TOC = Test of Cure

7. STATISTICAL ANALYSIS

7.1. General Statistical Considerations

All summary statistics will be presented by treatment group. For continuous variables, the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g. standard deviation) will be displayed to two decimal places greater than the original value. All analyses will be performed using SAS® Version 9.3.

7.2. Handling of Dropouts/Missing Data

Subjects who dropped out or had missing outcome data will be included in the denominator for response rate calculation. A clinical failure occurring at an earlier time point will be carried forward to the subsequent visits. Refer to Table 3 for more details.

Missing values for the other variables will not be imputed and only observed values will be used in data analysis and presentation.

7.3. Baseline Definition

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first dose of study drug.

For microbiological data, the algorithm for baseline pathogen(s) determination is presented in Table 7.

Table 7 Baseline CRE Pathogen(s) Determination

KNOWN CRE Subjects		
Screening	**Day 1**	**Baseline Selection**
CRE pathogen	CRE pathogen	Day 1 will be considered as Baseline
CRE pathogen	non-CRE pathogen	Screening will be considered as Baseline
CRE pathogen	No growth	Screening will be considered as Baseline
SUSPECTED CRE Subjects		
CRE pathogen	CRE pathogen	Day 1 will be considered as Baseline
Non-CRE pathogen	CRE pathogen	Day 1 will be considered as Baseline
CRE pathogen (*within 3 days of Day 1*)	Non-CRE pathogen	Screening will be considered as Baseline
CRE pathogen (*within 3 days of Day 1*)	No growth	Screening will be considered as Baseline
Non-CRE pathogen (*within 3 days of Day 1*)	Non-CRE pathogen	Day 1 will be considered as Baseline (in m-MITT, not mCRE-MITT)
Non-CRE pathogen (*within 3 days of Day 1*)	No growth	Screening will be considered as Baseline (in m-MITT, not mCRE-MITT)
No Growth (or growth >*3 days of Day 1*)	No Growth	Missing (Not in m-MITT or mCRE-MITT)

7.4. Subject Disposition

Subject disposition will be summarized for the MITT Population for each treatment group and in total. The following subject disposition categories will be included in the summary for the MITT Population:

- Subjects who completed the study treatment/ BAT,
- Subjects who did not complete the treatment/ BAT,
- Subjects who completed the study, and
- Subjects who did not complete the study.

For subjects who did not complete the treatment/ BAT, and subjects who did not complete the study, a summary will be provided by reason of discontinuation.

The above display will be repeated for the ITT population if the difference between the number of subjects in the ITT and the MITT population is greater than 2.

The following subject disposition categories will be included in the summary for the ITT Population:

- Subjects who received study drug/ BAT,
- Subjects who did not receive study drug/ BAT,

- Subjects who completed the study, and
- Subjects who did not complete the study.

In addition, the total number of subjects for each defined statistical population and disposition group will be tabulated overall and by infection type. Number and percent of patients with reasons leading to exclusion from the m-MITT and mCRE-MITT population, as specified in Section 6.4 and Section 6.5, will also be presented.

7.5. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the MITT, m-MITT, and mCRE-MITT Populations by treatment group and overall. Age, weight, height, body mass index (BMI), and creatinine clearance will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum). Gender, race, ethnicity, age group (<65, ⩾65, 65- < 75, and ≥75 years), alcohol usage, region, creatinine clearance group at baseline (<10 mL/min, >=10-19 mL/min, >=20-29 mL/min, >=30-49 mL/min, and >=50 mL/min), diabetes status, systemic inflammatory response syndrome (SIRS) status (yes and no), Charlson Comorbidity score (≤2, 3, 4, and 5) at baseline, and immunocompromised (yes and no) will be summarized with contingency tables. The algorithm to determine immunocompromised is included in Appendix 2.

7.6. Baseline Infection Characteristics

Baseline infection characteristics will be summarized with descriptive statistics for the MITT, m-MITT and mCRE-MITT populations. Infection type (cUTI/AP, cIAI, HABP/VABP, and bacteremia), CRE status (known CRE / suspected CRE), and prior treatment failure (yes/no) will be summarized to show the number and percentage of subjects in each category. The clinical conditions associated with the indication and sign and symptoms experienced by subjects at baseline will be summarized for each indication with contingency tables.

7.7. Medical History

Medical and surgical history will be summarized for the MITT Population for each treatment group and in total by system organ class (SOC) and preferred term.

All medical and surgical history will be listed by subject.

7.8. Prior and Concomitant Medications

Prior medications will include medications used before the first dose of study drug. Any medications used on or after the first dose of study drug will be included as concomitant medications. The number and percentage of subjects taking concomitant medications which started prior to the first dose of study drug and continued during the treatment period will be summarized for the MITT and m-MITT Populations by anatomic therapeutic chemical (ATC) Level 2 class and preferred term for each treatment group. The number and percentage of subjects receiving new concomitant medications, i.e., those started on or after the first dose of study drug will also be summarized by ATC Level 2 class and preferred term for each treatment group.

The number and percentage of subjects taking prior antibiotics will be summarized for the MITT, m-MITT, and MCRE-MITT Populations by ATC Level 2 class and preferred term for each treatment group. In addition, prior antibiotics used within 24 hours prior to the first dose of study drug will be summarized by ATC Level 2 class and preferred term. Other prior medications will be summarized similarly.

Prior antibiotics along with the duration of prior antibiotics will be listed by subject.

The number and percentage of subjects receiving concomitant procedures or non-drug therapy will also be summarized by ATC Level 2 class and preferred term for each treatment group.

All prior and concomitant medications and procedures will be listed by subject.

7.9. Dosing and Extent of Exposure

Overall extent of exposure in days will be calculated as the last dose date minus the first dose date of study drug plus 1. The overall extent of exposure to study drug will be summarized for the MITT, m-MITT, CE, mCRE-MITT and ME Populations by treatment group with descriptive statistics. In addition, contingency tables will be provided to show the number and percentage of subjects in each treatment group with exposure in the following categories: <7 days, 7 - <10 days, 10 - 14 days, and >14 days.

The overall compliance rate to study drug will be calculated as the total number of doses received divided by the total number of doses expected then multiplied by 100. The total number of expected doses is the number of medication days multiplied by the number of expected doses per day. Number of medication days is the total number of days from the date of the first infusion of study drug to the date of the last infusion of study drug.

Percent compliance will be calculated using the following formula:

$$\%\text{compliance} = \frac{\text{no. of doses received} * 100}{\text{expected doses per day} * \text{total number of medication days}}$$

The overall compliance rate will be summarized with summary statistics by treatment group and overall for the MITT Population. In addition, contingency tables will be provided to show the number and percentage of subjects in each treatment group with compliance in the following categories: <80% and ≥80%.

The total number of doses received will also be summarized by treatment group using descriptive statistics.

7.10. Efficacy Analyses

The efficacy analyses will be structured and presented by indications. However, a summary table including all primary efficacy endpoints for all indications will be presented along with their 95% two-sided exact binomial confidence intervals for m-MITT and mCRE-MITT populations. For indications with less than 8 total patients, only listings will be presented, but not tables. Due to limited sample size for the interim analysis, only m-MITT and mCRE-MITT populations will be analyzed.

7.10.1. Analyses of Overall Response

Success rate of overall response will be calculated as the proportion of subjects with a response of overall success. For cUTI/AP and cIAI, overall success is defined as clinical cure and microbiological eradication. For bacteremia, overall success is defined as clinical cure and clearance of bacteremia (microbiological eradication).

The following success rates will be calculated:

- Success rate at TOC visit for subjects with cUTI or AP (by FDA definition)
- Success rate at TOC visit for subjects with Bacteremia

Success rates at TOC will be summarized by infection type for the mCRE-MITT and m-MITT Populations. The 95% two-sided exact binomial confidence intervals of the success rates will also be presented.

In addition, the following success rates will be summarized:

- Success rate for subjects with cUTI or AP (by FDA definition) per baseline pathogen at TOC
- Success rate for subjects with Bacteremia per baseline pathogen at TOC

7.10.2. Analyses of Clinical Response

The clinical outcome will be categorized as cure, improvement, failure, and indeterminate. Cure rate of clinical response will be calculated as the proportion of subjects with clinical outcome of cure reported by investigator. The following cure rates will be calculated:

- Cure rate at Day 3, EOT, TOC, and LFU for subjects with cUTI or AP
- Cure rate at Day 3, EOT, TOC, and LFU for subjects with cIAI
- Cure rate at Day 3, EOT, TOC, and LFU for subjects with HABP or VABP
- Cure rate at Day 3, EOT, TOC, and LFU for subjects with Bacteremia

Cure rates will be summarized descriptively by infection type at Day 3, EOT, TOC, and LFU for the mCRE-MITT and m-MITT Populations. The 95% two-sided exact binomial confidence intervals of the cure rates will also be presented.

In addition, the number and percentage of subjects in each clinical response category (cure, improvement, failure, and indeterminate) will be summarized by infection type per baseline pathogen and for each scheduled visit.

Clinical response will be assessed by the Principal Investigator (PI). In addition, at each site a Blinded Investigator (BI) will be assigned to assess each subject's outcome at the EOT and TOC visits. A blinded adjudication committee will also be formed to independently evaluate clinical outcome data in cases where the PI and BI's assessment of outcome differ.

The clinical response will be analyzed using the assessment from the PI. In case the PI and BI's assessment of outcome differ, the assessment from the blinded adjudication committee will be used in the analysis.

Source Control

An independent assessor will review adequacy of source control in all cIAI patients. A sensitivity analysis will be performed based for subjects with adequate and inadequate source control (see details in Section 7.12).

7.10.3. Analyses of Microbiological Outcome

Microbiological Responses

Microbiological responses will be summarized for the mCRE-MITT and m-MITT Populations. The microbiological outcome will be categorized as eradication, persistence, recurrence, and indeterminate.

Microbiological eradication rate is calculated as the proportion of subjects with microbiological eradication. Relapse of cUTI or AP is defined as isolation of the same baseline bacterial pathogen(s) from culture after eradication, OR a positive blood culture with the same baseline organism that was identified as an uropathogen after eradication, which is accompanied by new or worsening signs and symptoms of infection since the previous visit requiring alternative antimicrobial therapy in the time period after EOT. Relapse of bacteremia is defined as isolation of the same baseline pathogen(s) from blood culture after eradication which is accompanied by new or worsening signs and symptoms of infection since the previous visit requiring alternative antimicrobial therapy in the time period after EOT.

The criteria of microbiological outcome is defined in Section 5.1.7.

The following microbiological responses will be calculated:

- Microbiological eradication rate at Day 3, EOT, TOC, and LFU for subjects with cUTI or AP, using both FDA and EMA definitions
- Microbiological eradication rate by pathogen at Day 3, EOT, TOC, and LFU for subjects with cUTI or AP, using both FDA and EMA definitions
- Microbiological eradication rate at Day 3, EOT, TOC, and LFU for subjects with cIAI
- Microbiological eradication rate by pathogen at Day 3, EOT, TOC, and LFU for subjects with cIAI
- Microbiological eradication rate at Day 3, EOT, TOC, and LFU for subjects with HABP or VABP
- Microbiological eradication rate by pathogen at Day 3, EOT, TOC, and LFU for subjects with HABP or VABP
- Microbiological eradication rate at Day 3, EOT, TOC, and LFU for subjects with Bacteremia
- Microbiological eradication rate by pathogen at Day 3, EOT, TOC, and LFU for subjects with Bacteremia
- Relapse/Recurrence rate of baseline cUTI or AP at LFU for the subjects with cUTI or AP
- Relapse/Recurrence rate of baseline cIAI at LFU for the subjects with cIAI

- Relapse/Recurrence rate of baseline bacterial pneumonia at LFU for the subjects with HABP or VABP
- Relapse/Recurrence rate of baseline bacteremia at LFU for the subjects with Bacteremia

Microbiological eradication rates will be summarized descriptively by infection type at Day 3, EOT, TOC, and LFU. The 95% two-sided exact binomial confidence intervals of the microbiological eradication rate will also be presented. Microbiological eradication rates by pathogen will be summarized similarly.

Relapse/recurrence rate will be summarized at after EOT.

In addition, microbiological responses will be summarized by infection type showing the number and percentage of subjects in each microbiological outcome category at each scheduled visit.

Microbiological Characteristics

Microbiological characteristics including culture and susceptibility testing results from the central laboratory based on urine specimens, respiratory tract specimens, and blood and other tissue specimens will be summarized for the m-MITT and mCRE-MITT Populations.

The baseline pathogens isolated from all specimens will be summarized with contingency tables by specimen source to show the number and percentage of subjects with the specific pathogen isolated.

The minimum inhibitory concentration (MIC) will be summarized by pathogen and by antibiotics using descriptive statistics (number of isolates, 50th percentile [MIC50], 90th percentile [MIC90], and range) for the two antibiotics: meropenem and meropenem-vaborbactam (vaborbactam fixed at 8 mcg/mL). The distribution of MIC will be summarized with contingency table to show the number and percentage of subjects in each MIC level for each pathogen by treatment and overall.

For subjects who had overall success, clinical cure, and microbiologic eradication, a contingency table will be presented by scheduled visit, baseline pathogen and actual MIC for the m-MITT and mCRE-MITT populations. Both FDA and EMA's criteria for microbiologic eradication will be summarized.

Fold change in MIC is defined as the ratio of post-baseline MIC over baseline MIC. For meropenem, meropenem-vaborbactam MIC, the number and percentage of subjects with at least 4 fold increase of MIC will be summarized and listed by baseline pathogen for each post-baseline visit. A distribution will also be presented for the actual fold increase in MIC if the increase is at least 4 fold.

7.10.4. All-Cause Mortality Rate

The following all-cause mortality rate will be calculated:

- All-cause mortality rate at Day 28 for the subjects with cUTI or AP

- All-cause mortality rate at Day 28 for the subjects with cIAI
- All-cause mortality rate at Day 28 for the subjects with HABP or VABP
- All-cause mortality rate at Day 28 for the subjects with Bacteremia
- All-cause mortality rate at Day 28 for the subjects with HABP or VABP, combined with all subjects with Bacteremia (not related to cUTI/AP, cIAI or HABP/VABP)

All-cause mortality rate at Day 28 based on Kaplan-Meier estimates along with the 95% confidence interval will be presented overall and by indication for the mCRE-MITT and m-MITT Populations. Subject whose survival status is unknown due to early termination or lost to follow up will be censored at the last day the subject was known to be alive.

7.10.5. Analyses of Other Efficacy Endpoints

The following efficacy endpoints will be summarized for the m-MITT and mCRE-MITT Populations.

Total Ventilator Days

Total ventilator days is defined as number of days from the date of the first dose of study drug to the date at which the ventilator is removed and remained off for all subsequent visits. Total ventilator days will be summarized with summary statistics by treatment group for the subjects with HABP or VABP.

Partial Pressure Arterial Oxygen to Fraction of Inspire Oxygen

The partial pressure arterial oxygen to fraction of inspire oxygen (PaO2:FiO2) at Day 3, Day 7, and EOT, and the change from baseline will be summarized by treatment group for the subjects with HABP or VABP.

Time-to-Event Efficacy Endpoints

The following time-to-event efficacy endpoints will be summarized using Kaplan-Meier method. Median time to each event as well as the 95% confidence interval will be presented.

- Time (days) to extubation in subjects who are on the ventilator at baseline for the subjects with HABP or VABP
- Time to bacterial clearance in the mCRE-MITT and m-MITT Populations for all subjects with bacteremia at baseline, regardless whether enrolled under indication of bacteremia.

Time to extubation is defined as number of days from the date of the first dose of study drug to the last date at which the ventilator is removed. Subjects who were on the ventilator at baseline but discontinued from the study without extubation will be considered censored.

Time to bacterial clearance is defined as number of days from the date of the first dose of study drug to the date at which bacterial pathogen(s) found at baseline is absent with repeat culture. For days where the culture assessment is missing, the last assessment will be carried forward to the missing days. If EOT is the date at which bacterial pathogen(s) is first found absent, no repeat culture is required. Subjects discontinued from the study prior to bacterial clearance will be considered censored.

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7.13. Subgroup Analyses

For subjects with cUTI/AP or bacteremia, overall responses at TOC using FDA criteria, clinical responses and microbiological responses at Day 3, EOT, TOC, and LFU using both FDA and EMA criteria will be summarized by the following subgroups for m-MITT and mCRE-MITT populations based on baseline characteristics:

- age group (<65, >=65, 65- < 75, and ≥75 years),
- gender,
- race,
- region,
- creatinine clearance group (<10 mL/min, >=10-19 mL/min, >=20-29 mL/min, >=30-49 mL/min, and >=50 mL/min),
- diabetes status,
- systemic inflammatory response syndrome (SIRS) status,
- Charlson Comorbidity score (≤2, 3, 4, and 5),
- status of immunocompromised.

7.14. Safety Analyses

All safety summaries and analyses will be performed on the Safety Population. All subjects will be summarized based on the actual treatment received.

All safety analyses will be performed for all subjects combined, and for subjects with cUTI/AP only.

7.14.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are adverse events with start date and time on or after the first dose of study drug.

An overview of adverse events will be provided which summarizes the incidence of the following information:

- All TEAEs,
- All TEAEs sorted by the frequency of total occurrence

- Drug-related TEAEs,
- Maximum severity of TEAEs,
- Deaths,
- Serious adverse events (SAEs), and
- Discontinuation due to TEAEs
- Drug related SAEs.
- AE of special interests (AESI).

  The following AESI will be summarized:

  - Hypersensitivity
  - Seizure
  - Pseudomembranous colitis/CDAD.

  The search term for these AESIs are included in Appendix 3.

Number and the percentage of subjects who experienced at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAEs, withdrawals due to TEAEs, and all SAEs will be summarized in the same manner.

Summaries will be provided by worst grade for the number and percentage of subjects with TEAEs and for subjects with drug-related TEAEs by system organ class and preferred term.

Although a subject may have two or more TEAEs, the subject is counted only once within a System Organ Class and Preferred Term category. The same subject may contribute to two or more preferred terms in the same System Organ Class category.

A list of subjects who have serious adverse events (SAEs), a list of subjects who discontinue from study drug with reasons for discontinuation, and a list of death with primary cause will be provided. All adverse events will be listed.

7.14.2. Clinical Laboratory Evaluations

Laboratory test results (hematology, serum chemistry, and urinalysis) at each scheduled visit and change from baseline will be summarized by treatment group.

Shift tables from baseline to each scheduled post-baseline visit will be provided for urinalysis, chemistry and hematology parameters. The following categories will be used: low, normal, and high based on the reference range.

The number and percentage of subjects with predefined potentially clinically significant (PCS) laboratory abnormalities at post baseline evaluations will be presented by treatment group for selected laboratory parameters. The percentages will be calculated relative to the number of subjects with non-PCS values at Baseline and at least one post-baseline assessment for the selected laboratory parameters.

The thresholds for the predefined changes and clinically significant laboratory abnormalities for selected parameters are listed in Table 8.

Table 8. Criteria for Potential Clinically Significant Abnormal Lab Tests

Parameter	Lower limit	Upper limit
Hematology		
Red Blood Cell Count	≤ 0.75× LLN	≥ 1.25×ULN
WBC's Count	<2.0 x 10^9/L	
Neutrophils Count	< 1.0 x 10^9/L	
Lymphocyte count	< 0.5 x 10^9/L	
Hematocrit	≤0.75x LLN	≥1.25x ULN
Hemoglobin	≤11.5 g/dL Male ≤9.5 g/dL Female	≥18.0 g/dL Male ≥16.0 g/dL Female
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
Serum Chemistry		
BUN		≥10.7 mmol/L
Calcium	≤7.0 mg/dL	≥15.5 mg/dL
CPK		≥3x ULN
Creatinine		≥2.0 mg/dL
Glucose	≤50 mg/dL	≥180 mg/dL
Potassium	≤3.0 mmol/L	≥5.5 mmol/L
Sodium	≤125 mmol/L	≥150 mmol/L
Liver Function Tests (LFTs)		
Alanine Transaminase (ALT/SGPT) ≥ 3x, 5x, 10x and 20x ULN		
Aspartate Transaminase (AST/SGOT) ≥ 3x, 5x, 10x and 20x ULN		
ALT or AST ≥ 3x, 5x, 10x, or 20x ULN		
Total bilirubin ≥ 1.5x and 2x ULN		
Alkaline Phosphatase (ALP) ≥ 1.5x and 3x ULN		
ALT/AST ≥ 3x ULN and Total bilirubin ≥ 2x ULN;		
Potential Hy's Law cases: ALT or AST ≥3×ULN, Total bilirubin ≥2×ULN, and ALP ≤ 2×ULN		

LLN: lower limit of the standard reference (normal) range.
ULN: upper limit of the standard reference (normal) range.

A listing will be provided for the PCS values. All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

7.14.3. Vital Signs

Descriptive statistics will be provided for the vital signs (blood pressure, heart rate, and respiratory rate) and changes from baseline for each scheduled visit.

The number and percentage of subjects with PCS changes in vital signs will be presented by treatment group, based on the following thresholds:

- Respiratory Rate $\leqslant$10 rpm;
- Respiratory Rate $\geqslant$30 rpm;
- Systolic blood pressure $\geqslant$180 mm Hg and increase $\geqslant$20 mm Hg from Baseline;
- Diastolic blood pressure $\geqslant$110 mm Hg and increase $\geqslant$15 mm Hg from Baseline;
- Systolic blood pressure $\leqslant$90 mm Hg and decrease $\geqslant$20 mm Hg from Baseline;
- Diastolic blood pressure $\leqslant$50 mm Hg and decrease $\geqslant$15 mm Hg from Baseline;
- Heart rate $\geqslant$120 bpm with increase $\geqslant$15 bpm from Baseline;
- Heart Rate $\leqslant$50 bpm with decrease $\geqslant$15 bpm from Baseline.

7.14.4. 12-Lead ECG

The statistical analysis plan for the ECG measurements will be documented in a separate file and analysis results will be submitted in a separate report.

All ECG measurements and the overall interpretation will be listed by subject.

7.14.5. Acute Kidney Injury

The incidence of acute kidney injury as defined by RIFLE criteria at day 3, day 7 and EOT as well as the maximum RIFLE grade achieved and the time to incidence of acute kidney injury will be summarized by treatment group for all subjects.

7.14.6. Physical Examination

Physical examination findings will be listed by subject.

7.15. Pharmacokinetic Concentration Analyses

Plasma PK concentrations will be listed by subject.

7.16. Protocol Deviations

Determination of major protocol deviations will be based on blinded data review and finalized prior to the database lock. A list of all protocol deviations will be included in the study report.

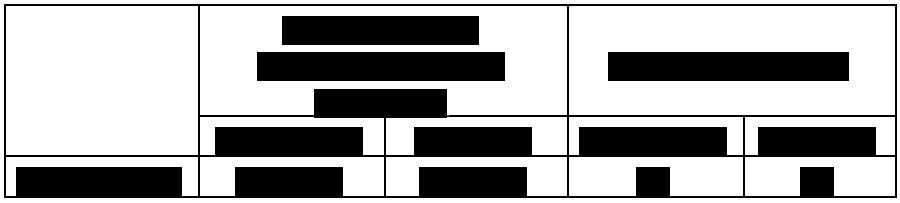
7.17. Interim Analyses

Forty-one subjects (25 meropenem- vaborbactam, 16 BAT) were included for this interim analysis. The goal of the interim analysis is to provide efficacy and safety data to support the NDA filing of Study 505, and there is no go/no go decision based on this analysis.

Enrollment will continue until at least 45 subjects (30 meropenem- vaborbactam, 15 BAT) with cUTI or AP are documented to have a CRE organism at baseline and until at least 30 subjects with cIAI with a documented CRE organism at baseline (20 meropenem-vaborbactam, 10 BAT) are enrolled. Once the specified number of subjects are enrolled in the cUTI and/or cIAI indications, data from these subjects may be submitted to regulatory agencies in support of a marketing application, and the enrollment of additional subjects into the specific indication(s) where enrollment was met may be stopped.

8. APPENDICES

[redacted]



	[redacted]
HABP/VABP	1. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] or [redacted]

8.2. Appendix 2 Algorithm to Determine Immunocompromised Patients

Statistics to programmatically make a list of patients who meet any of the following criteria:

1. In Medical History: Any patients with the following terms in medical history:
   - Leukemia
   - Lymphoma
   - Transplant
   - Immunocompromised
   - Splenectomy
2. In Con Medications any patients with the following ATC 2 terms:
   - Glucocorticoids
   - Selective Immunosuppressants
   - Calcineurin inhibitors
3. In laboratory data: Any patients with an absolute neutrophil count (ANC) less than 1000 cells/mm3 at baseline.

The list of subjects meeting any of the above criteria with treatment allocation blinded will be further reviewed by the medical team for consistency with the following definition:

Immunocompromised status was defined as any patients with any:

- Underlying lymphoma, leukemia, prior transplant or splenectomy.
- Active receipt of any immunosuppressants including calcineurin inhibitors, and selective immunosuppressants.
- Active receipt of high doses of systemic steroids (equivalent to $\geq$ 20mg prednisone daily) for the purposes of prevention of rejection or immunosuppression.
- Active receipt of bone marrow ablative chemotherapy

8.3. Appendix 3 SMQ for AESI Search Terms Hypersensitivity