Clinical Study Protocol

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
Amendment 2 Protocol Dated: 24 APR 2015, Version 3.0
Amendment 1 Protocol Dated: 22 AUG 2014, Version 2.0
Original Protocol Dated: 06 MAY 2014, Version 1.0

Phase 3
Investigational Product
Carbavance (Meropenem/RPX7009)

US IND # 120040 EudraCT # 2014-000546-30

Sponsor: Rempex Pharmaceuticals, Inc.
A wholly-owned subsidiary of
The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Version	Description
06 May 2014/Version 1.0	Original Protocol
22 Aug 2014/Version 2.0	Protocol incorporating Amendment 1
24 Apr 2015/Version 3.0	Protocol incorporating Amendment 2

2 SPONSOR—SIGNATURE PAGE

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*

Sponsor	Rempex Pharmaceuticals, Inc. A wholly owned subsidiary of The Medicines Company 8 Sylvan Way Parsippany, NJ 07054
Sponsor Representative	[redacted]

Signature Date

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INVESTIGATOR'S PROTOCOL AGREEMENT AND SIGNATURE PAGE

Protocol Number: Rempex-506 (Version 3.0, Dated 24-Apr-2015)

Protocol Title: 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*

The Investigator's Protocol Agreement and Signature Page must be signed by the Principal Investigator. The original or a copy must be kept on file at the Sponsor or the Sponsor's designee and the Investigator must retain the original or a copy. The completed Investigator's Protocol Agreement and Signature Page signifies review and acceptance of the protocol by the Principal Investigator prior to initiation of the study.

By my signature, I confirm that my staff and I have carefully read and understand this protocol, and agree to comply with the conduct and terms of the study specified herein. In particular, I/we have agreed to the following:

- Abide by all obligations stated on Form FDA 1572, Good Clinical Practice (GCP), or local authority regulatory requirements.
- Maintain confidentiality and assure security of the Sponsor's confidential documents such as the protocol, Case Report Forms, Investigator's Brochure, final study reports, manuscript drafts, unpublished data, correspondence, etc.
- Assure access by the Sponsor or monitors to original documents, data, and records.
- Obtain Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval of study, any amendments to the study, and periodic re-approval as required, unless performed by Sponsor.
- Keep the IEC/IRB informed of adverse events and periodically report the status of the study to them as required by local regulations and IEC/IRB requirements.
- Have read the Investigator's Brochure and are familiar with the results of the pharmacologic and toxicologic tests concerning Carbavance™ (meropenem/RPX7009) and acknowledge the probable risks of the study.
- Obtain written informed consent/assent from each participant or his/her legal representative.
- Make prompt reports of serious adverse events to the Sponsor or the Sponsor's designee as detailed in Section 14.6 of this protocol.
- Cooperate fully with any study-related GCP audit as performed by the Sponsor's designated quality assurance group and agree to comply with the principles of the Declaration of Helsinki.
- Abide by stipulations regarding data disclosure (Section 19.14).

Signature of Investigator Date

4 SYNOPSIS

Title	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*	
Indications	Subjects with serious infections, specifically complicated urinary tract infection (cUTI) or acute pyelonephritis (AP), complicated intra-abdominal infections (cIAI), hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and bacteremia, known or suspected to be caused by carbapenem-resistant *Enterobacteriaceae* (CRE).	US Investigational New Drug # 120040 EudraCT # 2014-000546-30
Study Duration	First subject enrolled: Third quarter 2014 Last subject enrolled: First quarter 2016	**Number of Global Sites:** Approximately 50 sites
Study Objectives	The objectives of this study are: • To evaluate the safety, tolerability and efficacy of Carbavance™ (meropenem/ RPX7009) in treatment of subjects with selected serious infections, suspected or known to be due to CRE; and • To assess the pharmacokinetics (PK) of meropenem and RPX7009 in subjects with selected serious infections, suspected or known to be due to CRE.	
Rationale	Beta-lactam antimicrobials are considered to be among the most useful classes of antimicrobial agents for treatment of bacterial infections. In particular, the development of broad-spectrum cephalosporin and carbapenem antimicrobials have represented a key advancement in replacing other classes of drugs with toxicities and limited spectra of activity against pathogens. In the current era of increased resistance to extended spectrum cephalosporins and penicillin/beta-lactamase inhibitor combinations, carbapenem antimicrobial agents are frequently the antibiotics of "last defense" for the most resistant pathogens in serious infections. However, the recent dissemination of serine carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemase [KPC]) in *Enterobacteriaceae* within many United States and global hospitals now poses a considerable threat to carbapenem and other members of the beta-lactam class of antimicrobial agents. Infections caused by CRE are associated with high mortality rates and have limited treatment options. The loss of the carbapenem class of antimicrobial agents for treatment of *Enterobacteriaceae* (the most frequently occurring pathogens in the hospital setting), *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* represents a critical setback in modern patient care. As a result of the current lack of an optimal treatment for patients who have infections due to a CRE, physicians manage these patients with the limited anti-infective options available, including aminoglycosides, polymyxin B, colistin, tigecycline, or various combinations of these. There are limited efficacy data available for many of these therapies when used to treat serious CRE infections, particularly in combination, but with limited or no alternative therapies currently	

	available, such treatments have become the Best Available Therapy (BAT) despite the toxicities associated with many of them. Meropenem is a broad-spectrum injectable carbapenem antibiotic used to treat a wide variety of infections. The spectrum of action includes many gram-positive bacteria, gram-negative bacteria, and anaerobic bacteria, and it is approved in many countries around the world at doses up to 2 g every 8 hours (q8h). Three-hour infusions of meropenem are commonly used to treat organisms with higher minimum inhibitory concentrations (MICs), such as *Pseudomonas aeruginosa*, to maximize the time above the MIC. RPX7009 is a novel beta-lactamase inhibitor that has inhibitory activity against many serine beta-lactamases and was optimized for inhibition of the KPC beta-lactamase and the potentiation of carbapenems against *Enterobacteriaceae*. RPX7009 is being developed for use with meropenem to address the challenges of treatment of serious infections caused by pathogens increasingly resistant to available treatments. Carbavance, the combination of meropenem and RPX7009 administered as a fixed combination by intravenous (IV) infusion, is being developed to treat serious gram-negative infections, such as cUTI, AP, cIAI, HABP, VABP, and bacteremia, including those infections caused by bacteria resistant to currently available carbapenems.
Study Design	This is a Phase 3, multi-center, randomized, open-label study of Carbavance (meropenem/RPX7009) versus BAT in the treatment of subjects with selected serious infections, specifically cUTI or AP, cIAI, HABP, VABP, and bacteremia, suspected or known to be caused by CRE. Approximately 150 subjects will be enrolled in a 2:1 ratio of Carbavance to BAT, respectively. The Treatment Arms in the study are as follows: • Treatment Arm A: Subjects (n = 100) will receive Carbavance (meropenem 2 g plus RPX7009 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, aminoglycoside (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam. Subjects (or subjects' legal representatives) 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 Carbavance (meropenem/RPX7009) or BAT.

	Any isolated bacterial pathogen will be identified by genus and species. The local laboratory will culture each subject sample for pathogen identification, quantification, and susceptibility testing. Isolated pathogens collected at the time points listed in the Schedule of Procedures 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 (Carbavance [meropenem/RPX7009] 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 the time points listed in the Schedule of Procedures. 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% (250 subjects) and 50% (500 subjects). 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. In order 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 treatment naïve throughout the course of the study. At each site a Blinded Investigator (BI) will be assigned to assess each subject's baseline status and Outcome Assessment during the EOT and TOC visits. A blinded adjudication committee will also be formed to independently evaluate clinical outcome data in cases where the Principal Investigator (PI) and BI's assessment of outcome differ. Further details regarding the blinded adjudication committee will be included in a Blinded Adjudication Committee Charter, which is the governing document of the committee.
Number of Subjects	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. Hospital acquired bacterial pneumonia and VABP will be stratified separately. Subjects will be stratified at randomization based on their presenting indication (cUTI/AP, cIAI, HABP, VABP, or bacteremia) and by region (North America vs. Europe vs. Asia Pacific vs. Rest of World). Enrollment will continue until at least 45 subjects (30 Carbavance [meropenem/RPX7009], 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 Carbavance [meropenem/RPX7009], 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.

Inclusion Criteria:	Subjects must meet all of the following criteria in order to be eligible for the study: 1. Willingness to comply with all study activities and procedures and to provide signed, written informed consent prior to any study procedures. If a subject is unable to provide informed consent due to their medical condition, the subject's legal representative will be provided with study information in order for consent to be obtained. 2. Hospitalized male or female, ≥18 years of age. 3. Weight ≤185 kg. 4. Have a confirmed diagnosis of a serious infection, specifically cUTI or AP, cIAI, HABP, VABP, and bacteremia, requiring administration of IV antibacterial therapy (See inclusion number 7 for criteria for all indications). 5. The following must be satisfied: For known CRE infection: • Have a known CRE infection based on evidence from CRE culture or other phenotypic or molecular testing within 72 hours prior to Day 1, alone or as a single isolate of a polymicrobial infection; • Have received no more than 24 hours of an antimicrobial agent to which the known CRE is susceptible prior to enrollment, OR • Have documented clinical evidence of failure (i.e., clinical deterioration or failure to improve) after at least 48 hours of treatment with an antimicrobial agent to which the known CRE is susceptible. For <u>suspected</u> CRE infection: • Have a suspected CRE infection based on evidence from CRE culture (KPC-producing, if known) or other phenotypic or molecular testing, alone or as a single isolate of a polymicrobial infection, from any source within 90 days prior to Day 1; • Have received no more than 24 hours of empiric antimicrobial therapy for gram negative organisms prior to enrollment. 6. Expectation, in the opinion of the Investigator, that the subject's infection will require treatment with IV antibiotics for a minimum of 7 days. 7. Expectation that subjects with an estimated creatinine clearance <10 ml/min (Cockcroft-Gault) will receive hemodialysis at least 2 times per week.

8. Diagnosis with either cUTI or AP, cIAI, HABP, VABP, and bacteremia as defined below:

Complicated Urinary Tract Infection

Expectation, in the judgment of the Investigator, that any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) will be removed or replaced (if removal is not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization, AND:

Indication	At least ONE of the following:	AND at least TWO of the following signs or symptoms:	AND at least ONE of the following:
cUTI	• Indwelling urinary catheter; • Neurogenic bladder with presence or history of urine residual volume of ≥100 mL; • Obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 hours post-randomization; • Azotemia due to intrinsic renal disease; • Urinary retention in men due to previously diagnosed benign prostatic hypertrophy	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3) or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Lower abdominal pain or pelvic pain	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; • WBC count ≥10 cells/hpf in urine sediment

cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.

Acute Pyelonephritis

Expectation, in the judgment of the Investigator, that any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) will be removed or replaced (if removal is not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization, AND:

Indication	Presence of an ascending tract infection including at least TWO of the following signs or symptoms:	AND at least ONE of the following:
AP	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3), or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Flank pain; • Costo-vertebral angle tenderness on physical examination	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; • WBC count ≥10 cells/hpf in urine sediment

AP = acute pyelonephritis; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.

Complicated Intra-Abdominal Infection (cIAI)

Patients may be enrolled approximately 24 hours before or 96 hours after the surgical procedure when the following conditions are met:

- Expectation, in the judgment of the investigator, that operative drainage/debridement/removal (including open laparotomy, percutaneous drainage, or laparoscopic surgery) of any intra-abdominal collection or other potential source of intra-abdominal infection will be performed;
- Expectation that cultures from the aforementioned procedure (including open laparotomy, percutaneous drainage, or laparoscopic surgery) will be sent for microbiological evaluation, including gram stain, culture and susceptibility testing, and Carbavance susceptibility testing AND:

Indication	At least ONE of the following either on intra-operative visualization of infection (e.g. pus within the abdominal cavity) OR supportive radiographic imaging:	AND at least ONE of the following:
cIAI	• Intra-abdominal abscess, including splenic or hepatic abscess; • Appendicitis or diverticulitis with peritonitis, perforation or abscess; • Perforation of stomach or intestine, associated with peritonitis, abscess or fecal contamination; • Cholecystitis or cholangitis with perforation, abscess or progression beyond the gallbladder wall or biliary tract.	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C; • Hypotension, systolic BP <90 mmHg; • Abdominal pain or tenderness; • Nausea or vomiting; • Abdominal mass on clinical examination; • Altered mental status.

BP = blood pressure; cIAI = complicated intra-abdominal infection.

Hospital Acquired Bacterial Pneumonia

Indication	All of the following:	AND signs or symptoms evidenced by at least TWO of the following:	AND at least ONE of the following:
HABP	• The onset of symptoms >48 hours after admission or ≤7 days after discharge from an inpatient acute or chronic care facility (e.g., LTAC, rehabilitation center, hospital, or skilled nursing home); OR • Admission from LTAC or rehabilitation center, or admission from home <7 days after discharge from an LTAC or rehabilitation center; • New or evolving infiltrate on chest x-ray obtained within 48 hours prior to randomization	• A new onset of cough (or worsening of baseline cough); • Auscultatory findings consistent with pneumonia/ pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • Dyspnea, tachypnea, or respiratory rate greater than 25/min; • Hypoxemia (O2 saturation <90% or pO2 <60 mmHg while breathing room air, or worsening of the O2sat/FiO2); OR The following criterion ALONE: • New onset need for mechanical ventilation	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC <4,500/mm^3); • Procalcitonin >0.25 µg/mL

HABP = hospital-acquired bacterial pneumonia; LTAC = long-term acute care; WBC = white blood cell.

Ventilator Associated Bacterial Pneumonia

Indication	All of the following:	AND signs or symptoms evidenced by at least TWO of the following:	AND at least ONE of the following:
VABP	• The onset of symptoms >48 hours after receiving ventilatory support via an endotracheal (or nasotracheal) tube; • Require ventilatory support; • New or evolving infiltrate on chest x-ray obtained within 48 hours prior to randomization and >48 hours after intubation	• Auscultatory findings consistent with pneumonia/ pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening oxygen saturation/FiO2 ratio; • Increased suctioning; • Tracheal aspirate change to purulence	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC <4,500/mm^3); • Procalcitonin >0.25 µg/mL

VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.

Bacteremia

Indication	All of the following:	AND at least ONE of the following:
Bacteremia	• Isolation of a CRE from at least 1 blood culture	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count (>10,000/mm^3); • Leukopenia (total WBC <4,500/mm^3); • Tachycardia >100 bpm; • Tachypnea >20 breaths/min; • Hypotension, systolic <90 mmHg

CRE = carbapenem-resistant *Enterobacteriaceae*; WBC = white blood cell.

9. Female subjects of childbearing potential, including those who are less than 2 years post-menopausal, must agree to, and comply with, using 2 highly effective methods of birth control (i.e., condom plus spermicide, combined oral contraceptive, implant, injectable, indwelling intrauterine device, sexual abstinence, or a vasectomized partner) while participating in this study. In addition, all women of childbearing potential must agree to continue to use 2 forms of birth control throughout the study and for at least 30 days after administration of the last dose of study drug.

* Evidence of fever within 24 hours of the screening visit is acceptable if observed and documented by a health care provider.

Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be enrolled in the study:

1. History of any significant hypersensitivity or severe allergic reaction to any beta-lactam antibiotics (e.g., cephalosporins, penicillins, carbapenems, or monobactams).
2. Known or suspected likely infection with New Delhi metallo- (NDM), Verona integron-encoded metallo- (VIM), or imipenemase-metallo-beta-lactamases or oxacillinase- (OXA)-beta-lactamases (i.e., Class B or Class D beta-lactamases).
3. For subjects to be enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:
    a. Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., subjects with vesico-ureteral reflux);
    b. Suspected or confirmed prostatitis;
    c. Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;
    d. Previous or planned cystectomy or ileal loop surgery;
    e. Uncomplicated urinary tract infection (for example, female subjects with urinary frequency, urgency or pain or discomfort without systemic symptoms or signs of infection);
    f. Complete, permanent obstruction of the urinary tract;

	g. Suspected or confirmed perinephric or renal corticomedullary abscess; h. Polycystic kidney disease; or i. Any recent history of trauma to the pelvis or urinary tract. 4. For subjects to be enrolled with the primary indication of cIAI, any of the following conditions: a. Incomplete drainage of suspected or known intra-abdominal source; b. Likely to receive ongoing antibacterial drug prophylaxis or chronic suppressive therapy after intravenous treatment of cIAI; c. Source of infection thought to be related to or involving a non-removable prosthesis (e.g. intra-abdominal mesh) or implantable device, line (e.g. peritoneal catheter) or stent (e.g. biliary stent); d. Uncomplicated intra-abdominal infection, such as simple appendicitis, simple cholecystitis or gangrenous cholecystitis without rupture; e. Patients with infected necrotizing pancreatitis or pancreatic abscess; f. Patients whose surgery will include staged abdominal repair or "open abdomen" technique, or marsupialization (i.e. patients who undergo a surgical procedure where fascial closure is performed are eligible. The skin incision may be left open for purposes of wound management as long as fascial closure is accomplished); g. Patients in whom the intra-abdominal process is deemed not likely to be infectious in origin (e.g. bowel obstruction, ischemic bowel without perforation, traumatic bowel perforation within past 12 hours, perforated gastroduodenal ulcer within 24 hours); or h. Non-intra-abdominal infection (e.g. infection or abscess of the abdominal wall without extension into the intra-abdominal cavity). 5. For subjects to be enrolled with the primary indication of HABP or VABP, any of the following conditions: a. Diagnosis of ventilator-associated tracheobronchitis; or b. Inability to obtain proper respiratory specimens for culture. 6. For subjects to be enrolled with the indication of bacteremia unrelated to cUTI or AP, cIAI, HABP, and VABP, any of the following: a. Unverified CRE infection; or b. Source of infection thought to be related to or involving a non-removable or implantable device or line.

	7. Evidence of immediately life-threatening disease where in the opinion of the Investigator, the subject is unlikely to survive more than 72 hours from randomization. 8. Acute Physiology and Chronic Health Evaluation (APACHE) II score >30. *An APACHE II score is only required if calculated*. 9. Known or suspected endocarditis, meningitis, or osteomyelitis. 10. Irremovable or implantable device or line thought to be the potential source of infection. 11. Evidence of significant hepatic, hematological, or immunologic disease or dysfunction determined by any of the following: a. Known fulminant viral hepatitis; b. Patients meeting Hy's criterion of ALT or AST >3 × upper limit of normal (ULN) AND total bilirubin >2 × ULN AND no other explanation such as hepatitis or acute liver injury, etc.; c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy; or d. Human immunodeficiency virus with either a CD4 count <200 cells/mm^3 at the last measurement, or current diagnosis of another Acquired Immune Deficiency Syndrome-defining illness. 12. Women who are pregnant or breastfeeding. 13. Require the use of inhaled antibiotics. 14. Participation in any study involving administration of an investigational agent or device within 30 days prior to randomization into this study or previous participation in the current study. 15. Previous participation in a study of RPX7009. 16. Any condition that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.
Microbiology	Accurate microbiologic results are critical to successfully meet the study objectives. All specimens will be sent to the local laboratory for culture and susceptibility testing per institutional standards. For all carbapenem-resistant gram-negative organisms, the MIC to carbapenems will be captured in the electronic Case Report Form (eCRF). Susceptibility to Carbavance as determined by Kirby-Bauer disk methodology will be captured at baseline. If the resistance mechanism for each carbapenem-resistant organism cultured during the study is known, it should be captured in source documents. Any isolated bacteria deemed to be contributory to the infectious process will be designated a pathogen by the PI and identified by genus and species. The local laboratory will culture each sample for organism identification, quantification (when applicable), and susceptibility testing per institutional standards. CRE isolates at baseline, and all post-baseline isolates cultured at the local laboratory and designated as pathogens by the PI will be sent to the central laboratory (Medpace Reference Laboratory [MRL]) for confirmation of identification and susceptibility testing results. All subjects must have a specimen sample from the site of infection (i.e., blood, urine, intra-abdominal fluid/tissue, or respiratory secretion) and two sets of blood samples from two separate venipuncture sites collected immediately prior to the first

	dose of study drug (or for cIAI specimens, 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. When it is not possible to collect specimens for culture immediately prior to the first dose of study drug, cultures that have been obtained no more than 72 hours (or 96 hours for cIAI) prior to the first dose of study drug are acceptable. The results of this culture will determine whether the subject meets the criteria for the Microbiological CRE Modified Intent-to-Treat (mCRE-MITT) Population or the Microbiological Modified Intent-to-Treat (m-MITT) Population. Kirby-Bauer disks for Carbavance (meropenem/RPX7009) susceptibility testing will be provided by the Sponsor for baseline testing. Susceptibility testing for BAT and other antimicrobials will be done per each institution's standard procedures. In instances where susceptibility testing indicates resistance to the study drug but the subject is clinically improving, the subject should remain on study drug at the Investigator's discretion. 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 no more than 72 hours before (or 96 hours for cIAI specimens) the first dose of study drug. <u>*Urine Specimens*</u> For subjects with cUTI or AP, urine samples will be collected by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration. CRE isolates at baseline, and all post-baseline isolates cultured at the local laboratory and designated as pathogens by the PI will be sent to the central laboratory for confirmation of identification and susceptibility testing results. The baseline urine cultures must grow at least one defined bacterial pathogen at concentration of $\geq 10^5$ CFU/mL. Up to 2 isolated pathogens will be allowed per baseline urine culture provided they are at concentrations of $\geq 10^5$ CFU/mL of urine. The baseline urine samples submitted for culture must have a microscopic evaluation (e.g., gram stain) and a dipstick analysis performed by the local microbiology laboratory. For all post-baseline urine cultures, only pathogens at concentrations of $\geq 10^3$ CFU/mL of urine will be sent to the central laboratory. Up to 2 isolated pathogens will be allowed per post-baseline urine culture provided they are at concentrations of $\geq 10^3$ CFU/mL. For both baseline and post-baseline cultures - if a subject grows 3 or more bacterial organisms in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if the organism also grows in a concurrently obtained blood culture. Isolates from contaminated samples should not be sent to the central lab. culture. Isolates from contaminated samples should not be sent to the central lab. <u>*Intra-abdominal Cultures*</u> For subjects with cIAI, acceptable specimens should include at least one intra-abdominal culture obtained during the time of surgical (or percutaneous)

	intervention. The specimen must be collected within approximately 96 hours before or 24 hours after of the first dose of study drug (preferably prior to study drug administration). Baseline specimens should be sent for gram stain, pathogen identification and susceptibility testing at the local laboratory. Isolates from the baseline specimen will also be sent to the central laboratory for confirmatory testing. Post-baseline specimens should be collected as clinically indicated and sent to the local laboratory for testing. Isolates from all post-baseline specimens should be sent to the central laboratory for confirmatory testing. To be considered adequate, a specimen should consist of at least 1mL of fluid or tissue representative of the material associated with the clinical infection. Gram stains will be conducted per institutional standards and gram stain data should be captured in source documents. If any intra-abdominal culture is performed (including cultures taken on swab), pathogens exhibiting significant growth on cultures identified by the site laboratory's routine procedures should be sent to the central lab, even if from a specimen that does not meet the aforementioned adequacy criteria. *Respiratory Tract Specimens* For subjects with HABP or VABP, acceptable specimens should include at least one positive pretreatment sample obtained by Protected Specimen Brush (PSB) with bronchial alveolar lavage (BAL) or mini-BAL, non-bronchoscopic-BAL (NBBAL), or Protected Endotracheal Catheter obtained prior to randomization and treatment. Non-ventilated subjects may have specimens obtained via deep expectoration or expectorated/induced sputum. All specimens should be sent for gram stain, quantitative culture, pathogen identification and susceptibility testing. To be adequate, respiratory samples from expectorated or induced sputum should show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100x field. Colony counts $\geq 10^3$ CFU/mL are considered the threshold for identifying pathologic bacteria from PSB and the CombiCath® NBBAL, $\geq 10^4$ CFU/mL for bronchoscopic BAL or the BALCath NBBAL, and $\geq 10^6$ CFU/mL for endotracheal aspirate specimens. Gram stains will be conducted per institutional standards, and gram stain data should be captured in source documents. Colony counts are not expected to be performed on expectorated or induced sputum. If the sputum is cultured, all pathogens exhibiting significant growth identified by the site laboratory's routine procedures should be sent to the central lab, even if from a specimen that does not meet the specimen adequacy criteria described above. *Blood and Other Tissue Specimens* Two sets of samples from 2 separate venipuncture sites are required for blood cultures in all study participants. If a blood culture is positive at baseline, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). Additional blood cultures, including blood cultures taken during fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) may also be collected at the Investigator's discretion.

	Isolated pathogens (e.g., considered not to be a contaminant by the PI) from each individual positive blood culture will be sent to the central lab. If a tissue sample (e.g., kidney biopsy) is collected to determine target pathogen, it should be obtained 72 hours prior to first dose of study drug. The isolated pathogen should be shipped to the central laboratory for confirmation and susceptibility testing. In the event that pre-randomization urine and blood cultures are negative and the subject has a positive tissue culture, the isolated pathogen may qualify as a defined baseline CRE pathogen.
Duration of Treatment and Trial Participation	The duration of study participation for each subject is approximately 29 days (~4 weeks), with a maximum duration of study participation of 31 days: • Screening (and Randomization) Period, 1 day; • Treatment Period, 7-14 days (final dose day of study drug is EOT); and • Follow-up Period, 5-16 days (including TOC and LFU visits).
Investigational Product/Dose/ Route/Regimen	Subjects will receive a dosage regimen of Carbavance (meropenem/RPX7009) consisting of 2 g meropenem plus 2 g RPX7009 via 3-hour IV infusion q8h. Dose adjustments are permitted based on estimated creatinine clearance (Cockcroft-Gault) for subjects with renal insufficiency. Subjects will receive infusions every 8 hours (±2 hours). Infusions that fall outside of the q8h dosing (± 2 hours) will be captured as protocol deviations.
Reference Therapy, Dose/Route	Subjects will receive BAT, with IV antibiotics, either alone or in combination, chosen from the following: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycoside (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam. Ceftazidime-avibactam may also be used as BAT, but may not be given in combination with other BAT agents, with the exception of concurrent aminoglycoside therapy for either 72 hours/pending susceptibility testing in patients with cIAI, HABP, VABP and bacteremia, similar to Carbavance (see Concomitant Antibiotics below). Details for dose and frequency of administration of BAT (as well as warnings, precautions, and contraindications) can be found in the referenced summaries of product characteristics for the specific antibacterials selected by the Investigator as BAT. Investigators will be instructed to select only country-approved therapies.
Concomitant Antibiotics	Subjects with cUTI or AP who are randomized to Carbavance (meropenem/ RPX7009) or to BAT, and receive ceftazidime-avibactam should receive Carbavance (meropenem/RPX7009) or ceftazidime-avibactam alone, respectively. Subjects with cIAI, HABP, VABP, or bacteremia who are randomized to Carbavance (meropenem/RPX7009) or to BAT and are treated with ceftazidime-avibactam should receive Carbavance (meropenem/RPX7009) or ceftazidime-avibactam alone, respectively. However, if the Investigator believes it is medically necessary, subjects may receive supportive aminoglycoside therapy in conjunction with Carbavance (meropenem/RPX7009) or ceftazidime-avibactam until culture information is available or for the first 72 hours, whichever is the shorter. Aminoglycoside treatment should be discontinued once the subject's organism is shown to be susceptible to Carbavance (meropenem/RPX7009) or ceftazidime-avibactam and the subject is clinically improving. The use of an aminoglycoside beyond 72 hours in subjects with a pathogen(s) susceptible to Carbavance (meropenem/RPX7009) or ceftazidime-avibactam will be considered a treatment failure.

	Subjects in both treatment arms may receive coverage (e.g., vancomycin or linezolid) for gram-positive organisms, as deemed necessary by the Investigator. Subjects with cIAI randomized to the BAT treatment arm may receive metronidazole. Inhaled antibiotics are not permitted. Bladder irrigation with antibiotics or antibiotics administered directly via a urinary catheter are not permitted. Intra-abdominal irrigation with antibiotics or antibiotics administered through a peritoneal dialysis catheter or other intra-abdominal catheter are not permitted.
Analysis Populations	The Intent-to-Treat (ITT) Population will include all subjects screened and randomized to study drug (Carbavance [meropenem/RPX7009] or BAT). 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. 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. The PK Population will include subjects who meet the MITT criteria and have at least one plasma PK sample drawn. The m-MITT Population will include subjects who meet the MITT criteria and have a baseline gram negative bacterial pathogen(s). The mCRE-MITT Population (i.e., Primary Efficacy Population) will include subjects who meet the m-MITT criteria and who have a baseline *Enterobacteriaceae* that is confirmed to be meropenem-resistant. 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 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 if classified as a failure on clinical outcome, or receive ≥5 days of study drug if classified as a cure on clinical outcome. 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 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

<table>
<tr><td></td><td>
Receive ≥3 days of study drug if classified as a failure on overall outcome, or receive ≥5 days of study drug if classified as a cure on overall outcome.
The CRE Microbiological Evaluable (CRE-ME) Population will include subjects who meet the ME criteria and who have a baseline Enterobacteriaceae that is confirmed to be meropenem-resistant.
</td></tr>
<tr><td>Efficacy Assessments</td><td>
<u>Efficacy Assessments for cUTI or AP</u>

<u>Primary Endpoint</u>

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 below). 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 below).

To meet the primary endpoint for EMA and FDA, 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 the following at TOC:
<table>
<tr><th>Parameter</th><th>Analysis for EMA</th><th>Analysis for FDA</th></tr>
<tr><td>Outcome measure</td><td>Microbiological eradication[a)]</td><td>Overall Success (Clinical cure[b)] and microbiological eradication[a)])</td></tr>
<tr><td>Efficacy time point(s)</td><td>TOC[c)]</td><td>TOC[c)]</td></tr>
</table>
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 surgical intervention or 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.
</td></tr>
</table>

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.

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 the test of cure (TOC) visit. To meet the primary endpoint, 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 microbiological failure, clinical failure, or tolerability. In addition, subjects cannot require any 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 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, 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 Carbavance (meropenem/RPX7009) 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.

Efficacy Assessments for *HABP and VABP*

Primary Endpoint

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 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 and VABP such that no further surgical intervention or 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 Carbavance (meropenem/RPX7009) 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).

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 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 pathogens) found at baseline is absent with repeat culture.

  Clinical assessment of cure is defined as complete resolution or significant improvement of the baseline signs and symptoms of bacteremia, such that no further surgical intervention or 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 Carbavance (meropenem/RPX7009) 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.
Safety Assessments	The following will be assessed to determine the safety of Carbavance (meropenem/RPX7009): • Assessment of adverse events from Day 1 through LFU visit (or, if applicable, early termination visit); and • Changes from baseline in physical examination findings, electrocardiograms (ECGs), safety laboratory test results, and vital signs will be evaluated.
Data Analysis	**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. **Criteria for Outcome Measures** Study populations are as follows: ITT, MITT, Safety Population, m-MITT, mCRE-MITT (i.e., Primary Efficacy Population), CE, ME, and CRE-ME. Please refer to the Statistical Analysis Populations diagram provided in Appendix 1. **Efficacy** The efficacy analyses will be descriptive summaries of the proportion of subjects in the mCRE-MITT Population at the TOC visit with a response of success defined according to primary indication. A descriptive summary of all-cause mortality for subjects with HABP, VABP, and bacteremia will be provided. Two-sided, exact binomial 95% confidence intervals for the true proportion of responses of success for the primary efficacy endpoint will be reported. 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. **Pharmacokinetics** Pharmacokinetic characterization, evaluation of plasma PK, and exposures of meropenem and RPX7009 in treated subjects will be performed. Analysis of the PK data will be described in a separate Statistical Analysis Plan. A pharmacodynamic analysis will be conducted to link meropenem and RPX7009 exposures in each subject with clinical and microbiological outcomes. **Safety** All subjects who receive at least 1 dose of study drug (i.e., the MITT Population) will be included in the safety analyses and analyzed based on actual treatment received. Adverse events will be collected throughout the study duration. Treatment-emergent adverse events (TEAEs) will be tabulated by National Cancer Institute Common Terminology Criteria for Adverse Events Grade. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a TEAE for each unique System Organ Class and Preferred Term will be tabulated. Treatment-emergent adverse events will also be tabulated by severity and by the relationship to study drug in treatment groups as assessed by the Investigator. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a serious adverse event will be tabulated. The number and percentage of subjects (in each treatment group) prematurely discontinuing study

	drug treatment due to a TEAE will be tabulated by System Organ Class and Preferred Term. Safety laboratory data will be presented by change from baseline. The number and percentage of subjects with laboratory, vital sign, ECG, or physical examination abnormalities at baseline, subsequent visits, or early termination from the study will be tabulated by treatment group. The results of all laboratory test results, physical examination findings, ECGs, and vital signs will be presented in data listings.

Table 1. Schedule of Procedures

	Screening	Treatment									Follow-Up		Early Termination[e]
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/RPX7009) 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 within 72 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.

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ALT	Alanine aminotransferase
AM	Alveolar macrophage
AP	Acute pyelonephritis
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BAL	Bronchial alveolar lavage
BAT	Best Available Therapy
BI	Blinded Investigator
CE	Clinical Evaluable
CFR	Code of Federal Regulations
CFU	Colony-forming unit
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
C_{max}	Maximum plasma concentration
CRE	Carbapenem-resistant *Enterobacteriaceae*
CRE-ME	Carbapenem-resistant *Enterobacteriaceae* Microbiological Evaluable
CT	Computed tomography
cUTI	Complicated urinary tract infection
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELF	Epithelial lining fluid
EMA	European Medicines Agency
EOT	End of Treatment
ESRD	End stage renal disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HABP	Hospital-acquired bacterial pneumonia

Abbreviation	Definition
HD	Hemodialysis
hpf	High-powered field
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
KPC	*Klebsiella pneumoniae* carbapenemase
LCE	Leukocyte esterase
LFU	Late Follow-up
LTAC	Long-term acute care
mCRE-MITT	Microbiological Carbapenem-resistant *Enterobacteriaceae* Modified Intent-to-Treat
ME	Microbiological Evaluable
MIC	Minimum inhibitory concentration
MITT	Modified Intent-to-Treat
m-MITT	Microbiological Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
NBBAL	Non-bronchoscopic bronchial alveolar lavage
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDM	New Delhi metallo
OXA	Oxacillinase
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMN	Polymorphonuclear leukocyte
PSB	Protected Specimen Brush
q8h	Every 8 hours
QA	Quality assurance
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TOC	Test of Cure

Abbreviation	Definition
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
UTI	Urinary tract infection
VABP	Ventilator-associated bacterial pneumonia
VIM	Verona integron-encoded metallo
V_{ss}	Steady-state volume of distribution
WBC	White blood cell

7 INTRODUCTION

Beta-lactam antimicrobials are considered to be among the most useful classes of antimicrobial agents for treatment of bacterial infections. In particular, the development of broad-spectrum cephalosporin and carbapenem antimicrobials have represented a key advancement in replacing other classes of drugs with toxicities and limited spectra of activity against pathogens.

In the current era of increased resistance to extended spectrum cephalosporins and penicillin/ beta-lactamase inhibitor combinations, carbapenem antimicrobial agents are frequently the antibiotics of "last defense" for the most resistant pathogens in serious infections. However, the recent dissemination of serine carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemase [KPC]) in *Enterobacteriaceae* within many United States (US) and global hospitals now poses a considerable threat to carbapenem and other members of the beta-lactam class of antimicrobial agents.[1,2,3]

Infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are associated with high mortality rates and have limited treatment options.[1] The loss of the carbapenem class of antimicrobial agents for treatment of *Enterobacteriaceae* (the most frequently occurring pathogens in the hospital setting), *Acinetobacter baumannii* and *Pseudomonas aeruginosa* represents a critical setback in modern patient care.

Meropenem is a broad-spectrum injectable carbapenem antibiotic used to treat a wide variety of infections. The spectrum of action includes many gram-positive bacteria, gram-negative bacteria, and anaerobic bacteria, and it is approved in many countries around the world at doses up to 2 g every 8 hours (q8h). Three-hour infusions of meropenem are commonly used to treat organisms with higher minimum inhibitory concentrations (MICs), such as *Pseudomonas aeruginosa,* to maximize the time above the MIC.

RPX7009 is a novel beta-lactamase inhibitor that has inhibitory activity against many serine beta-lactamases and was optimized for inhibition of the KPC beta-lactamase and the potentiation of carbapenems against *Enterobacteriaceae*. RPX7009 is being developed for use with meropenem to address the challenges of treatment of serious infections caused by pathogens increasingly resistant to available treatments.

Carbavance, the combination of meropenem and RPX7009 administered as a fixed combination by intravenous (IV) infusion, is being developed to treat serious gram-negative infections, such as complicated urinary tract infections (cUTI), acute pyelonephritis (AP), complicated intra-abdominal infections (cIAI), hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and bacteremia, including those infections caused by bacteria resistant to currently available carbapenems.

7.1 Overview of the Current Treatment of Infections due to CRE

As a result of the current lack of an optimal treatment for patients who have infections due to a CRE, physicians manage these patients with the limited anti-infective options available, including aminoglycosides, polymyxin B, colistin, tigecycline, or various combinations of these. There are limited efficacy data available for many of these therapies when used to treat serious CRE infections, particularly in combination, but with limited or no alternative therapies currently available, such treatments have become the BAT despite the toxicities associated with many of them.

To inform on the efficacy of these regimens as well as the target patient population with CRE infections, Rempex recently performed an international, multi-center, retrospective study of infections due to known CRE (Study 506NH). This study was conducted in 22 major medical centers in 4 countries – the US, UK, Italy and Greece. The study population consisted of male and female patients, over 18 years of age with serious bacterial infections including cUTI/AP, HABP, VABP, and bacteremia due to known carbapenem-resistant *Enterobacteriaceae* occurring over a 6 month period from September 1, 2013 to March 1, 2014. Data were collected from 257 patients with known CRE infections: 76 cases of cUTI/AP, 21 cases of HABP, 20 cases of VABP, and 140 cases of bacteremia. Among study patients, there was a high prevalence of comorbid conditions: overall 33% of study patients had moderate-to-severe renal disease, with 20% requiring hemodialysis; 35% of patients had underlying malignancy; 16% of patients had undergone prior organ/tissue transplantation; and 16% of patients had deep-tissue infection (predominantly cIAI) (See Table 2). The average duration of hospitalization prior to identification of CRE in cultures was 22 days. The average duration of hospital stay for the index CRE infection was 14 days, with an average duration of intensive care unit stay of 8 days. The outcomes associated with these infections were poor. The average 28-day mortality was 28% with an in-house mortality of 33%. These mortality rates varied by indication, with cUTI showing the lowest 28-day mortality rate (18%) and VABP the highest at 35%. Rates of both clinical and microbiological cure were correspondingly poor. Only 41% of patients achieved a response of clinical cure and only 52% of patients had a microbiological response of eradication of the baseline pathogen. These data indicate the significant comorbidities, the underlying severity of illness and the poor outcomes associated with CRE infections and the need for new agents against CRE pathogens.

Based on these data and in consultation with study investigators and key opinion leaders, the current amended protocol more accurately reflects the comorbidities and severity of illness associated with patients infected with CRE. The changes include expanded inclusion criteria, allowing patients with moderate-severe renal dysfunction, neutropenia, and patients on immunosuppressive medications to be included, and a modification of the exclusion criteria – eliminating exclusion of patients with neuromuscular disorders, elevated liver function tests, and history of seizure disorders. The goal of these changes is to make the study population more representative of the eventual target patient population of Carbavance – specifically patients with severe infections due to carbapenem-resistant *Enterobacteriaceae*.

Table 2. Patient Demographics in Study 506NH

	Number (%) of Patients				
	Infection Type				
	HABP (n= 21)	**VABP (n = 20)**	**cUTI/AP (n= 76)**	**Bacteremia (n=140)**	**All (n= 257)**
Age	60.3 (16.9)	55.5 (17.2)	63 (16.9)	62.5 (15.6)	61.8 (62.2)
Gender (%)					
Male	15 (71%)	13 (65%)	36 (47%)	87 (62%)	151 (59%)
Female	6 (29%)	7 (35%)	40 (53%)	53 (38%)	106 (41%)
Mild liver disease (%)	2 (9.5%)	1 (5.0%)	4 (5.3%)	12 (8.6%)	19 (7.4%)
Moderate liver disease (%)	2 (9.5%)	2 (10%)	5 (6.6%)	14 (10%)	23 (8.9%)
Solid tumor, any (%)	7 (33%)	3 (15%)	12 (16%)	34 (24%)	56 (22%)
Hematologic malignancy (leukemia/lymphoma)	3 (14.3%)	1 (5%)	9 (12%)	22 (16%)	35 (14%)
Prior transplant (%)	3 (14.3)	4 (20%)	10 (13.2%)	24 (17.1%)	41 (16.0%)
Moderate-severe renal disease	5 (23.8%)	9 (45%)	28 (36.8%)	47 (33.6%)	83 (33.1%)
Need for dialysis	2 (9.5%)	9 (45%)	8 (10.5)	32 (22.9%)	51 (19.8%)
Deep tissue infection (endocarditis, cIAI, meningitis	2 (9.5%)	3 (15%)	10 (13.2%)	27 (19.3%)	42 (16.3%)
Other*	8 (38%)	9 (45%)	30 (39.5%)	75 (51%)	119 (46.3%)

AP = acute pyelonephritis; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia.

Table 3. Outcomes of CRE Infections in Study 506NH by Infection Type and Overall

	Number (%) of Patients				
	Infection Type				
Outcome	HABP (n= 21)	VABP (n = 20)	cUTI/AP (n= 76)	Bacteremia (n=140)	All (n= 257)
Duration of hospitalization for IV antibiotics (mean±SD)	11.7 (7.2)	12.4 (6.4)	8.1 (12.6)	17.9 (17.5)	14 (15.4)
Duration of ICU stay (mean±SD)	7.7 (16.1)	14.1 (12.0)	3.6 (11.5)	9.5 (15.8)	8.0 (14.7)
28 day mortality (%)	7 (33%)	7 (35%)	14 (18%)	45 (32%)	73 (28%)
In-house mortality (%)	7 (33%)	9 (45%)	15 (20%)	53 (38%)	84 (33%)
Number (%) with clinical cure (PI-ascertained)	9 (43%)	9 (45%)	54 (71%)	74 (53%)	146 (57%)

AP = acute pyelonephritis; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infection; HABP = hospital-acquired bacterial pneumonia; ICU = intensive care unit; IV = intravenous; PI = Principal Investigator; SD = standard deviation; VABP = ventilator-associated bacterial pneumonia.

7.2 Carbavance (Meropenem/RPX7009)

Carbavance (meropenem/RPX7009) is a combination of the approved carbapenem antibiotic meropenem and the investigational beta-lactamase inhibitor RPX7009. This drug combination is being developed for IV administration for the treatment of patients with severe gram-negative infections, including those caused by bacteria resistant to currently available drugs.

Meropenem is a broad-spectrum carbapenem antibiotic active against gram-positive and gram-negative bacteria, including the *Enterobacteriaceae* (the most frequently occurring pathogens in the hospital setting) and other key pathogens associated with hospital-acquired infections, such as *Pseudomonas aeruginosa*, Acinetobacter sp., and anaerobes. While meropenem has excellent stability to many bacterial beta-lactamases (the major pathway of resistance to penicillins and cephalosporins), resistance to meropenem (and other carbapenems) can be mediated by Class A serine carbapenemases, especially KPC. Meropenem is approved in most countries in the developed world. In many countries, meropenem is approved for treatment of both urinary tract infections (UTIs) and cUTIs. In the US, it is marketed under the proprietary name of Merrem IV or its generic version, Meropenem for Injection, United States Pharmacopeia (USP), and is indicated for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and bacterial meningitis.[4] Approved dosing regimens for meropenem in adults include 500 mg, 1000 mg, and 2000 mg administered as 15- to 30-minute infusions q8h. While the approved infusion times for meropenem include bolus and 15- to 30-minute infusions, prolonged infusions for administration of meropenem are widely used, including the 3-hour infusions planned for evaluation in this study. There is no indication in the literature that the use of prolonged infusions affects the established safety profile of meropenem, and prolonged infusion of meropenem has been associated with increased probability of target attainment.[5] The clinical study that evaluated the combination of meropenem and RPX7009, Rempex-501, confirmed that meropenem was safe when administered as 3-hour infusions q8h.

RPX7009 is the first member of a new class of cyclic boronic acid beta-lactamase inhibitors. It has no antimicrobial activity alone, but has broad inhibitory activity against several clinically important bacterial beta-lactamases, particularly KPC. The pharmacological properties of

RPX7009 enable it to be administered in combination with meropenem. In vitro and in vivo studies show that the combination is highly active against gram-negative pathogens, including KPC-producing CRE.

The Sponsor has developed an IV formulation of Carbavance (meropenem/RPX7009) for evaluation in clinical trials, and will administer Carbavance (meropenem/RPX7009) in a fixed combination by IV infusion.

7.3 Microbiology

7.3.1 Susceptibility Testing

Carbavance (meropenem/RPX7009) has primary activity against gram-negative organisms. The potency and MICs of Carbavance (meropenem/RPX7009) have been evaluated against a variety of contemporary clinical strains. In the presence of RPX7009, the potency of meropenem was enhanced at least 32-fold against a panel of characterized gram-negative test strains. See the Investigator's Brochure.[6]

7.4 Nonclinical Pharmacology and Toxicology

A toxicology and safety assessment program to support clinical trials with RPX7009 was conducted. RPX7009 had no discernible effects in any of the safety pharmacology studies, demonstrated a similar pharmacokinetic (PK) profile to that of meropenem in preclinical species studies, and was devoid of mutagenic, clastogenic, and genotoxic effects for in vivo and in vitro Good Laboratory Practice (GLP) genotoxicity studies. See the Investigator's Brochure.[6]

7.4.1 Mechanism of Action

RPX7009 alone has no antimicrobial activity; however, when combined with meropenem in vitro and in vivo, it markedly enhanced the potency of meropenem against *Enterobacteriaceae* strains expressing KPC enzymes. See the Investigator's Brochure.[6]

7.4.2 Metabolism and Excretion

There is no evidence of accumulation with multiple RPX7009 doses and no differences in PK between males and females. RPX7009 has low plasma protein binding, is stable in human microsomes and hepatocytes, and shows no induction or inhibition of cytochrome P450 isoenzymes. It shows no inhibition of key renal transporters, nor does it appear to be a substrate of them. See the Investigator's Brochure.[6]

7.5 Overview of Clinical Pharmacology

7.5.1 Rempex 402 and Rempex 501 – Single and Multiple-Ascending Dose Studies in Healthy Volunteers

Two ascending-dose studies in healthy volunteers have been conducted. Both studies evaluated RPX7009 when administered as a 3-hour infusion q8h for 7 days at a dose range of 250 mg to 2 g. The first-in-human study evaluated RPX7009 alone (Study 402), while the second study evaluated RPX7009 in combination with 1 g and 2 g doses of meropenem (Rempex-501). The RPX7009 PK

data from these two studies were very consistent and demonstrated the similarity of PK profiles between the two drugs, as well as a lack of drug-drug interaction. The PK parameters for RPX7009 after single and multiple 2 g doses administered either alone or in combination with a 1 g or 2 g dose of meropenem are shown in Table 4. The PK parameters of meropenem after single and multiple 1 g or 2 g doses administered either alone or in combination with RPX7009 doses of 1 g and/or 2 g are shown in Table 5.

In both clinical studies, RPX7009 exposure in subjects (maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC]) increased with increasing dose. The mean C_{max} and AUC values for RPX7009 following administration of a 2 g dose q8h for 7 days were 41 mg/L and 145 mg·h/mL, respectively. The terminal half-life was less than 2 hours, resulting in no accumulation of drug between multiple doses of RPX7009 alone or in combination with meropenem. Volume of distribution and plasma clearance were independent of dose, and mean values ranged from 17.50 L to 24.95 L and 10.42 L/h to 17.61 L/h, respectively.

There were no significant changes in RPX7009 PK when it was administered with 1 g or 2 g doses of meropenem. Likewise, the PK parameters for meropenem, and its metabolite, hydrolyzed meropenem, remain unchanged with co-administration of RPX7009.

Table 4. Comparison Across Clinical Pharmacology Studies of RPX7009 Pharmacokinetic Parameters (Mean ±Standard Deviation) Following Single- and Multiple-Dose Administration of RPX7009 2 g Alone and in Combination with Meropenem (Preliminary Data)

Parameter	Study 402		Rempex-501					
	Alone		Alone	w/ Meropenem 1 g		Alone	w/ Meropenem 2 g	
	Single[a] (N=6)	Last[a] (N=6)	Single[b] (N=8)	First[c] (N=8)	Last[c] (N=7)	Single[b] (N=8)	First[c] (N=8)	Last[c] (N=8)
C_{max} (mg/L)	41.6 ±4.75	40.9 ±4.68	39.20 ±4.29	41.44 ±4.38	34.93 ±3.96	51.44 ±16.16	51.66 ±7.26	55.61 ±10.96
AUC[d] (mg·h/L)	144 ±13.9	145 ±15.8	133.26 ±20.89	141.02 ±21.35	112.31 ±8.56	159.21 ±44.58	170.44 ±31.99	190.43 ±32.90
Half-Life (h)	1.51 ±0.08	1.66 ±0.10	1.31 ±0.32	1.43 ±0.22	1.19 ±0.21	1.39 ±0.20	1.98 ±0.81	1.37 ±0.24
V_{ss} (L)	21.8 ±2.26	33.4 ±4.52	22.02 ±2.24	22.43 ±2.00	24.95 ±2.63	21.37 ±3.33	21.84 ±3.50	17.50 ±1.99
Plasma Clearance (L/h)	14.0 ±1.40	14.0 ±1.78	15.32 ±2.33	14.44 ±1.97	17.61 ±1.44	13.43 ±3.23	12.08 ±2.09	10.42 ±1.85

a. The single dose of RPX7009 was administered on Day 1, and the last dose of RPX7009 following multiple-dose administration was on Day 8.
b. The single dose of RPX7009 was administered on either Day 1 or Day 4, depending on whether the subject was randomized to receive RPX7009 first or meropenem first.
c. The first dose of multiple-dose administration of meropenem/RPX7009 was on Day 8, and the last dose of every 8-hour dose administration was on Day 14.
d. $AUC_{(0-\infty)}$ values are provided for single doses, and $AUC_{(0-Tlast)}$ values are provided for the last day of multiple dosing.
AUC = area under the concentration-time curve; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 to infinity; $AUC_{(0-Tlast)}$ = area under the concentration-time curve from time 0 to the last recorded measurement; C_{max} = maximum plasma concentration; SD = standard deviation; V_{ss} = steady-state volume of distribution; w/ = with.

Table 5. Preliminary Mean (±Standard Deviation) Meropenem Pharmacokinetic Parameters Following Single and Multiple Doses of Meropenem Administered Alone or in Combination with RPX7009 as 3-Hour Infusions to Healthy Volunteers in Study Rempex-501

Parameter	Meropenem 1 g						Meropenem 2 g		
	Alone	w/ RPX7009 1 g		Alone	w/ RPX7009 2 g		Alone	w/ RPX7009 2 g	
	Single[a] (N=9)	First[b] (N=5)	Last[b] (N=5)	Single[a] (N=14)	First[b] (N=7)	Last[b] (N=7)	Single[a] (N=14)	First[b] (N=8)	Last[b] (N=8)
C_{max} (mg/L)	18.93 ±3.65	20.16 ±3.97	17.04 ±1.65	17.31 ±2.45	18.21 ±2.06	15.81 ±1.29	42.54 ±15.24	48.83 ±5.88	43.35 ±8.82
AUC[c] (mg·h/L)	59.77 ±12.09	65.88 ±15.33	54.52 ±6.96	53.78 ±8.81	58.69 ±9.91	48.06 ±2.01	130.34 ±34.95	142.55 ±28.72	137.71 ±26.37
Half-Life (h)	0.96 ±0.11	1.15 ±0.21	0.94 ±0.03	0.96 ±0.09	1.01 ±0.31	1.08 ±0.15	1.14 ±0.36	1.51 ±0.98	1.07 ±0.16
V_{ss} (L)	21.59 ±3.21	21.06 ±4.50	21.19 ±2.43	23.46 ±2.53	22.36 ±1.89	24.97 ±2.41	22.59 ±5.24	21.74 ±3.05	20.08 ±3.20
Plasma Clearance (L/h)	17.39 ±3.71	15.84 ±3.57	18.4 ±2.24	19.11 ±3.44	17.39 ±2.41	20.65 ±0.84	16.13 ±3.33	14.49 ±2.67	14.77 ±2.84

a. The single dose of RPX7009 was administered on either Day 1 or Day 4, depending on whether the subject was randomized to receive RPX7009 first or meropenem first.
b. The first dose of multiple-dose administration of meropenem/RPX7009 was on Day 8, and the last dose of every 8-hour dose administration was on Day 14.
c. $AUC_{(0-\infty)}$ values are provided for single doses, and $AUC_{(0-Tlast)}$ values are provided for the last day of multiple dosing.
AUC = area under the concentration-time curve; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 to infinity; $AUC_{(0-Tlast)}$ = area under the concentration-time curve from time 0 to the last recorded measurement; C_{max} = maximum plasma concentration; V_{ss} = steady-state volume of distribution.

7.5.2 Rempex 503 – Randomized, Open-label Study of the Pulmonary Pharmacokinetics of Meropenem and RPX7009 (Carbavance) in Healthy Volunteers

Study 503 was a randomized, open-label study in healthy adult subjects to evaluate the plasma, epithelial lining fluid (ELF), and alveolar macrophage (AM) penetration of a single dose level of 2 g of meropenem/2 g of RPX7009 (Carbavance) after 3 doses, given 8 hours apart, administered as 3-hour infusions; safety and tolerability were also evaluated.

Twenty-five subjects underwent bronchoscopy and BAL at 1 of 5 time points (1.5, 3.25, 4, 6, and 8 hours) after the third dose of IV meropenem and RPX7009. Bronchial alveolar lavage samples provided ELF and AM concentrations for meropenem and RPX7009 for pulmonary PK analysis, and blood samples provided plasma concentrations for meropenem and RPX7009 plasma PK analysis.

Preliminary data showed that IV dosing of 2 g meropenem/2 g RPX7009 (Carbavance) every 8 hours, administered as 3-hour infusions, produced steady-state ELF concentrations of approximately 50% and 60% of simultaneous plasma concentrations for RPX700 and meropenem, respectively. See the Investigator's Brochure for details.[6]

7.5.3 Rempex 504- A Phase 1, Open-Label, Single-dose Study to Determine the Safety and Pharmacokinetics of Carbavance in Subjects With Renal Insufficiency (Including Subjects on Standard Hemodialysis)

Study 504 was an open-label study in adult subjects with varying degrees of renal insufficiency, including those requiring hemodialysis (HD), or normal renal function. The safety and PK of a single IV dose of 1 g meropenem plus 1 g RPX7009 (Carbavance), infused over 3 hours, was evaluated. Forty-one subjects were enrolled in 5 groups based on their degree of renal insufficiency.

Preliminary data demonstrate that meropenem and RPX7009 plasma clearance followed a linear PK model in subjects with decreasing renal function (see Appendix 4). This allows the ratio of meropenem and RPX7009 to be maintained for dose adjustment in subjects with reduced renal function (See the Investigator's Brochure[6]). For subjects with an estimated creatinine clearance below 20 ml/min, including those on standard hemodialysis, data were recently obtained, and 2 subgroups were noted. The first included subjects with an estimated creatinine clearance between 10 ml/min and 19 ml/min (including those requiring hemodialysis). The second included all subjects with an estimated creatinine clearance below 10 ml/min (including those on hemodialysis).

For subjects with an estimated creatinine clearance of 10-19 ml/min, the dosing strategy with the highest probability of target attainment was 500 mg of Carbavance (500 mg meropenem/500 mg RPX7009) every 12 hours. For subjects with estimated creatinine clearance below 10 ml/min, a dose of Carbavance (500 mg meropenem/500 mg RPX7009) every 24 hours best accounted for intersubject variability and had the greatest probability of target attainment across all subjects with exposure levels to both meropenem and RPX7009 that were well under the highest exposure achieved in this study, which was well tolerated in the setting of twice weekly hemodialysis. Subjects with an estimated creatinine clearance of less than 10 ml/min are required to receive dialysis at least twice per week.

Based on this data, the following are recommended Carbavance dosing regimens for subjects with impaired renal function.

Table 6. Reduced Renal Function Dose Adjustment Table

Estimated Creatinine Clearance, ml/min (Cockcroft-Gault)	Carbavance Dosage Regimen (All doses infused over 3 hours)
≥50	Meropenem 2 g / RPX7009 2 g q8h
≥30 – 49	Meropenem 1 g / RPX7009 1 g q8h
≥20 – 29	Meropenem 1 g / RPX7009 1 g q12h
≥10-19	Meropenem 500 mg / RPX7009 500 mg q12h
<10	Meropenem 500 mg / RPX7009 500 mg q24h[a]

a. Subjects with an estimated creatinine clearance of less than 10 ml/min are required to receive dialysis at least twice per week. Maintenance doses of Carbavance in these subjects should be administered as soon as possible after the dialysis session. For example, if a subject is scheduled to receive Carbavance at 18:00 but receives hemodialysis at 13:00, the planned 18:00 Carbavance dose should be given after the dialysis session is completed (rather than waiting until 18:00).

q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.

7.6 Justification of Carbavance Dose Selection for Registration Clinical Program

The Carbavance (meropenem/RPX7009) program was initiated with the goal of treating KPC-containing *Enterobacteriaceae* by combining meropenem with RPX7009 and improving the coverage against *P. aeruginosa* and *Acinetobacter* spp. by optimizing the dose and dose regimen of meropenem.

The PK-pharmacodynamic parameter for efficacy of meropenem is free drug time above the MIC and the magnitude of this parameter necessary to achieve maximal efficacy is free drug above the MIC for 30% to 50% of the dosage interval. From the PK data obtained in Rempex-501, a meropenem dose of 2 g administered by 3 hour infusion every 8 hours will maintain concentrations above the 8 mg/L for 30% to 50% of the dosage interval.[6] This meropenem dosage regimen has been chosen for this study to increase the likelihood of clinical success in difficult to treat infections.

For RPX7009, studies both *in vitro* and *in vivo* were used to determine the minimum exposure required to potentiate meropenem against strains containing the KPC enzyme (or expressing KPC) as well as reduce the development of resistance during therapy. Based on *in vitro resistance* development studies, a minimum concentration of 8 mg/L of RPX7009 (in combination with 8 mg/L of meropenem) was required to be present for 24 hours to prevent resistance. This became the basis for the minimum AUC (8 mg/L * 24 h = 192 mg*h/L) target in animal models and *in vitro* pharmacodynamic models. From the data obtained from Rempex-501, a dose of 2 g administered by 3 hour infusion every 8 hours was required to maintain an AUC above 192 mg*h/L.[6] This RPX7009 dosage regimen has been chosen for this study and for the Registration Clinical Development Program.

The selected combination dosage regimen of 2 g meropenem /2 g RPX7009 was further studied using *in vitro* pharmacodynamic and animal models of infection against *Enterobacteriaceae* and *P. aeruginosa* strains with Carbavance MICs as high as 8 mg/L. In each of these models, the dosage regimen proved to not only be efficacious, but prevented the development of resistance in those studies. If this data is confirmed in the Registration Clinical Development Program, it may justify a Carbavance MIC breakpoint as high as 8 mg/L.

Overall, based on the PK data from Rempex-501 and the *in vitro* and *in vivo* PK and pharmacodynamic data generated, the dose of 2 g meropenem in combination with 2 g RPX7009 infused over 3 hours, every 8 hours, was chosen for development.

7.7 Overview of Clinical Safety

7.7.1 Rempex 402 and Rempex 501 – Single and Multiple-Ascending Dose Studies in Healthy Volunteers

There have been no safety signals identified in the clinical pharmacology studies conducted with RPX7009 alone (Study 402) and in combination with meropenem (Rempex-501). Events related to the infusion site (dosing catheter) and/or PK catheter site (blood collections only) were the most prevalent events reported and were evenly distributed across subjects treated with placebo, RPX7009 alone, meropenem alone, and meropenem/RPX7009, indicating no evidence of local adverse events related to RPX7009 dosing, either alone or in combination with meropenem. Common adverse events in subjects treated with RPX7009 or meropenem/RPX7009, outside of

infusion site/PK catheter site events, were limited to headache, lethargy, dizziness, nausea, and diarrhea. Of these events, headache was the most frequently reported adverse event in both studies, being reported in 42% of subjects in RPX7009 multiple-dose groups in Study 402 and 30% in meropenem/RPX7009 dose groups in Rempex-501. In comparison, the incidence of headache was 50% in subjects treated with meropenem alone in Rempex-501, and 25% in subjects treated with placebo in Studies 402 and Rempex-501. With the exception of 1 case of headache in a placebo subject in Rempex-501, the episodes of headache were mild in severity.

Lethargy was reported in Study 402 in 1 of 6 subjects (17%) that received RPX7009 1 g q8h and 4 of 6 subjects (67%) that received RPX7009 2 g q8h, for an overall incidence of 21% in subjects treated with RPX7009 in Study 402; however, lethargy was not reported in a single subject that received RPX7009 alone or in combination with meropenem q8h in Rempex-501. All episodes of lethargy in Study 402 were considered to be mild in severity.

Dizziness, nausea, and diarrhea were all reported in a single RPX7009 subject (4%) each in Study 402 and 4 (9%) subjects that received either RPX7009 250 mg alone (1 of 8 subjects [13%] for each event) or a combination of meropenem/RPX7009 (3 of 37 subjects [8%] for each event) in Rempex-501. In addition, 1 (6%) and 2 (13%) subjects that received meropenem 1 g reported dizziness and diarrhea, respectively. All episodes of dizziness, nausea, and diarrhea were considered mild in severity.

Two subjects in Remepx-501 had asymptomatic elevations in their alanine aminotransferase (ALT) levels to > 3 x ULN which were felt to be study drug-related by the Investigator. One subject was in the meropenem 1 g cohort and one was in the meropenem/RPX7009 1 g/ 2 g cohort. Neither were associated with alkaline phosphatase or bilirubin elevations and both resolved spontaneously after study drug treatment was completed. There were no other clinically significant trends in clinical laboratory parameters, or clinically significant changes in vital signs, physical examinations, or electrocardiogram (ECG) parameters in either study.

7.7.2 Rempex 503 – Randomized, Open-label Study of the Pulmonary Pharmacokinetics of Meropenem and RPX7009 (Carbavance) in Healthy Volunteers

Study 503 was a randomized, open-label, PK study conducted in healthy adult male and female subjects to evaluate the lung penetration of 2 g meropenem/2 g RPX7009 (Carbavance) every 8 hours administered as a 3-hour infusion. Twenty-five subjects underwent bronchoscopy and BAL at 1 of 5 time points (1.5, 3.25, 4, 6, and 8 hours) after the third dose of IV meropenem and RPX7009. Bronchial alveolar lavage samples provided ELF and AM concentrations for meropenem and RPX7009 for pulmonary PK analysis, and blood samples provided plasma concentrations for meropenem and RPX7009 plasma PK analysis.

Twenty-six subjects were randomized and 25 subjects completed the study. One subject withdrew from the study during the second infusion of meropenem/RPX7009 because of chest pressure of unknown etiology that was moderate in intensity, lasted 90 minutes, resolved spontaneously when the infusion was stopped, and was considered by the investigator to be possibly related to study drug administration.

Carbavance (meropenem/RPX7009) given as a 2 g/2 g dose was well tolerated in Study 503.

There were no serious adverse events or deaths reported.

There were no clinically significant changes in laboratory values, vital signs, or ECG parameters during the study.

For further details and a full list of all treatment-emergent adverse from Study 503 reference the Investigator's Brochure.[6]

7.7.3 Rempex 504 – Open-label Study of the Safety and PK of a Single Dose of Meropenem and RPX7009 (Carbavance) in Volunteers with Varying Degrees of Renal Insufficiency or Normal Renal Function, and in Patients with Hemodialysis

All subjects in the normal, mild, moderate, and severe renal function groups received a single 3-hour IV infusion of Carbavance (1 g meropenem and 1 g RPX7009). Subjects in the end stage renal disease (ESRD) group received two infusions, one infusion immediately prior to HD, and the other infusion following HD on different days separated by a washout period to ensure that study drug administration was at least 6 days apart and no more than 14 days apart.

Overall, 14 subjects (34.1%) reported a total of 20 treatment-emergent adverse events (TEAEs) during the conduct of the study. The most frequently reported TEAEs were diarrhoea, headache, abdominal pain, and dermatitis contact. All TEAEs were mild in severity except 1 moderate TEAE (abdominal pain) and 2 severe TEAEs (1 prostate cancer metastatic and 1 diarrhoea haemorrhagic). A similar proportion of subjects reported at least 1 TEAE in the mild (2 subjects [25.0%]), moderate (3 subjects [37.5%]), severe (1 subject [12.5%]), and normal (2 subjects [25.0%]) renal function groups. In the ESRD group, a larger proportion of subjects in Period 2 (i.e., when dialysis occurred prior to study drug administration) (5 subjects [62.5%]) reported TEAEs as compared to the Period 1 group (2 subjects [22.2%]; i.e., when dialysis occurred after study drug administration); however, the type and severity of these adverse events in the ESRD group were similar to those adverse events observed in the other renal function groups. The higher incidence of these mild TEAEs reported during Period 2, as opposed to Period 1, is consistent with the PK data indicating that both meropenem and RPX7009 are cleared by hemodialysis.

Eight of the 20 TEAEs reported in the study were either "possibly" or "probably" related to study treatment and were reported by 7 subjects (17.1%). Only 1 TEAE (prostate cancer metastatic) was ongoing at study completion. Two (2) SAEs were reported (1 prostate cancer metastatic and 1 diarrhoea haemorrhagic) in subjects with ESRD. The event of prostate cancer metastatic resulted in an interruption to study drug dose administration, and the subject did not receive the second dose. No adverse events resulted in death.

There were no clinically significant trends in 12-lead ECG data, vital signs data, clinical laboratory results, or physical examination data.

Overall Carbavance was well tolerated across all levels of renal insufficiency, including in subjects with severe renal insufficiency and those on hemodialysis. Guidelines on dosing of Carbavance in subjects with renal impairment is outlined in Section 11.1.2.

7.8 Benefits and Risks Conclusions

No safety signal was identified in any of the four clinical pharmacology studies, which is consistent with the preclinical toxicology and safety studies conducted with RPX7009 alone and in combination with meropenem. In those preclinical studies, no toxicity was attributed to RPX7009, minimal toxicity was attributed to meropenem, and the addition of RPX7009 to meropenem did not impact the known toxicity profile of meropenem. The PK data from animals and humans also support that the two drugs have similar PK profiles and do not affect the PK profiles of each other. Overall, the PK and safety results from the preclinical and clinical studies of the administration of RPX7009 alone and in combination with meropenem support the use of this drug combination in clinical studies up to the highest doses tested (2 g/2 g) infused over 3 hours, and support the inclusion of subjects with severe renal insufficiency in this study, including those on hemodialysis.

8 STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the safety, tolerability, and efficacy of Carbavance (meropenem/RPX7009) in treatment of subjects with selected serious infections, suspected or known to be due to CRE; and
- To assess the PK of meropenem and RPX7009 in subjects with selected serious infections, suspected or known to be due to CRE.

9 OVERALL STUDY DESIGN

9.1 Study Design

This is a Phase 3, multi-center, randomized, open-label study of Carbavance (meropenem/ RPX7009) versus BAT in the treatment of subjects with selected serious infections, specifically cUTI or AP, cIAI, HABP, VABP, and bacteremia, suspected or known to be caused by CRE. See Appendix 2 for a flow diagram of the study.

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 ≤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, 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 Carbavance to BAT, respectively.

The Treatment Arms in the study are as follows:

- Treatment Arm A: Subjects (n = 100) will receive Carbavance (meropenem 2 g plus RPX7009 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 (see Section 11.1.2).
- 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 Carbavance (meropenem/RPX7009) or BAT.

Any isolated bacterial pathogen will be identified by genus and species. The local laboratory will culture each subject 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 (Carbavance [meropenem/ RPX7009] 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).

9.1.1 Blinding

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

9.1.1.1 Subject Treatment Bias

In order 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.

9.1.1.2 Blinded Investigator (BI)

Each site will assign a Blinded Investigator(s) (BI) to evaluate criteria for Clinical Outcomes during designated study visits (See Table 1). A BI must be qualified to perform medical evaluations and determine medical diagnoses (e.g., physician, physician's assistant, or nurse practitioner [within the US]). A BI should have no other role in the study other than making blinded assessments. For consistency, whenever possible the same BI should complete all blinded assessments for a study subject. All efforts should be made to keep a BI blinded during the course of the study. Data collection by the BI will be used for adjudication purposes only.

9.2 Independent Monitoring Committees

9.2.1 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% (250 subjects) and 50% (500 subjects). 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.

9.2.2 Blinded Adjudication Committee

A blinded adjudication committee will also be formed to independently evaluate clinical outcome data in cases where the PI's and BI'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.

9.3 Rationale for Study Design

There is a current lack of an optimal treatment for patients who have infections due to a CRE, making the use of a blinded comparator impractical due to the limited anti-infective options available. In addition, the different regimens, combinations, and toxicities associated with the various combinations and lack of a true comparator would make maintaining a blind nearly impossible. Therefore, an open-label study design is appropriate for this study.

To minimize potential bias, efforts will be made to keep the subject unaware of their treatment assignment, a BI used to assess outcomes, and an adjudication committee used as described in Section 9.2.2.

Eligible subjects will require at least 7 days of IV therapy, and mortality is generally high for this population of subjects with serious infections even with the best anti-microbial therapy available. Treatment with a placebo comparator would be unacceptable in this subject population. Therefore, using the BAT with any of the following IV antibiotics, alone or in combination, is the appropriate option for this study: carbapenems (meropenem, ertapenem, imipenem), tigecycline, colistin, aminoglycoside (amikacin, tobramycin, gentamicin), polymyxin B, and (where available) ceftazidime-avibactam.

Randomization will be used to assure that study populations are similar between the test and control groups, and to avoid systemic differences between the 2 study groups with respect to known or unknown baseline variables that could affect outcome.

10 SELECTION OF STUDY POPULATION

The following criteria for enrollment must be followed explicitly. The subject cannot be randomized until he/she satisfies the following inclusion and exclusion criteria. The Investigator or other study site personnel must document in the source documents (e.g., the hospital or clinic chart) that the subject's informed consent was obtained. If a subject is unable to provide informed consent due to their medical condition, the subject's legal representative will be provided with study information in order for consent to be obtained. The presence of inclusion criteria and the absence of exclusion criteria will be verified in the electronic case report form (eCRF).

10.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. Willingness to comply with all study activities and procedures and to provide signed, written informed consent prior to any study procedures. If a subject is unable to provide informed consent due to their medical condition, the subject's legal representative will be provided with study information in order for consent to be obtained.
2. Hospitalized male or female, ≥18 years of age.
3. Weight ≤185 kg.
4. Have a confirmed diagnosis of a serious infection, specifically cUTI or AP, cIAI, HABP, VABP, and bacteremia, requiring administration of IV antibacterial therapy (See inclusion number 7 for criteria for all indications).
5. The following must be satisfied:
   For known CRE infection:
   - Have a known CRE infection based on evidence from CRE culture or other phenotypic or molecular testing within 72 hours prior to Day 1, alone or as a single isolate of a polymicrobial infection;
   - Have received no more than 24 hours of an antimicrobial agent to which the known CRE is susceptible prior to enrollment,

     OR
   - Have documented clinical evidence of failure (i.e., clinical deterioration or failure to improve) after at least 48 hours of treatment with an antimicrobial agent to which the known CRE is susceptible.

   For suspected CRE infection:
   - Have a suspected CRE infection based on evidence from CRE culture (KPC-producing, if known) or other phenotypic or molecular testing, alone or as a single isolate of a polymicrobial infection, from any source within 90 days prior to Day 1;
   - Have received no more than 24 hours of empiric antimicrobial therapy for gram negative organisms prior to enrollment.
6. Expectation, in the opinion of the Investigator, that the subject's infection will require treatment with IV antibiotics for a minimum of 7 days.

7. Expectation that subjects with an estimated creatinine clearance <10 ml/min (Cockcroft-Gault) will receive hemodialysis at least 2 times per week.

8. Diagnosis with either cUTI or AP, cIAI, HABP, VABP, and bacteremia as defined below:

   Complicated Urinary Tract Infection

   Expectation, in the judgment of the Investigator, that any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) will be removed or replaced (if removal is not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization, AND:

Indication	At least ONE of the following:	AND at least TWO of the following signs or symptoms:	AND at least ONE of the following:
cUTI	• Indwelling urinary catheter; • Neurogenic bladder with presence or history of urine residual volume of ≥100 mL; • Obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 hours post-randomization; • Azotemia due to intrinsic renal disease; • Urinary retention in men due to previously diagnosed benign prostatic hypertrophy	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3) or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Lower abdominal pain or pelvic pain	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; • WBC count ≥10 cells/hpf in urine sediment

cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.

Acute Pyelonephritis

Expectation, in the judgment of the Investigator, that any indwelling urinary catheter or instrumentation (including nephrostomy tubes and/or indwelling stents) will be removed or replaced (if removal is not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization, AND:

Indication	Presence of an ascending tract infection including at least TWO of the following signs or symptoms:	AND at least ONE of the following:
AP	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3), or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Flank pain; • Costo-vertebral angle tenderness on physical examination	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; • WBC count ≥10 cells/hpf in urine sediment

AP = acute pyelonephritis; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.

Complicated Intra-Abdominal Infection (cIAI)

Patients may be enrolled approximately 24 hours before or 96 hours after the surgical procedure when the following conditions are met:

- Expectation, in the judgment of the investigator, that operative drainage/debridement/removal (including open laparotomy, percutaneous drainage, or laparoscopic surgery) of any intra-abdominal collection or other potential source of intra-abdominal infection will be performed;
- Expectation that cultures from the aforementioned procedure (including open laparotomy, percutaneous drainage, or laparoscopic surgery) will be sent for microbiological evaluation, including gram stain, culture and susceptibility testing, and Carbavance susceptibility testing AND:

Indication	At least ONE of the following, either on intra-operative visualization of infection (e.g. pus within the abdominal cavity) OR supportive radiographic imaging) :	AND at least ONE of the following:
cIAI	• Intra-abdominal abscess, including splenic or hepatic abscess; • Appendicitis or diverticulitis with peritonitis, perforation or abscess; • Perforation of stomach or intestine, associated with peritonitis, abscess or fecal contamination; • Cholecystitis or cholangitis with perforation, abscess or progression beyond the gallbladder wall or biliary tract.	• Chills, rigors, or fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C; • Hypotension, systolic BP <90 mmHg; • Abdominal pain or tenderness; • Nausea or vomiting; • Abdominal mass on clinical examination; • Altered mental status.

BP = blood pressure; cIAI = complicated intra-abdominal infection.

Hospital Acquired Bacterial Pneumonia

Indication	All of the following:	AND signs or symptoms evidenced by at least TWO of the following:	AND at least ONE of the following:
HABP	• The onset of symptoms >48 hours after admission or ≤7 days after discharge from an inpatient acute or chronic care facility (e.g., LTAC, rehabilitation center, hospital, or skilled nursing home); OR • Admission from LTAC or rehabilitation center, or admission from home <7 days after discharge from an LTAC or rehabilitation center; • New or evolving infiltrate on chest x-ray obtained within 48 hours prior to randomization and >48 hours after hospitalization	• A new onset of cough (or worsening of baseline cough); • Auscultatory findings consistent with pneumonia/ pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • Dyspnea, tachypnea, or respiratory rate greater than 25/min; • Hypoxemia (O2 saturation <90% or pO2 <60 mmHg while breathing room air, or worsening of the O2sat/FiO2); OR The following criterion ALONE: • New onset need for mechanical ventilation	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC <4,500/mm^3); • Procalcitonin >0.25 µg/mL

HABP = hospital-acquired bacterial pneumonia; LTAC = long-term acute care; WBC = white blood cell.

Ventilator Associated Bacterial Pneumonia

Indication	All of the following:	AND signs or symptoms evidenced by at least TWO of the following:	AND at least ONE of the following:
VABP	• The onset of symptoms >48 hours after receiving ventilatory support via an endotracheal (or nasotracheal) tube; • Require ventilatory support; • New or evolving infiltrate on chest x-ray obtained within 48 hours prior to randomization and >48 hours after intubation	• Auscultatory findings consistent with pneumonia/ pulmonary consolidation (e.g., rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening oxygen saturation/FiO2 ratio; • Increased suctioning; • Tracheal aspirate change to purulence	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC <4,500/mm^3); • Procalcitonin >0.25 µg/mL

VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.

Bacteremia

Indication	All of the following:	AND at least ONE of the following:
Bacteremia	• Isolation of a CRE from at least 1 blood culture	• Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count (>10,000/mm^3); • Leukopenia (total WBC <4,500/mm^3); • Tachycardia >100 bpm; • Tachypnea >20 breaths/min; • Hypotension, systolic <90 mmHg

CRE = carbapenem-resistant *Enterobacteriaceae*; WBC = white blood cell.

9. Female subjects of childbearing potential, including those who are less than 2 years post-menopausal, must agree to, and comply with, using 2 highly effective methods of birth control (i.e., condom plus spermicide, combined oral contraceptive, implant, injectable, indwelling intrauterine device, sexual abstinence, or a vasectomized partner) while participating in this study. In addition, all women of childbearing potential must agree to continue to use 2 forms of birth control throughout the study and for at least 30 days after administration of the last dose of study drug.

* Evidence of fever within 24 hours of the screening visit is acceptable if observed and documented by a health care provider.

10.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be enrolled in the study:

1. History of any significant hypersensitivity or severe allergic reaction to any beta-lactam antibiotics (e.g., cephalosporins, penicillins, carbapenems, or monobactams).
2. Known or suspected likely infection with New Delhi metallo- (NDM), Verona integron-encoded metallo- (VIM), or imipenemase-metallo-beta-lactamases or oxacillinase (OXA)-beta-lactamases (i.e., Class B or Class D beta-lactamases).
3. For subjects to be enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:
    a. Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., subjects with vesico-ureteral reflux);
    b. Suspected or confirmed prostatitis;
    c. Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;
    d. Previous or planned cystectomy or ileal loop surgery;
    e. Uncomplicated UTI (for example, female subjects with urinary frequency, urgency or pain or discomfort without systemic symptoms or signs of infection);
    f. Complete, permanent obstruction of the urinary tract;

g. Suspected or confirmed perinephric or renal corticomedullary abscess;

h. Polycystic kidney disease; or

i. Any recent history of trauma to the pelvis or urinary tract.

4. For subjects to be enrolled with the primary indication of cIAI, any of the following conditions:

   a. Incomplete drainage of suspected or known intra-abdominal source;

   b. Likely to receive ongoing antibacterial drug prophylaxis or chronic suppressive therapy after intravenous treatment of cIAI;

   c. Source of infection thought to be related to or involving a non-removable prosthesis (e.g. intra-abdominal mesh) or implantable device, line (e.g. peritoneal catheter) or stent (e.g. biliary stent);

   d. Uncomplicated intra-abdominal infection, such as simple appendicitis, simple cholecystitis or gangrenous cholecystitis without rupture;

   e. Patients with infected necrotizing pancreatitis or pancreatic abscess;

   f. Patients whose surgery will include staged abdominal repair or "open abdomen" technique, or marsupialization (i.e. patients who undergo a surgical procedure where fascial closure is performed are eligible. The skin incision may be left open for purposes of wound management as long as fascial closure is accomplished);

   g. Patients in whom the intra-abdominal process is deemed not likely to be infectious in origin (e.g. bowel obstruction, ischemic bowel without perforation, traumatic bowel perforation within past 12 hours, perforated gastroduodenal ulcer within 24 hours); or

   h. Non-intra-abdominal infection (e.g. infection or abscess of the abdominal wall without extension into the intra-abdominal cavity).

5. For subjects to be enrolled with the primary indication of HABP or VABP, any of the following conditions:

   a. Diagnosis of ventilator-associated tracheobronchitis; or

   b. Inability to obtain proper respiratory specimens for culture.

6. For subjects to be enrolled with the indication of bacteremia unrelated to cUTI or AP, cIAI, HABP, and VABP, any of the following:

   a. Unverified CRE infection; or

   b. Source of infection thought to be related to or involving a non-removable or implantable device or line.

7. Evidence of immediately life-threatening disease where in the opinion of the Investigator, the subject is unlikely to survive more than 72 hours from randomization.
8. Acute Physiology and Chronic Health Evaluation (APACHE) II score >30. *An APACHE II score is only required if calculated*.
9. Known or suspected endocarditis, meningitis, or osteomyelitis.
10. Irremovable or implantable device or line thought to be the potential source of infection.
11. Evidence of significant hepatic, hematological, or immunologic disease or dysfunction determined by any of the following:
    a. Known fulminant viral hepatitis
    b. Subjects meeting Hy's criterion of ALT or AST >3 × ULN AND total bilirubin >2 × ULN AND no other explanation such as hepatitis or acute liver injury, etc.;
    c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy; or
    d. Human immunodeficiency virus with either a CD4 count <200 cells/mm^3 at the last measurement, or current diagnosis of another Acquired Immune Deficiency Syndrome-defining illness.
12. Women who are pregnant or breastfeeding.
13. Require the use of inhaled antibiotics.
14. Participation in any study involving administration of an investigational agent or device within 30 days prior to randomization into this study or previous participation in the current study.
15. Previous participation in a study of RPX7009.
16. Any condition that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.

10.3 Prior and Concomitant Treatment

Reasonable efforts will be made to determine all relevant concomitant medications received during the study and within 14 days before administration of study drug. Relevant concomitant treatments (non-pharmacologic treatments) which include any surgical or diagnostic procedures will also be captured in the source documents.

10.3.1 Permitted Non-antibacterial Treatment

Subjects may continue standard non-antibacterial therapy (unless excluded in Section 10.3.4).

10.3.2 Permitted Antibacterial Treatments

Subjects in both treatment arms may receive coverage (e.g., vancomycin or linezolid) for gram-positive organisms, as deemed necessary by the Investigator.

Subjects with cIAI randomized to the BAT treatment arm may receive metronidazole.

Subjects with cUTI or AP who are randomized to Carbavance (meropenem/RPX7009) or to BAT and are treated with ceftazidime-avibactam should receive Carbavance (meropenem/RPX7009) or ceftazidime-avibactam alone, respectively.

Subjects with cIAI, HABP, VABP, or bacteremia who are randomized to Carbavance (meropenem/ RPX7009) or to BAT and are treated with ceftazidime-avibactam should receive Carbavance (meropenem/RPX7009) or ceftazidime-avibactam alone, respectively. However, if the Investigator believes it is medically necessary, subjects may receive supportive aminoglycoside therapy in conjunction with Carbavance (meropenem/RPX7009) or ceftazidime-avibactam until culture information is available or for the first 72 hours, whichever is the shorter. Aminoglycoside treatment should be discontinued once the subject's organism is shown to be susceptible to Carbavance (meropenem/RPX7009) or ceftazidime-avibactam and the subject is clinically improving. The use of an aminoglycoside beyond 72 hours in subjects with a pathogen(s) susceptible to Carbavance (meropenem/RPX7009) or ceftazidime-avibactam will be considered a treatment failure.

Inhaled antibiotics, including aminoglycosides, are not permitted.

Bladder irrigation with antibiotics or antibiotics administered directly via a urinary catheter are not permitted.

Intra-abdominal irrigation with antibiotics or antibiotics administered through a peritoneal dialysis catheter or other intra-abdominal catheter are not permitted.

10.3.3 Permitted Anti-infective Adjunctive Therapies and Procedures

Local care for superficial wounds is permitted (i.e., topical antiseptic therapy, topical antibiotic ointment, wet-to-dry dressing change). The use of topical antibiotic therapy with activity against gram-negative organisms is discouraged, but will not constitute a failure of the primary antibiotic regimen if administered.

10.3.4 Concomitant Medication Precautions and Exclusions

Caution should be used in subjects receiving concurrent valproic acid or probenecid as use of carbapenems may lower the serum concentration of these agents. Physicians are therefore advised to consider checking serum levels of these agents frequently in patients receiving concurrent Carbavance or carbapenems. A one-time dose of vecuronium, rocuronium, or other paralytic agent during intubation is permitted. Due to drug-drug interactions between rocuronium, vecuronium, and similar paralytic agents and several BAT agents (including aminoglycosides and polymyxins) investigators are cautioned not to choose aminoglycosides or polymyxins as BAT in patients with ongoing receipt (i.e. continuous infusion) of rocuronium, vecuronium, or other paralytic agent.

10.4 Randomization and Treatment Group Assignment

Subjects will be randomized to receive either Carbavance (meropenem/RPX7009) 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. A manual will be provided that describes the IWRS and includes complete user instructions.

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. Asia Pacific vs. Rest of World).

Enrollment will continue until at least 45 subjects (30 Carbavance [meropenem/RPX7009], 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 Carbavance [meropenem/RPX7009], 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 eCRF.

10.5 Subject Numbering

Subjects will be assigned a screening number during screening. Once enrolled in the study, subjects will be assigned a unique study subject number by IWRS.

11 STUDY DRUGS

Intravenous study drug will be administered in an open-label design. The following drugs will be administered in this study:

- Carbavance (meropenem/RPX7009) for IV infusion, administered as a 2 g/2 g dose diluted in normal saline to a volume of 250 mL and infused for 3 hours q8h; and
- Subjects will receive BAT, with IV antibiotics, either alone or in combination, chosen from the following: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycoside (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam. Details for dose and frequency of administration of BAT (as well as warnings, precautions, and contraindications) can be found in the referenced summaries of product characteristics for the specific antibacterials selected by the Investigator as BAT.[4,7,8,9,10,11,12,13,14] Investigators will be instructed to select only country-approved therapies.

Infusions of IV study drugs will occur for 7 to 14 days. Subjects whose cultured pathogen is shown not to be susceptible to Carbavance (meropenem/RPX7009) or the treatment chosen as BAT may continue that treatment as long as the subject is clinically improving. If, more than 72 hours post-randomization, the subject is not clinically improving, and the cultured pathogen is shown not to be susceptible to Carbavance (meropenem/RPX7009) or the treatment chosen as BAT and the Investigator elects to change antibacterial therapy, EOT procedures should be performed and the subject should complete further visits as planned.

11.1 Description of Carbavance (Meropenem/RPX7009)

Meropenem is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. When reconstituted as instructed, each 1 g vial will deliver 1 g of meropenem for injection.

RPX7009 is a sterile, lyophilized white to off-white powder presented in 20 mL single-use vials. Each labeled vial contains enough RPX7009 to deliver either 500 mg or 1000 mg RPX7009 when reconstituted and prepared according to instructions. Once reconstituted, it is a clear, colorless to yellow solution.

11.1.1 Administration of Carbavance (Meropenem/RPX7009)

A pharmacist will be responsible for providing Carbavance (meropenem/RPX7009) to the study personnel for administration. The study drug will be provided ready for IV infusion. Subjects will receive Carbavance (meropenem/RPX7009) 2 g/2 g diluted in normal saline to a volume of 250 mL infused for 3 hours q8h.

Each dose of IV study drug will be delivered over approximately 3 hours by programmable infusion pump. The time at which the infusion is started and stopped must be recorded. Instances where a dose is interrupted by more than 10 minutes should be noted in the source documents, including the reason for interruption. The reasons for missed doses should be noted in the source documents. Subjects will receive infusions every 8 hours (±2 hours). Infusions that fall outside of that q8h dosing (± 2 hours) will be captured as protocol deviations.

Dosing time is considered to be relative to the start of infusion. For additional information on drug product dilution, infusion volumes, and dispensing instructions, refer to the Rempex-506 Pharmacy Manual.

11.1.2 Dosing in Subjects with Renal Insufficiency

As summarized in Section 7.5.3 and Appendix 4, in subjects with impaired renal function, both meropenem and RPX7009 continue to follow a linear PK profile, allowing the ratio of meropenem and RPX7009 to be maintained in subjects with reduced renal function.

Table 7 summarizes recommended Carbavance dosing regimens for subjects with renal impairment, including subjects receiving hemodialysis.

Sites will be responsible for testing estimated creatinine clearance in the local laboratory per institutional standard operating procedures and are responsible for ensuring dose adjustments are made accordingly. Estimated creatinine clearance and dose adjustment data will be captured in source documents and in eCRF.

Table 7. Reduced Renal Function Dose Adjustment Table

Estimated Creatinine Clearance, ml/min (Cockcroft-Gault)	Carbavance Dosage Regimen (All doses infused over 3 hours)
≥50	Meropenem 2 g / RPX7009 2 g q8h
≥30 – 49	Meropenem 1 g / RPX7009 1 g q8h
≥20 – 29	Meropenem 1 g / RPX7009 1 g q12h
≥10-19	Meropenem 500 mg / RPX7009 500 mg q12h
<10	Meropenem 500 mg / RPX7009 500 mg q24h[a]

a. Subjects with an estimated creatinine clearance of less than 10 ml/min are required to receive dialysis at least twice per week. Maintenance doses of Carbavance in these subjects should be administered as soon as possible after the dialysis session. For example, if a subject is scheduled to receive Carbavance at 18:00 but receives hemodialysis at 13:00, the planned 18:00 Carbavance dose should be given after the dialysis session is completed (rather than waiting until 18:00).

q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.

11.2 Description of Best Available Therapy

Subjects randomized to BAT will be treated with IV antibiotics, either alone or in combination, chosen from the following: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin or gentamicin), polymyxin B, and ceftazidime-avibactam. The doses and combinations for BAT will be determined by the Investigator.

Ceftazidime-avibactam may also be used as BAT, but may not be given in combination with other BAT agents, with the exception of concurrent aminoglycoside therapy for either 72 hours/pending susceptibility testing in patients with cIAI, HABP, VABP and bacteremia, similar to Carbavance (See Section 10.3.2). Details for dose and frequency of administration of BAT (as well as warnings, precautions, and contraindications) can be found in the summaries of product characteristics for the specific antibacterials selected by the Investigator for BAT.[4,7,8,9,10,11,12,13,14,16] Investigators will be instructed to select only country-approved therapies.

Investigators will be asked to identify the choice of BAT in advance of randomization to minimize potential selection bias. Modification of BAT is permitted based on susceptibility information for up to 72 hours post-randomization. Changes in treatment (other than dose adjustment) more than 72 hours post-randomization will constitute a clinical outcome of failure. End of Treatment procedures should be performed and treatment changed as determined by the Investigator. Subjects will complete all study visits and procedures according to Table 1.

11.3 Carbavance (Meropenem/RPX7009) Labeling and Packaging

The Sponsor or their designee will package, label, and supply Carbavance (meropenem/RPX7009) according to applicable regulatory requirements. Other medications to be used in the BAT treatment arm will be obtained through usual processes as directed by the investigative sites.

The investigational medicinal product will be labeled in appropriate local language according to Annex 13 Good Manufacturing Practices (GMP) and country specific requirements, packaged, stored released, and distributed according to current GMP.

11.4 Study Drug Storage Conditions

The Investigator or an approved representative (e.g., pharmacist) will ensure that all Carbavance (meropenem/RPX7009) is stored in a locked secured area (with limited access available to appropriate study personnel) only under recommended storage conditions and in accordance with applicable regulatory requirements. Best Available Therapy medications will be stored in accordance with their label, as directed by the Investigator and/or associated care team members.

All study drug should be stored, per labeling. Refer to the Pharmacy Manual and Temperature Excursion Process for temperatures and allowances.

11.5 Receipt of Supplies

Upon receipt of Carbavance (meropenem/RPX7009), the pharmacist or designated study site personnel will visually inspect the shipment and verify the drug information, quantity, and condition of the kits received. An investigational drug transmittal and receipt form will be completed and signed by the pharmacist. Receipt of shipment will be verified through the IWRS.

11.6 Study Drug Accountability

It is the responsibility of the Investigator to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and available to regulatory agencies for inspection at any time.

11.7 Carbavance (Meropenem/RPX7009) Handling and Return

Upon the completion or termination of the study, the Sponsor or the Sponsor's representative will provide disposal instructions for all unused and/or partially used Carbavance (meropenem/RPX7009) at the investigational site. It is the Investigator's responsibility to ensure that the instructions provided by the Sponsor or the Sponsor's representative are followed and that appropriate records of the return or disposal of Carbavance (meropenem/RPX7009) are documented and maintained. No unused drug may be returned or destroyed until it has been fully accounted for by the Sponsor's monitor (or designee).

12 STUDY ASSESSMENTS AND PROCEDURES

12.1 Screening (Day -1 or Day 1 Pre-randomization)

The screening visit can occur up to 24 hours prior to first dose of study drug unless otherwise noted below. Screening procedures done only for study purposes may only be performed after informed consent has been obtained. If a subject is unable to provide informed consent due to their medical condition, the subject's legal representative will be provided with study information in order for consent to be obtained. If the screening sample for culture is taken per standard of care before the subject signs informed consent (or consent is obtained from the subject's legal representative), that isolate may be used for baseline and sent to the central laboratory as long as the sample was collected within 72 hours (96 hours for cIAI) of the first dose of study drug. Screening assessments will include the following:

- Review of all inclusion and exclusion criteria (See Section 10.1 and Section 10.2, respectively);
- Record medical/surgical history including all clinically significant past and present illnesses (See Section 12.4.2);
- Record relevant prior and concomitant medications taken within the previous 14 days and all current drugs taken (See Section 12.4.3);
- Record demographic information including name, sex, age, race, weight, and alcohol use (See Section 12.4.4);
- Record height and weight (See Section 12.4.4);
- Perform complete physical examination (See Section 12.4.4);
- Perform a chest x-ray, magnetic resonance imaging (MRI), or computed tomography (CT) scan in subjects with HABP or VABP only; a chest x-ray, MRI, or CT scan performed for standard of care in order to support a diagnosis within 48 hours of randomization is acceptable (See Section 12.4.4);
- Obtain vital sign measurements, including blood pressure, heart rate, respiratory rate, and temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (see Section 12.4.6);
- Perform serum and urine pregnancy test (for women of childbearing potential only) (See Section 12.4.9);
- Perform 12-lead ECG (See Section 12.4.7);
- Urine sample for screening laboratory assessments; labs collected for standard of care in order to support a diagnosis within 48 hours of randomization are acceptable (See Section 12.4.9);
- Blood samples for screening laboratory assessments: labs collected for standard of care in order to support a diagnosis within 48 hours of randomization are acceptable (See Section 12.4.9); and
- Identify choice for BAT in the event the subject is randomized to BAT.

12.2 Treatment Period (Day 1 up to Day 14)

The date of the first dose of study drug will be considered Day 1, and subsequent study days are defined by calendar days thereafter. Starting on Day 1, subjects are expected to receive daily IV treatment for 7 to 14 days.

The following procedures will be performed daily throughout the treatment period unless otherwise indicated:

- Continue to administer routine care according to local standard;
- Assess adverse events (See Section 14.1);
- Record concomitant medications (See Section 12.4.3);
- Perform a limited physical examination (If a subject does not display symptoms, no limited physical examination needs to be performed) (See Section 12.4.4);
- Continue IV study drug therapy and record study drug dosing information (time of administration, dose) daily;
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6); and
- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to the local lab for analysis (See Section 12.4.14).

12.2.1 Day 1 Pre-Dose

Day 1 may be the same day as screening, or may occur up to 24 hours after screening. The calendar date of the first dose of study drug will be considered Day 1. The following procedures will be performed on Day 1 (in addition to any screening procedures also performed):

- Review all inclusion and exclusion criteria, including microbiology data (if available) (See Section 10.1 and Section 10.2, respectively);
- Assess adverse events (See Section 14.1);
- Record relevant concomitant medications (See Section 12.4.3);
- Obtain vital sign measurements, including blood pressure, heart rate, and respiratory rate. Screening vital signs may be used if collected within 4 hours of the first dose of IV study drug. (See Section 12.4.5);
- Assess pre-dose clinical signs/symptoms. Screening clinical signs and symptoms may be used if collected within 4 hours of the first dose of IV study drug. (See Section 12.4.6);
- Collect pre-dose urine sample for urinalysis and send to the central lab (See Section 12.4.9);
- Collect pre-dose blood samples for serum chemistry and hematology analyses and send to the central lab (See Section 12.4.9);
- Collect pre-dose infection site-specific sample for culture and send to local lab for analysis and susceptibility testing (See Section 12.4.14);
- Collect blood cultures and send to local lab for analysis. (See Section 12.4.14);

- Blinded Investigator performs a baseline assessment of signs and symptoms (See Section 12.4.6);
- Obtain randomized treatment assignment via the IWRS; and
- For subjects with cIAI, operative drainage/debridement/removal (including open laparotomy, percutaneous drainage, or laparoscopic surgery) of any intra-abdominal collection or other potential source of intra-abdominal infection should be performed within 96 hours before or 24 hours after the first dose of study drug.

12.2.2 Study Day 1 Post-Dose

The following procedures will be performed on Day 1 after administration of first dose of study drug:

- Administer IV study drug at appropriate times during the day and record start and stop time of study drug administration;
- Assess adverse events (See Section 14.1); and
- For subjects receiving Carbavance (meropenem/RPX7009) only: Collect PK blood samples within 30 minutes and 2 to 3 hours after end of first infusion (See Section 12.4.10).

12.2.3 Day 3

All subjects will be assessed on Day 3 of treatment. The following procedures will be performed on Day 3:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medications (See Section 12.4.3);
- Perform complete physical examination (See Section 12.4.4);
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6);
- Record clinical outcome (See Section 12.4.6);
- Collect urine sample for urinalysis (See Section 12.4.9);
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9);
- Administer IV study drug therapy at appropriate times and record study drug dosing information (time of administration, dose);
- For subjects receiving Carbavance (meropenem/RPX7009) only: Collect PK blood sample within 30 minutes after end of one of that day's infusions (See Section 12.4.10);
- Collect infection site-specific sample for culture (See Section 12.4.14); and
- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to local lab for analysis (See Section 12.4.14).

12.2.4 Day 5

All subjects will be assessed on Day 5 of treatment. The following procedures will be performed on Day 5:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medications (See Section 12.4.3);
- Perform a complete physical examination (See Section 12.4.4);
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6);
- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to local lab for analysis (See Section 12.4.14);
- Administer IV study drug therapy and record study drug dosing information (time of administration, dose) daily; and
- For subjects receiving Carbavance (meropenem/RPX7009) only: Collect PK blood sample within 30 minutes after end of one of that day's infusions (See Section 12.4.10).

12.2.5 Day 7

All subjects will be assessed on Day 7 of treatment. The following procedures will be performed on Day 7:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medications (See Section 12.4.3);
- Perform complete physical examination (See Section 12.4.4);
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6);
- Record clinical outcome (See Section 12.4.6);
- Collect urine sample for urinalysis (See Section 12.4.9);
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9);
- Administer IV study drug therapy at appropriate times and record study drug dosing information (time of administration, dose); and
- Collect infection site-specific sample for culture (see Section 12.4.14).

12.2.6 End of Treatment (EOT)

All subjects will be assessed on their last day of treatment, +1 day (any time from Day 7 to Day 14). If EOT is on Day 7, visit activities will be combined. If a subject's treatment is changed after 72 hours post-randomization based on susceptibility data, EOT procedures will be performed and the subject will complete further visits as planned (See Section 11). The following procedures will be performed at the EOT visit:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medication (See Section 12.4.3);

- Perform complete physical examination (See Section 12.4.4);
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6);
- Record clinical outcome (See Section 12.4.6);
- Blinded Investigator completes assessment of signs and symptoms and records clinical outcome (See Section 12.4.6);
- Perform 12-lead ECG (See Section 12.4.7);
- Perform urine and serum pregnancy test (for women of childbearing potential only) (See Section 12.4.9);
- Collect urine samples for urinalysis (See Section 12.4.9);
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9);
- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to local lab for analysis (See Section 12.4.14);
- Administer IV study drug therapy at appropriate times and record study drug dosing information (time of administration, dose); and
- Collect infection site-specific sample for culture (See Section 12.4.14).

12.3 Follow-up Period

12.3.1 Test of Cure (TOC) Visit (7 days [±2 days] post-EOT)

Assessments for TOC will be performed 7 days (±2 days) post-EOT (Day 12 to Day 23). Any subjects receiving treatment for less than 7 days should have a TOC visit on Day 12 (+2 days). The following procedures will be performed at the TOC visit:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medications (See Section 12.4.3);
- Perform limited physical examination (If a subject does not display symptoms, no limited physical examination needs to be performed) (See Section 12.4.4);
- Perform a chest x-ray, MRI, or CT scan in subjects with HABP or VABP only (See Section 12.4.4);
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6);
- Record clinical outcome (See Section 12.4.6);
- Blinded Investigator assesses signs and symptoms and records clinical outcome (See Section 12.4.6);
- Collect urine samples for urinalysis (See Section 12.4.9);
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9);
- Collect infection site-specific sample for culture (See Section 12.4.14); and

- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to local lab for analysis (See Section 12.4.14).

12.3.2 Late Follow-Up (LFU) Visit (14 days [±2 days] post-EOT)

Assessments for LFU will be performed 14 days (±2 days) post-EOT (Day 19 to Day 30). Any subjects receiving treatment for less than 7 days should have an LFU visit on Day 19 (+2 days). 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. For any outpatient subjects with an LFU visit occurring before Day 28, a phone call to assess survival will be made on Day 28. The following procedures will be performed at the LFU visit:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medications (See Section 12.4.3);
- Perform limited physical examination (If a subject does not display symptoms, no limited physical examination needs to be performed) (See Section 12.4.4);
- Assess clinical signs/symptoms and vital signs (See Section 12.4.6);
- Record clinical outcome (See Section 12.4.6);
- Collect urine samples for urinalysis (See Section 12.4.9);
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9);
- Collect infection site-specific sample for culture (See Section 12.4.14); and
- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to local lab for analysis (See Section 12.4.14).

12.3.3 Early Termination

Subjects who withdraw from the study for any reason prior to the completion of the trial will complete an early termination visit. The following procedures will be performed at the early termination visit:

- Assess adverse events (See Section 14.1);
- Record relevant concomitant medication (See Section 12.4.3);
- Perform complete physical examination (See Section 12.4.4);
- Obtain vital sign measurements, including blood pressure, heart rate, respiratory rate and temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (See Section 12.4.6);
- Record clinical outcome (See Section 12.4.6);
- Blinded Investigator performs a review of blinded vital signs and laboratory data, an assessment of signs and symptoms, and an assessment of clinical outcome (See Section 12.4.6);
- Perform 12-lead ECG (See Section 12.4.7);

- Perform urine and serum pregnancy test (for women of childbearing potential only) (See Section 12.4.9);
- Collect urine samples for urinalysis (See Section 12.4.9);
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9);
- Collect infection site-specific sample for culture (See Section 12.4.14); and
- When applicable (e.g., subjects with active bacteremia), collect blood cultures and send to local lab for analysis (See Section 12.4.14).

12.4 Study Interventions/Procedures

12.4.1 Informed Consent

Informed consent should be obtained by the Investigator from the subject prior to study participation in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.

All subjects will be informed of the nature and purpose of this study. An informed consent document approved by a regional Independent Ethics Committee (IEC)/Institutional Review Board (IRB) must be signed and dated prior to any study-related procedures being performed at screening. The original signed informed consent form for each participating subject will be filed with records kept by the Investigator(s) and will be documented in the clinical or research record. A copy of the signed/dated informed consent document must be provided to the subject and/or the subject's legal representative. The rights and welfare of the subjects will be protected by emphasizing to them (or their legal representative) that the quality of their care will not be adversely affected if they decline to participate in or withdraw from the study. Subjects may withdraw from the study at any time.

For non-English speaking subjects, a translated version of the informed consent document will be available and the consent process will take place in that subject's primary language.

12.4.2 Medical History

Relevant medical history, surgical history, and allergies will be collected at screening.

12.4.3 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. See Section 10.3.4 for precautions and exclusions of concomitant medications during the study.

12.4.4 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 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.

All physical examinations will be performed by site personnel who are experienced and routinely conduct physical examinations (e.g., physician, physician's assistant, or nurse practitioner [within the US]).

12.4.5 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, will be measured at the indicated visits. Vital signs at approximately the same time as the assessment of signs and symptoms and recorded in the source and eCRF.

12.4.6 Assessment of Signs and Symptoms

Each sign/symptom for each respective presenting indication (Table 8) will be assigned a classification of new onset, continuing (increased, decreased, no change), or resolved (returned to pre-infection state). Responses should be collected by the PI or qualified Sub-investigator and recorded in the source documents on each study day. When possible the same investigator should collect the information at approximately the same time each day. Indication specific Signs and Symptoms are only collected for a subject's primary site of infection (i.e., if a subject has a cUTI and bacteremia, only cUTI information is collected).

Table 8. Signs and Symptoms for Presenting Indications

Presenting Indication	Signs and Symptoms	
cUTI or AP	• Urinary frequency, • Urinary urgency, • Dysuria, • Nausea, • Vomiting, • Abdominal pain,	• Supra-pubic pain or discomfort, • Flank pain, • Costo-vertebral angle tenderness on examination, and • Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F])
cIAI	• Chills, rigors, or fevers (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature≥38.3°C [≥100.9°F]) Hypotension, systolic BP < 90mmHg	• Abdominal pain, • Nausea or vomiting, • Abdominal mass on clinical examination, • Altered mental status, and • Elevated total peripheral WBC count (> 10,000/mm)
HABP/VABP mechanically ventilated subjects	• Rales, • Dullness on percussion, • Bronchial breath sounds, • Egophony,	• Purulent secretion, and • Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F])
HABP/VABP non-mechanically ventilated subjects	• Cough, • Rales, • Dullness on percussion, • Bronchial breath sounds, • Egophony,	• Dyspnea, • Respiratory rate >25 per minute, and • Fever (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F])
Bacteremia	• Heart rate >100 bpm, • Respiratory rate >25 per minute, • Systolic blood pressure <90 mmHg, and • Fever* (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F])	

*Maximum daily temperature over the previous 24 hours will be recorded when fever is reported.

Findings from the Assessment of Signs and Symptoms will be captured on a Signs and Symptoms CRF and should not be documented as adverse events.

12.4.7 12-Lead ECG

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
- QT_c 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.

12.4.8 Chest X-Ray/Radiology

Chest x-rays, CT scans or MRIs will be performed in subjects with HABP or VABP at designated time points as specified by the Schedule of Procedures (Table 1) to evaluate for the presence of infiltrates. Imaging should be conducted per institutional guidelines and results recorded in the source documents and the eCRF.

12.4.9 Clinical Laboratory Assessments

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 (manual differential at baseline), platelet count, hemoglobin, and hematocrit).
- 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.

12.4.10 Pharmacokinetic Sampling

Pharmacokinetic sampling will be completed in subjects randomized to Carbavance (meropenem/RPX7009) 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.

For specific collection and storage procedures, please refer to the Study Reference Manual.

12.4.11 Hospitalization Assessments

Hospital admissions, transfers, and discharges will be captured in the source documents for each enrolled subject over the course of the study. Date and time will be captured for the original admission as well as each time a subject is transferred from an ICU to a non-ICU. The date and time of hospital discharge will be captured as well as where each subject was discharged to (e.g., home, another hospital, long term adult care facility, etc.).

12.4.12 Mechanical Ventilator Assessments

Subjects whose primary indication for enrollment into the study is HABP or VABP, and require mechanical ventilation support, will be managed by the study investigators per institutional guidelines. Data regarding mechanical ventilation will be captured in the source documents and the eCRFs.

12.4.13 Infection Source Control

It is expected that prior to enrollment adequate source control (in the opinion of the PI) should be achieved for each subject's index infection (for example, for a subject enrolled due to cIAI, the intra-abdominal source should be properly drained/debrided/removed; for a subject with cUTI, any indwelling catheter should be removed or replaced). Any secondary drainage that occurs within 4 days of the initial procedure will be counted as a second part of the initial planned procedure. It is further expected that such control should be maintained throughout the subject's participation in the study to the extent possible (i.e. if the subject has a recurrent intra-abdominal abscess, this should be drained in accordance with site-specific practices). A qualified independent reviewer will access the adequacy of source control in subjects whose outcome is clinical failure, death or indeterminate. Additional medical records will be collected and submitted to the reviewer as appropriate.

12.4.14 Microbiology Assessments

Accurate microbiologic results are critical to successfully meet the study objectives. All specimens will be sent to the local laboratory for culture and susceptibility testing per institutional standards. For all carbapenem-resistant gram-negative organisms, the MIC to carbapenems will be captured in the eCRF. Susceptibility to Carbavance as determined by Kirby-Bauer disk methodology will be captured at baseline. If the resistance mechanism for each carbapenem-resistant organism cultured during the study is known, it should be captured in source documents.

Any isolated bacteria deemed to be contributory to the infectious process will be designated a pathogen by the PI and identified by genus and species. The local laboratory will culture each sample for organism identification, quantification (when applicable), and susceptibility testing per institutional standards. CRE cultures at baseline and all post-baseline isolates cultured at the local laboratory and designated as pathogens by the PI will be sent to the central laboratory (Medpace Reference Laboratory [MRL]) for confirmation of identification and susceptibility testing results.

All subjects must have a specimen sample from the site of infection (i.e., blood, urine, intra-abdominal fluid/tissue, or respiratory secretion) and two sets of blood samples from two separate venipuncture sites collected 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. When it is not possible to collect specimens for culture immediately prior to the first dose of study drug, cultures that have been obtained no more than 72 hours prior to (or for cIAI, 96 hours before or 24 hours after) the first dose of study drug are acceptable. The results of this culture will determine whether the subject meets the criteria for the Microbiological CRE Modified Intent-to-Treat (mCRE-MITT) Population or the Microbiological Modified Intent-to-Treat (m-MITT) Population.

Kirby-Bauer disks for Carbavance (meropenem\RPX7009) susceptibility testing will be provided by the Sponsor for baseline testing. Susceptibility testing for BAT and other antimicrobials will be done per each institution's standard procedures. In instances where susceptibility testing indicates resistance to the study drug but the subject is clinically improving, the subject should remain on study drug at the Investigator's discretion.

If the screening sample for culture is taken per standard of care before the subject (or a 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 within 72 hours of (or for cIAI, 96 hours before or 24 hours after) the first dose of study drug.

12.4.14.1 Urine Specimens

For subjects with cUTI or AP, urine samples will be collected by clean catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration.

CRE isolates at baseline, and all post-baseline isolates cultured at the local laboratory and designated as pathogens by the PI will be sent to the central laboratory for confirmation of identification and susceptibility testing results.

The baseline urine cultures must grow at least one defined bacterial pathogen at concentration of $\geq 10^5$ CFU/mL. Up to 2 isolated pathogens will be allowed per baseline urine culture provided they are at concentrations of $\geq 10^5$ CFU/mL of urine.

The baseline urine samples submitted for culture must have a microscopic evaluation (e.g., gram stain) and a dipstick analysis performed by the local microbiology laboratory.

For all post-baseline urine cultures, only pathogens at concentrations of $\geq 10^3$ CFU/mL of urine will be sent to the central laboratory. Up to 2 isolated pathogens will be allowed per post-baseline urine culture provided they are at concentrations of $\geq 10^3$ CFU/mL.

For both baseline and post-baseline cultures - if a subject grows 3 or more bacterial organisms in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if the organism also grows in a concurrently obtained blood culture. Isolates from contaminated samples should not be sent to the central lab.

12.4.14.2 Intra-abdominal Specimens

For subjects with cIAI, acceptable specimens should include at least one intra-abdominal culture obtained during the time of surgical (or percutaneous) intervention. The specimen must be collected within approximately 96 hours before or 24 hours after of the first dose of study drug (preferably prior to study drug administration). Baseline specimens should be sent for gram stain, pathogen identification, and susceptibility testing at the local laboratory. Isolates from the baseline specimen will also be sent to the central laboratory for confirmatory testing.

Post-baseline specimens should be collected as clinically indicated and sent to the local laboratory for testing. Isolates from all post-baseline specimens should be sent to the central laboratory for confirmatory testing.

To be considered adequate, a specimen should consist of at least 1mL of fluid or tissue representative of the material associated with the clinical infection.

Gram stains will be conducted per institutional standards and gram stain data should be captured in source documents. If any intra-abdominal culture is performed (including cultures taken on swab), pathogens exhibiting significant growth on cultures identified by the site laboratory's routine procedures should be sent to the central lab, even if from a specimen that does not meet the aforementioned adequacy criteria.

12.4.14.3 Respiratory Tract Specimens

For subjects with HABP or VABP, acceptable specimens should include at least one positive pretreatment sample obtained by Protected Specimen Brush (PSB) with bronchial alveolar lavage (BAL) or mini-BAL, by non-bronchoscopic-BAL (NBBAL), or by Protected Endotracheal Catheter obtained prior to randomization and treatment. Non-ventilated subjects may have specimens obtained via deep expectoration or expectorated/induced sputum.

All specimens should be sent for gram stain, quantitative culture, pathogen identification and susceptibility testing.

To be adequate, respiratory samples from expectorated or induced sputum should show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100x field. Colony counts $\geq 10^3$ CFU/mL are considered the threshold for identifying pathologic bacteria from PSB and the CombiCath® NBBAL, $\geq 10^4$ CFU/mL for bronchoscopic BAL or the BALCath NBBAL, and $\geq 10^6$ CFU/mL for endotracheal aspirate specimens.

Gram stains will be conducted per institutional standards and gram stain data should be captured in source documents. Colony counts are not expected to be performed on expectorated or induced sputum. If the sputum is cultured all pathogens exhibiting significant growth identified by the site

laboratory's routine procedures should be sent to the central lab, even if from a specimen that does not meet the specimen adequacy criteria described above.

12.4.14.4 Blood and Other Tissue Specimens

Two sets of samples from 2 separate venipuncture sites are required for blood cultures in all study participants. If a blood culture is positive at baseline, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more).

Additional blood cultures, including blood cultures taken during fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) may also will be collected at the Investigator's discretion.

Isolated pathogens (e.g., considered not to be a contaminant by the PI) from each individual positive blood culture will be sent to the central lab.

If a tissue sample (e.g., kidney biopsy) is collected to determine target pathogen, it should be obtained 72 hours prior to first dose of study drug. The isolated pathogen should be shipped to the central laboratory for confirmation and susceptibility testing. In the event that pre-randomization urine and blood cultures are negative and the subject has a positive tissue culture, the isolated pathogen may qualify as a defined baseline CRE pathogen.

13 SUBJECT AND STUDY DISCONTINUATION

A clear distinction will be made between subjects who withdraw from study drug dosing and those who withdraw from the study. All subjects who withdraw from study drug dosing should be encouraged to follow all study procedures to the LFU visit for safety assessment, even if they withdraw from dosing in absence of a clinical outcome of failure.

The clinical report will include the reason(s) for subject withdrawal from either study drug or the study, as well as details relevant to the withdrawal. If a subject is withdrawn from the study prior to study completion, the subject will undergo early termination procedures (See Section 12.3.3). Any subject withdrawn due to an adverse event (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator or a monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Subjects withdrawn for reasons other than drug-related adverse events may be replaced per Investigator and Sponsor discretion.

13.1 Screening Failures

Subjects who sign and date the informed consent form but who fail to meet the inclusion and exclusion criteria will be defined as screen failures. A screening log, which documents the subject's initials, screening number, and reason(s) for screen failure, is to be maintained by the Investigator for all screen failures. A copy of the log should be retained in the Investigator's study files. Screen Failures will be captured in IWRS.

13.2 Withdrawal from Study Drug

Study drug administration may be discontinued for any of the following reasons at the discretion of the Investigator or the Sponsor's Medical Monitor:

- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject;
- Subject's decision to withdraw;
- Requirement of prohibited concomitant medication; or
- Lack of clinical improvement.

Any subject who prematurely discontinues study drug should complete the study through the LFU visit. The EOT procedures will be performed on the day study drug is discontinued (+1 day).

13.3 Withdrawal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Lost to follow-up;
- Subject's decision to withdraw;
- Withdrawal of consent for reasons other than an adverse event;
- Non-compliance or unwillingness to comply with the procedures required by the protocol; or
- Termination of the study by the Sponsor or designee, contract research organization, US Food and Drug Administration (FDA), or other regulatory authorities.

13.4 Study Site Discontinuation

Reasons for discontinuation of the study at an investigational site may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects;
- Subject enrollment is unsatisfactory;
- Investigator request to withdraw from participation;
- Sponsor decision;
- Serious and/or persistent non-compliance by the Investigator with the protocol, the clinical research agreement, and/or applicable regulatory guidelines in conducting the study;
- Decision by the IRB or IEC to terminate or suspend approval for the investigation or the Investigator; or
- Investigator fraud (i.e., altered data, omitted data, or manufactured data).

14 SAFETY ASSESSMENTS

Safety assessments will include adverse events, clinical laboratory evaluations, vital signs, physical examinations, and ECGs. Relevant changes in physical examinations, vital signs, and safety laboratory tests that are identified as occurring after receiving the first dose of study drug, regardless of whether the change is in an examination finding, test result, or sign or symptom reported by a subject, and regardless of relationship to study drug, will be reported.

14.1 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 most updated version of the Medical Dictionary for Regulatory Activities available (version 15.0 or higher).

Adverse events, which include clinically significant laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Treatment-emergent adverse events, which include clinically significant laboratory test variables, will be monitored and documented from the first dose of study drug until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. Investigators should make assessments for adverse events and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion) should be recorded as an adverse event, not the procedure. The protocol specific Assessment of Signs and Symptoms (see Section 12.4.6) associated with the index infection (cUTI, AP, cIAI, HABP, VABP or bacteremia) and protocol defined Treatment Failure should not be documented as adverse events.

Any medical condition already present at screening or baseline should not be reported as an adverse event, unless the medical condition or signs or symptoms present at baseline worsen in severity or seriousness at any time during the study. In this case, it may be reported as an adverse event at the discretion of the Investigator.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings detected during the study or that are present at baseline and significantly worsen during the study should be reported as adverse events. At the discretion of the Investigator, all National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 laboratory values

should be reported as adverse events. If a clinically significant abnormal laboratory value or assessment is clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the Adverse Event eCRF, not the individual laboratory values. The Investigator will exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require being reported as an adverse event.

14.2 Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

14.3 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For Carbavance (meropenem/RPX7009), the reference safety information is included in the Investigator's Brochure.

Product information for BAT includes referenced summaries of product characteristics (SmPCs) for meropenem, ertapenem, imipenem, tigecycline, colistin, amikacin, tobramycin, gentamicin, polymyxin B, and ceftazidime-avibactam. [4,7,8,9,10,11,12,13,14,16]

The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

14.4 Assessment and Reporting of Adverse Events by the Investigator

The Investigator will review each event and assess its relationship to study drug treatment (not related, unlikely, possible, or probable). Each sign or symptom reported will be graded on the NCI-CTCAE V4.0 toxicity grading 5-point severity scale (Grade 1, 2, 3, 4, and 5), details of which can be found in Appendix 3. The date and time of onset, duration, and outcome (Recovered/Resolved, Recovering/Resolving, Resolved with Sequelae, Not recovered/Resolved, Fatal, or Unknown/Lost to follow-up) of each event will be noted.

Adverse events, including those not listed on the NCI-CTCAE grading system, will be graded on the 5-point scale (mild, moderate, severe, life-threatening, death) and reported in detail as indicated on the eCRF according to the following definitions for rating severity:

- Grade 1 - Mild: asymptomatic or mild symptoms OR clinical or diagnostic observations only OR intervention not indicated.
- Grade 2 - Moderate: minimal, local or noninvasive intervention indicated OR limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

- Grade 3 - Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated OR disabling OR limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, not being bedridden).

  Note: An experience may be severe but may not be serious (e.g., severe headache).
- Grade 4 - Life-threatening consequences: urgent intervention indicated.
- Grade 5 - Death related to adverse event.

Causality Assessment

The relationship of each adverse event will be assessed using the following definitions:

Not related	• Event occurring before dosing. • Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	• Poor temporal relationship with drug treatment. • Event easily explained by subject's clinical state or other factors.
Possible	• Reasonable temporal relationship with drug treatment. • Event could be explained by subject's clinical state or other factors.
Probable	• Reasonable temporal relationship with drug treatment. • Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. • Event cannot easily be explained by subject's clinical state or other factors.

The following factors should also be considered:

- The temporal sequence from study drug administration–
  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases–
  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug–
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug–
  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses–
  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug–
  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

14.5 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
  - NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;

  NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. As the subjects in this study will already be hospitalized, it is likely that unexpected complications and/or prolongation of hospitalization will be the only applicable aspect of this criterion.
- Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will NOT be considered inpatient hospitalizations;
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

14.6 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, the SAE form should be completed electronically in the EDC system for the study. When the form is completed, Medpace Clinical Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to the Medpace Clinical Safety Department (email listed below) or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Fax: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Medpace SAE hotline – Europe:
Telephone: +49-89-89-55-718-44
Fax: +49-89-89-55-718-104
e-mail: EUsafetynotification@medpace.com

Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

14.7 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of becoming aware of the pregnancy. Medpace Clinical Safety will then provide the Exposure In Utero form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

14.8 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the applicable competent authorities concerned, and to the Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

Please refer to the Investigator's Brochure for a list of expected adverse reactions associated with Carbavance (meropenem/RPX7009).

For a list of expected adverse reactions associated with BAT, please refer to the referenced SmPCs for the following antibacterials: meropenem[4], ertapenem[7], imipenem[8], tigecycline[9], colistin[10], amikacin[11], tobramycin[12], gentamicin[13], polymyxin B[14], and ceftazidime-avibactam[16].

All other suspected unexpected serious adverse reactions for Carbavance (meropenem/RPX7009) and BAT will be reported to the applicable competent authorities concerned and to the Ethics Committee concerned as soon as possible, but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

15 EFFICACY EVALUATION

15.1 Efficacy Assessments

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 9). 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 9).

To meet the primary endpoint for EMA and FDA, 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 9.

Table 9. 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 surgical intervention or 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.

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 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, 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 Carbavance (meropenem/RPX7009) 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.

Efficacy Assessments for *HABP and VABP*

Primary Endpoint

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 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 surgical intervention or 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 Carbavance (meropenem/RPX7009) 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).

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 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 surgical intervention or 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 Carbavance (meropenem/RPX7009) 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]

15.1.2 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 10.

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 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 unplanned surgical procedures/percutaneous drainage or initiation of non-study antimicrobials, in addition to the criteria in Table 10 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 10. Criteria for Clinical Outcome

Category	Criteria
Cure	Complete resolution or significant improvement of the baseline signs and symptoms, such that no further surgical intervention 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 require unplanned surgical procedures or percutaneous drainage; • Surgical site wound infection; • 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.

15.1.3 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 11.

Table 11. 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 12.

Table 12. 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.

15.1.4 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 13.

Table 13. 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.

16 PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic characterization, evaluation of plasma PK, and exposures of meropenem and RPX7009 in treated subjects will be performed. Analysis of the PK data will be described in a separate Statistical Analysis Plan.

A pharmacodynamic analysis will be conducted to link meropenem and RPX7009 exposures in each subject with clinical and microbiological outcomes.

17 DATA MANAGEMENT

Study data will be entered into eCRFs at the study sites. Prior to database lock, programmed computer edit checks will be run against the database to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks will be resolved.

Standard eCRFs from the clinical research organization will be used for the study. The data contained in the eCRFs will be obtained directly from the clinical data at the site and will be source-document verified. Each eCRF will be reviewed and signed off by the Investigator.

The data management system to be used will be a fully-integrated study management and clinical database.

Visual and computerized methods of data validation will be applied in order to ensure accurate, consistent, and reliable data for the subsequent statistical analysis.

All raw data generated in connection with this study will be retained in the scientific archives of the site and/or stored by the site in a designated storage facility until at least 2 years after the last approval of a marketing application in an International Conference of Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

18 STATISTICAL METHODS AND DATA ANALYSIS

18.1 Analysis Populations

A schematic summary of the analysis populations for this study is provided in Appendix 1.

The Intent-to-Treat (ITT) Population will include all subjects screened and randomized to study drug (Carbavance [meropenem/RPX7009] or BAT).

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.

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.

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

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

The mCRE-MITT Population (i.e., Primary Efficacy Population) will include subjects who meet the m-MITT criteria and who have a baseline *Enterobacteriaceae* that is confirmed to be meropenem-resistant.

The 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 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 if classified as a failure on clinical outcome, or receive ≥5 days of study drug if classified as a cure on clinical outcome.

The 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 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 if classified as a failure on overall outcome, or receive ≥5 days of study drug if classified as a cure on overall outcome.

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

18.2 Disposition, Demographics, Baseline Characteristics, and Exposure

The number of subjects randomized, treated, completed, and discontinued early from treatment and from study, and the reasons for discontinuation, will be summarized descriptively. Demographic and baseline characteristics will be summarized descriptively. The number of doses of study drug taken by subjects will be summarized descriptively for each treatment group.

18.3 Efficacy Analysis

The efficacy analyses will be descriptive summaries of the proportion of subjects in the mCRE-MITT Population at the TOC visit with a response of success defined according to primary indication. A descriptive summary of all-cause mortality for subjects with HABP, VABP, and bacteremia will be provided. Two-sided, exact binomial 95% confidence intervals (CIs) for the true proportion of responses of success for the primary efficacy endpoint will be reported.

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.

Analyses of the other secondary and exploratory endpoints will be conducted in a similar manner as the analyses above.

18.4 Safety Analysis

All subjects who receive at least 1 dose of study drug (i.e., the MITT Population) will be included in the safety analyses and analyzed based on the actual treatment received. Adverse events will be collected throughout the study duration. A TEAE is defined as an adverse event with a start date and time on or after the first dose of study drug. Treatment-emergent adverse events will be tabulated by NCI-CTCAE Grade. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a TEAE for each unique System Organ Class and Preferred Term will be tabulated. Treatment-emergent adverse events will also be tabulated by severity and by the relationship to study drug in treatment groups as assessed by the Investigator. The number and percentage of subjects in each treatment group reporting at least one occurrence of an SAE will be tabulated. The number and percentage of subjects (in each treatment group) prematurely discontinuing study drug treatment due to a TEAE will be tabulated by System Organ Class and Preferred Term.

Safety laboratory data will be presented by change from baseline. The number and percentage of subjects with laboratory, vital sign, ECG, or physical examination abnormalities at baseline, subsequent visits, or early termination from the study will be tabulated by treatment group. The

results of all laboratory tests, physical examination findings, ECG, and vital signs will be presented in data listings.

18.5 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/or bacteremia.

Subjects will be stratified at randomization based on their presenting indication and by region (North America vs. Europe vs. Asia Pacific vs. Rest of World).

Enrollment will continue until at least 45 subjects (30 Carbavance [meropenem/RPX7009, 15 BAT) with cUTI or AP are documented to have a CRE organism at baseline and until at least 30 subjects with cIAI (20 Carbavance [meropenem/RPX7009], 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.

19 REGULATORY AND ADMINISTRATIVE ASPECTS

19.1 Compliance with Regulatory Requirements

This study will be conducted in compliance with the protocol and all regulatory requirements, in accordance with GCP, including ICH guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

19.2 Institutional Review Board

This protocol, the informed consent document, and all relevant supporting data must be submitted to an IRB/IEC for approval. The IRB/IEC approval of the protocol and informed consent form must be obtained before the study may be initiated.

The Investigator is responsible for keeping the IRB/IEC advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The Investigator is also responsible for notifying the IRB/IEC of all unanticipated risks involving human subjects that occur during the study.

The Office for Human Research Protections considers unanticipated risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

19.3 Informed Consent

The informed consent document must be signed and dated prior to any study-related procedures being performed at screening. The original signed informed consent form for each participating subject will be filed with records kept by the Investigators. A copy of the informed consent document must be provided to the subject and/or the subject's legal representative. Where applicable, the informed consent form will be provided in a certified translation of the local language.

19.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor and the clinical research organization (if applicable); the IRB/IEC approving this research; and the FDA and EMA as well

as any other applicable regulatory authorities, will be granted direct access to study subject original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, subject identity will remain confidential.

19.5 Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

19.6 Protocol Amendment

If a protocol has been filed with regulatory agencies or submitted to an IRB/IEC and requires significant changes, a protocol amendment must be written. Any changes to the protocol will be made by the Sponsor. All amendments will be sent to the study sites that are then responsible for submitting the amendment to their IRB/IEC for approval.

19.7 Case Report Forms: Electronic

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be electronically signed by the PI or a sub-investigator. It is the responsibility of the PI to ensure the eCRFs are completed in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change and person making change). At the completion of the study, a disk will be provided to the Sponsor that will include the per subject eCRF in an individual subject profile.

19.8 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and drug accountability records. All source documents produced in this study will be maintained by the Investigator(s) and made available for inspection by the Sponsor's representatives, the FDA and EMA, or other regulatory authorities.

19.9 Study Monitoring Requirements

Site visits will be conducted by an authorized Sponsor representative (the monitor) to inspect study data, subject's medical records, and eCRFs in accordance with ICH guidelines, GCP, and the respective US or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs.

The Investigator will permit representatives of the Sponsor, the FDA and EMA, and/or respective health authorities to inspect facilities and records relevant to this study.

19.10 Study File Management

It will be the responsibility of the Investigator to assure that the study file at the site is maintained. The Investigator must retain all study records required by the Sponsor and by the applicable regulatory agencies in a secure and safe facility. The Investigator must consult the Sponsor (or designee) before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files.

19.11 Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period;
- All eCRFs properly completed by appropriate study personnel and electronically signed and dated by the Investigator;
- Complete Drug Accountability records (drug inventory log and an inventory of returned or destroyed clinical material);
- Copies of protocol amendments and IRB/IEC approval/notification if appropriate; and
- A summary of the study prepared by the PI (an IRB/IEC summary letter is acceptable).

19.12 Audits

During the course of the study, or after completion of the study, study sites will be selected for an audit by a Quality Assurance (QA) Auditor from the Sponsor (or an auditor appointed by the Sponsor or the Sponsor's authorized representative) and/or an inspector from the FDA, EMA, and/or other regulatory authority.

19.13 Retention of Records

The Sponsor follows US and other national regulations and ICH guidelines in its retention policy.

In the US, the Code of Federal Regulations (CFR) requires for Investigational New Drugs (21 CFR 312.62) that records and documents pertaining to the conduct of this study and the distribution of investigational drugs including eCRFs, consent forms, laboratory test results, and medication inventory records be kept on file by the PI for 2 years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified. International Conference on Harmonization guidelines indicate that documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to US and ICH policies. No study records should be destroyed without prior authorization from the Sponsor.

19.14 Disclosure of Data

The Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of Investigators, their addresses, qualifications and extent of involvement. It is understood that the Investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the FDA and other regulatory authorities, by the Sponsor, and the IRB/IEC as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

19.15 Financial Disclosure

Investigators must provide financial disclosure statements to the Sponsor prior to the start of the study and on a yearly basis and also when any change occurs up to 1 year after the completion of the study.

19.16 Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

20 REFERENCES

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6. Investigator's Brochure: Carbavance™ (Meropenem/RPX7009). San Diego, CA; Rempex Pharmaceuticals, Inc.:2014.

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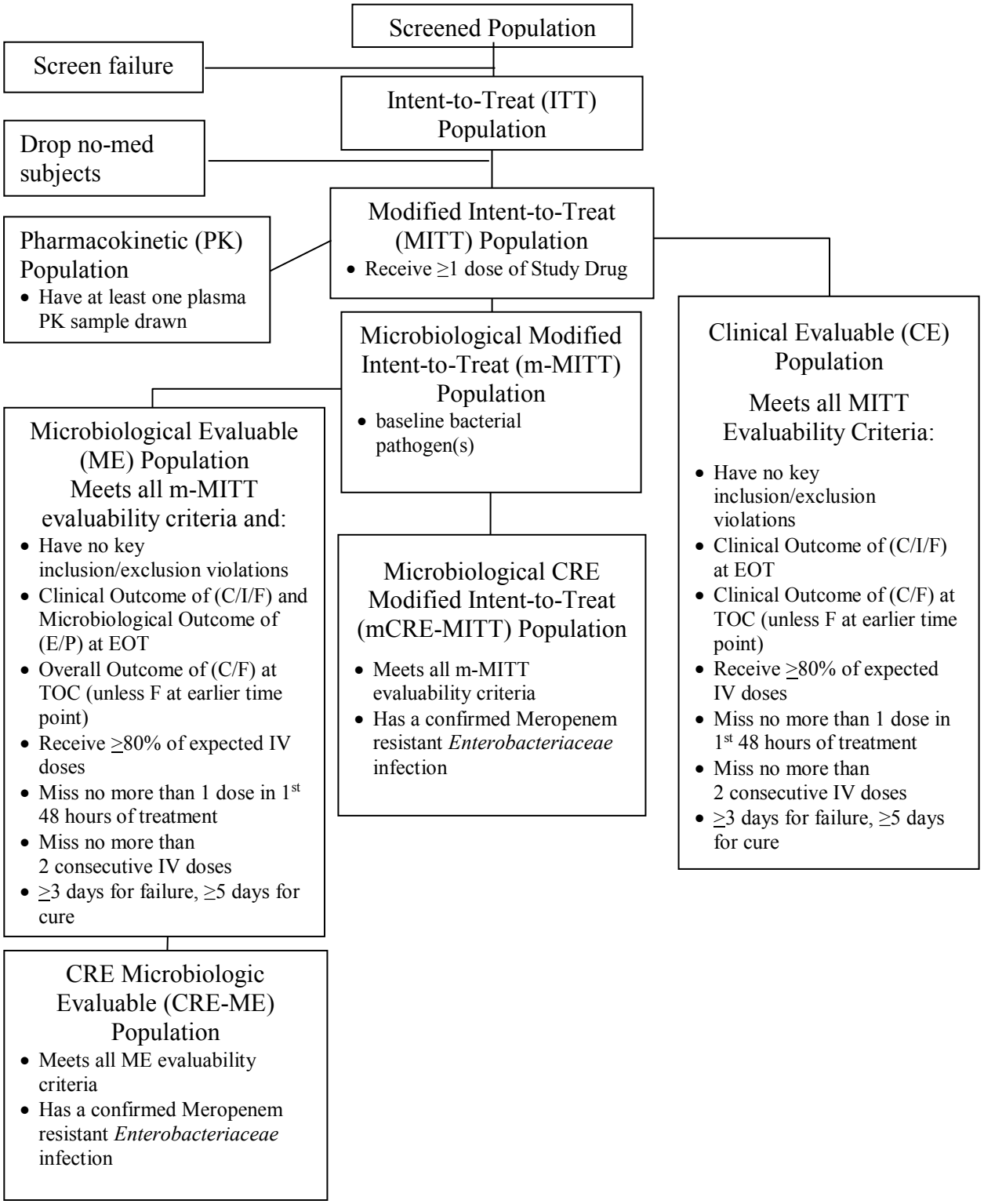
16. US Package Insert. AVYCAZ (ceftazidime-avibactam) for injection, for intravenous use; Cincinnati, OH; Forest Pharmaceuticals, Inc: 2015.

APPENDIX 1: STATISTICAL ANALYSIS POPULATIONS

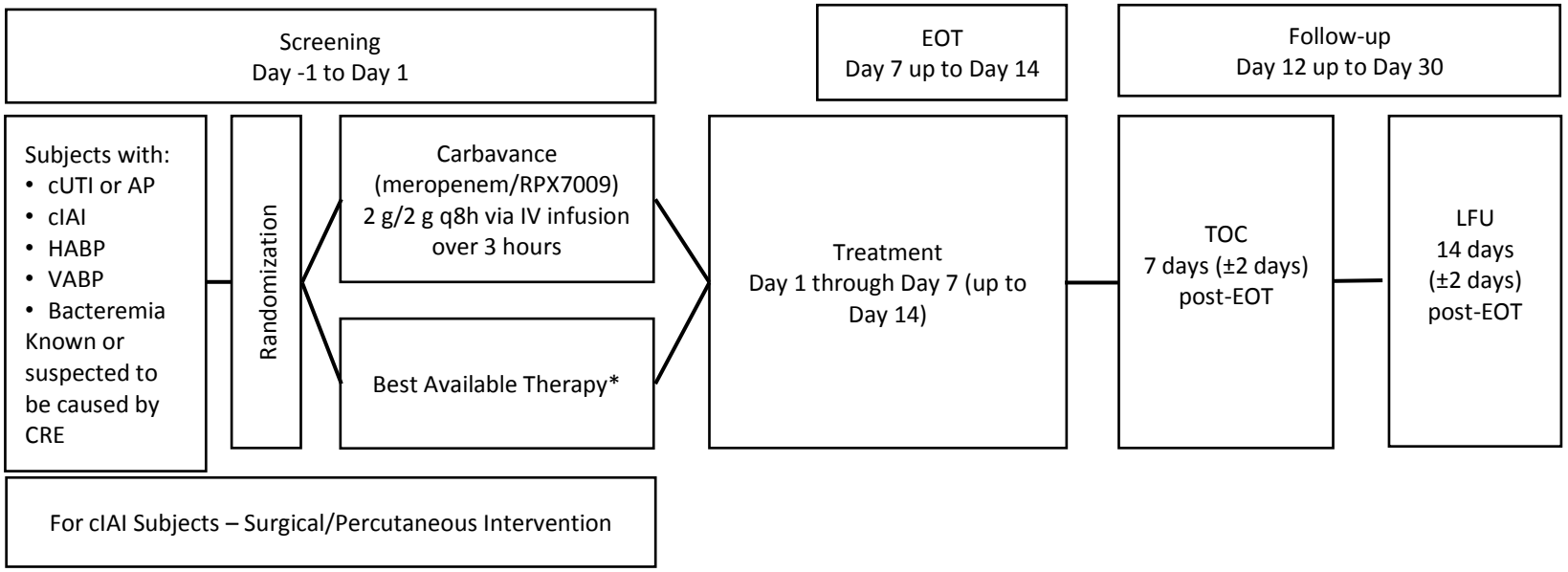


C = Cure; E = Eradication; EOT = End of Treatment; F = Failure; I = Improvement; IV = intravenous; P = Persistence; PK = pharmacokinetic; TOC = Test of Cure

APPENDIX 2: STUDY SCHEMA

REMPEX 506 Carbavance (Meropenem/RPX7009)

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.

The objectives of this study are:

To evaluate the safety, tolerability and efficacy of Carbavance (meropenem/RPX7009) in treatment of subjects with selected serious infections, suspected or known to be due to carbapenem-resistant *Enterobacteriaceae*; and

To assess the PK of meropenem and RPX7009 in subjects with selected serious infections, suspected or known to be due to carbapenem-resistant *Enterobacteriaceae*.

APPENDIX 3: COMMON TOXICITY CRITERIA TABLE

For details on Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC), see the online references at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

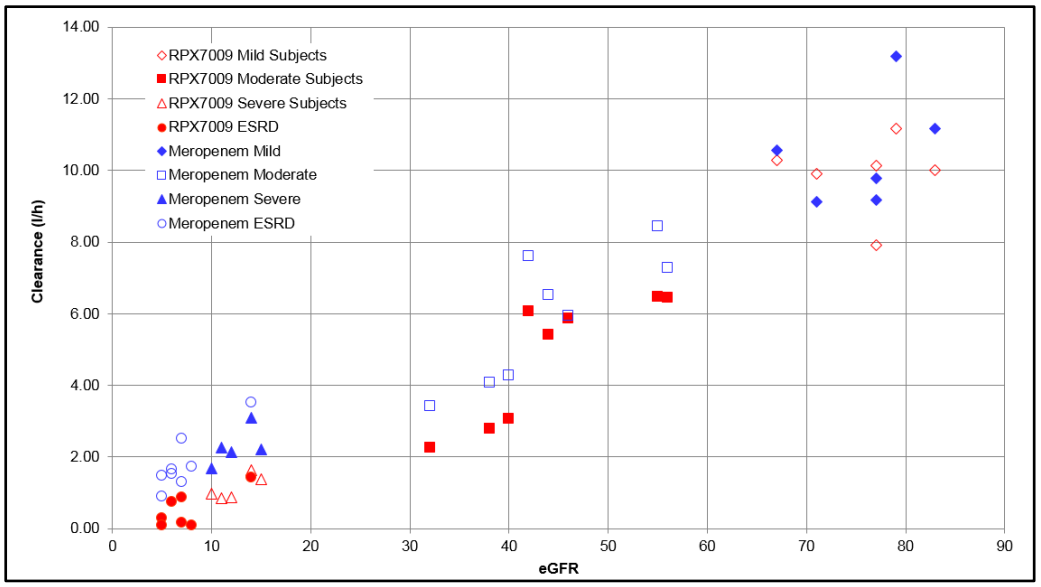
APPENDIX 4: A PHASE 1, OPEN-LABEL, SINGLE-DOSE STUDY TO DETERMINE THE SAFETY AND PHARMACOKINETICS OF CARBAVANCE IN SUBJECTS WITH RENAL INSUFFICIENCY (INCLUDING SUBJECTS ON STANDARD HEMODIALYSIS)

Study 504 was an open-label study in adult subjects with varying degrees of renal insufficiency, including those requiring hemodialysis (HD). The safety and PK of a single IV dose of 1 g meropenem plus 1 g RPX7009, infused over 3 hours, was evaluated. Forty-one subjects were enrolled in 5 groups based on their degree of renal insufficiency. The five cohorts included: subjects with normal renal function (CrCl ≥90 ml/min), mild renal impairment (CrCl 60-89 ml/min), moderate renal impairment (CrCl 30-<60 ml/min), severe renal impairment (CrCl <30 ml/min, and subjects with end stage renal disease requiring hemodialysis. Patients on renal replacement therapy other than standard hemodialysis (including continuous veno-venous hemofiltration, continuous veno-venous hemodialysis and continuous renal replacement therapy) were not studied.

Figure 1 shows the relation between estimated GFR (eGFR) and meropenem or RPX7009 plasma clearance. The plasma clearance of both drugs remained similar throughout the range of renal function as evidenced by the clustering of values and the linear decline in clearance with decreasing renal function.

The removal of meropenem and RPX7009 during hemodialysis was studied in 9 patients with severe renal insufficiency on chronic hemodialysis. Patients received a single meropenem 1 g/ RPX7009 1 g dose, followed by a hemodialysis session. Both meropenem and RPX7009 were removed from plasma by hemodialysis. These data indicate that maintenance doses of each drug (adjusted for degree of underlying endogenous renal function) should be administered after a dialysis session.

Figure 1: Meropenem and RPX7009 clearance according to creatinine clearance in subjects with varying degrees of renal impairment



Determination of Carbavance (meropenem/RX7009) Dosage in Renal Impairment

Dosage adjustment according to degree of renal impairment was determined by analysis of estimates of each subject's pharmacokinetics and exposures determined by analysis of various potential dosage regimens of meropenem or RPX7009. The objective was to maintain exposures (as AUC) across the range of renal function to be as consistent as possible across the spectrum of renal function. In view of PK-PD analyses in nonclinical models that show AUC is linked to efficacy for RPX7009, AUC was the appropriate controller of efficacy for this agent. Since T>MIC is the PK-PD index important for meropenem, different dosing intervals were evaluated to insure $T>MIC_{breakpoint}$ was above threshold values (T>MIC $\geq$40%) for efficacy. For purposes of this analysis, the forecasted susceptibility breakpoint for meropenem based on the 2 gram dose and 3 hr infusion was 8 ug/ml. For purposes of this analysis, the forecasted susceptibility breakpoint for meropenem based on the 2 gram dose and 3 hr infusion was 8 ug/ml. This breakpoint was determined by results of in vitro resistance development experiments which showed that a a minimum concentration of 8 mg/L of RPX7009 (in combination with 8 mg/L of meropenem) was required to be present for 24 hours to prevent resistance. Free drug was considered for both meropenem and RPX7009 (plasma protein binding of 6% and 33%, respectively). Free drug was considered for both meropenem and RPX7009 (plasma protein binding of 6% and 33%, respectively).

Meropenem

Table 1 shows meropenem Time > MIC (T> MIC) measured in each patient and PK-PD indices for three potential dosage regimens in each subject according to measured meropenem PK in each subject. Meropenem dosage regimens were identified for each of the strata of renal function that would meet or achieve target exposures (T>MIC of at least 40% of the dosing interval) in all subjects (see shaded cells).

Table 1. Analysis of different meropenem dosing regimens by individual subjects enrolled in Study 504. The pharmacokinetic target for meropenem is a Time>MIC of at least 40% of the dosing interval where the MIC is 8 µg/mL. The green shading denotes the recommended meropenem dosing regimen.

Expected Meropenem Time, in hours per day, (% of dosing interval) Above MIC of 8 µg/mL According to Dosage Regimen						
Estimated Creatinine Clearance (ml/min)	**2g q8h**	**1g q8h**	**1g q12h**	**1g q24h**	**500 mg q12h**	**500 mg q24h**
Normal	**Mean 13.8 (58) Range 10.5 - 16.5 (44 - 69)**					
> 50 mL/min group						
83	16.5 (69)	13.5 (56)	9 (38)	4.5 (19)	7 (29)	3.5 (15)
79	15.0 (63)	12 (50)	8 (33)	4 (17)	6 (25)	3 (13)
77	16.5 (69)	13.5 (56)	9 (38)	4.5 (19)	7 (29)	3.5 (15)
77	16.5 (69)	13.5 (56)	9 (38)	4.5 (19)	7.6 (32)	3.8 (16)
71	20 (83)	16.5 (69)	11 (46)	5.5 (23)	8 (33)	4 (17)
67	16.5 (69)	13.5 (56)	9 (38)	4.5 (19)	7 (29)	3.5 (15)
56	20 (83)	16.5 (69)	11 (46)	5.5 (23)	9 (38)	4.5 (19)
55	20 (83)	16.5 (69)	11 (46)	5.5 (23)	7.6 (32)	3.8 (16)
30 - 49 ml/min group						
46	24 (100)	18 (75)	12 (50)	6 (25)	10 (42)	5 (21)
44	24 (100)	18 (75)	12 (50)	6 (25)	9 (38)	4.5 (19)
42	24 (100)	16.5 (69)	11 (46)	5.5 (23)	8 (33)	4 (17)
40	24 (100)	24 (100)	16 (67)	8 (33)	12 (50)	6 (25)
38	24 (100)	24 (100)	20 (83)	10 (42)	12 (50)	6 (25)
32	24 (100)	24 (100)	20 (83)	10 (42)	14 (58)	7 (29)
10 - 19 ml/min group						
15	24 (100)	24 (100)	24 (100)	12 (50)	20 (83)	10 (42)
14	24 (100)	24 (100)	24 (100)	12 (50)	16 (67)	8 (33)
14	24 (100)	24 (100)	20 (83)	10 (42)	16 (67)	8 (33)
12	24 (100)	24 (100)	24 (100)	12 (50)	20 (83)	10 (42)
11	24 (100)	24 (100)	24 (100)	12 (50)	16 (67)	8 (33)
10	24 (100)	24 (100)	24 (100)	14 (58)	24 (100)	12 (50)
5 - 9 ml/min group						
8	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)	12 (50)
7	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)	12 (50)
7	24 (100)	24 (100)	24 (100)	14 (58)	20 (83)	10 (42)
6	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)	12 (50)
6	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)	12 (50)
5	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)
5	24 (100)	24 (100)	24 (100)	24 (100)	24 (100)	12 (50)

RPX7009

Table 2 shows RPX7009 AUC measured in each subject and 24h AUC for three potential dosage regimens according to measured RPX7009 clearance in each subject. Since AUC is the target PK metric and RPX7009 clearance remained close to meropenem clearance, unit and 24 hr doses remained at a 1:1 ratio throughout the range of renal function.

Considerations for subjects with creatinine clearance < 10 ml/min

As noted in the Figure 1, as creatinine clearance falls below 10 ml/min, meropenem non-renal clearance assumes a greater proportion of total clearance. In contrast, RPX7009 has no measureable non-renal clearance. Thus, to maintain a 1:1 dose ratio and, more importantly provide therapeutic exposures of each component and to avoid accumulation of RPX7009, patients with a creatinine clearance <10 ml/min should receive hemodialysis at least every 3 days (i.e., at least twice weekly).

Table 2. Analysis of different RPX7009 dosing regimens by individual subjects enrolled in Study 504. The green shading denotes the recommended RPX7009 dosing regimen.

Expected RPX7009 Free Drug 24h AUC (mg*hr/L)							
Estimated Creatinine Clearance (ml/min)	**Observed $AUC_{0\text{-}inf}$ following a 1 g dose**	**2g q8h**	**1g q8h**	**1g q12h**	**1g q24h**	**500 mg q12h**	**500 mg q24h**
Normal		**Mean 357.9 Range 283 - 470**					
> 50 mL/min group							
83	*70.0*	420.0	210.0	140.0	70.0	70.0	35.0
79	*62.7*	376.3	188.2	125.4	62.7	62.7	31.4
77	*69.2*	415.0	207.5	138.3	69.2	69.2	34.6
77	*88.4*	530.5	265.2	176.8	88.4	88.4	44.2
71	*70.7*	424.2	212.1	141.4	70.7	70.7	35.4
67	*68.1*	408.7	204.3	136.2	68.1	68.1	34.1
56	*108.4*	650.6	325.3	216.9	108.4	108.4	54.2
55	*108.0*	648.1	324.0	216.0	108.0	108.0	54.0
30 - 49 ml/min group							
46	*119.3*	715.7	357.8	238.6	119.3	119.3	59.6
44	*129.1*	774.5	387.2	258.2	129.1	129.1	64.5
42	*115.2*	690.9	345.5	230.3	115.2	115.2	57.6
40	*228.1*	1368.4	684.2	456.1	228.1	228.1	114.0
38	*251.1*	1506.5	753.3	502.2	251.1	251.1	125.5
32	*310.6*	1863.5	931.8	621.2	310.6	310.6	155.3
10 - 19 ml/min group							
15	*505.1*	3030.3	1515.2	1010.1	505.1	505.1	252.5
14	*427.3*	2563.8	1281.9	854.6	427.3	427.3	213.7
14	*493.6*	2961.8	1480.9	987.3	493.6	493.6	246.8
12	*790.7*	4744.3	2372.2	1581.4	790.7	790.7	395.4
11	*830.3*	4981.6	2490.8	1660.5	830.3	830.3	415.1
10	*719.6*	4317.6	2158.8	1439.2	719.6	719.6	359.8
5 - 9 ml/min group							
8	*8617.7*	51706.2	25853.1	17235.4	8617.7	8617.7	4308.9
7	*4189.5*	25137.0	12568.5	8379.0	4189.5	4189.5	2094.8
7	*794.5*	4767.0	2383.5	1589.0	794.5	794.5	397.3
6	*923.3*	5539.8	2769.9	1846.6	923.3	923.3	461.7
6	*840.0*	5040.0	2520.0	1680.0	840.0	840.0	420.0
5	*7581.7*	45490.2	22745.1	15163.4	7581.7	7581.7	3790.9
5	*2289.0*	13734.0	3270.0	4578.0	2289.0	2289.0	1144.5

Based on the above analysis, the Carbavance dosage regimens in Table 3 are recommended for subjects with impaired renal function.

Table 3: Carbavance Dosage according to renal function

Estimated Creatinine Clearance, ml/min (Cockcroft-Gault)	Carbavance Dosage Regimen (All doses infused over 3 hrs)
≥50	Meropenem 2 g / RPX7009 2 g q8h
≥30 - 49	Meropenem 1 g / RPX7009 1 g q8h
≥20 - 29	Meropenem 1 g / RPX7009 1 g q12h
≥10-19	Meropenem 500 mg / RPX7009 500 mg q12h
<10	Meropenem 500 mg / RPX7009 500 mg q24h[1]

[1] Dosage regimen assumes subjects receive hemodialysis at least twice per week. Maintenance doses of Carbavance in these subjects should be administered as soon as possible after the dialysis session.
q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.