Supplementary Online Content 1


Study Protocol
Clinical Study Protocol

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF CARBAVANCE (MEROPENEM/RPX7009) COMPARED TO PIPERACILLIN/TAZOBACTAM IN THE TREATMENT OF COMPLICATED URINARY TRACT INFECTIONS, INCLUDING ACUTE PYELONEPHRITIS, IN ADULTS

Protocol Number: REMPEX-505
Amended Protocol Dated: 14 JAN 2016, Version 4.0
Amended Protocol Dated: 02 APR 2015, Version 3.0
Amended Protocol Dated: 06 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 #2014-000545-78

Rempex Pharmaceuticals, a wholly-owned subsidiary of

The Medicines Company

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
This document is confidential. It contains proprietary information belonging to Rempex Pharmaceuticals, Inc. (Rempex). Any viewing or disclosure of such information that is not authorized in writing by Rempex is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.
1  PROTOCOL REVISION HISTORY

<table>
<thead>
<tr>
<th>Date/Version</th>
<th>Description</th>
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<tbody>
<tr>
<td>06 MAY 2014, Version 1.0</td>
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</tr>
<tr>
<td>14 JAN 2016, Version 4.0</td>
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</tbody>
</table>
2 SPONSOR SIGNATURE

A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy Study to Evaluate the Efficacy, Safety, and Tolerability of Carbavance (Meropenem/RPX7009) Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Adults

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\[ \text{Signature} \quad \text{14 JAN 2016} \]

Date
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INVESTIGATOR’S PROTOCOL AGREEMENT AND SIGNATURE PAGE

Protocol Number:  Rempex-505 (Version 4.0, Dated 14 JAN 2016)

Protocol Title:  A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy Study to Evaluate the Efficacy, Safety, and Tolerability of Carbavance (Meropenem/RPX7009) Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Adults

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 with 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 and data concerning the study drug 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 (SAEs) 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 (QA) group and agree to comply with the principles of the Declaration of Helsinki.
- Abide by stipulations regarding data disclosure (Section 19.15).

________________________________________  __________________________
Signature of Investigator                                      Date

Print Name of Investigator
## SYNOPSIS

<table>
<thead>
<tr>
<th>Title</th>
<th>A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy Study to Evaluate the Efficacy, Safety, and Tolerability of Carbavance (Meropenem/RPX7009) Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Adults</th>
</tr>
</thead>
</table>
| Indication | Subjects with a complicated urinary tract infection (cUTI) or acute pyelonephritis (AP) with or without concurrent bacteremia | US IND # 120040  
EudraCT #2014-000545-78 |
| Study Duration | First subject enrolled: 3Q2014  
Last subject enrolled: 2Q2016 | Number of Sites: Approximately 100 global sites |
| Number of Subjects | Approximately 500 subjects |
| Study Objectives | The objectives of the study are the following:  
• To assess the efficacy of Carbavance (meropenem/RPX7009) administered by intravenous (IV) infusion in subjects with cUTI or AP;  
• To assess the safety and tolerability of Carbavance (meropenem/RPX7009) administered by IV infusion in subjects with cUTI or AP; and  
• To assess the population pharmacokinetics (PK) of meropenem and RPX7009 in subjects with cUTI or AP. |
| Rationale | Urinary tract infections (UTIs) are a major cause of hospital admissions and are associated with significant morbidity and mortality, as well as a high economic burden. The majority of UTIs are those acquired in the community setting (57.4%), whereas 35.6% are healthcare associated and 7% are nosocomial. Urinary tract infections can be classified according to the anatomic site of infection, such as cystitis or pyelonephritis, and are further classified into complicated or uncomplicated, irrespective of the site and severity of the infection. Complicated UTIs occur in subjects with anatomic or functional abnormalities of the urinary tract or in those with significant medical or surgical co-morbidities. The microbiology of cUTIs is characterized by a greater variety of organisms and an increased likelihood of antimicrobial resistance as compared with uncomplicated UTIs.  
*Escherichia coli* is the most common etiologic agent of cUTIs, causing approximately 60% to 80% of community-acquired UTIs and approximately 50% of hospital-acquired UTIs. Other frequently identified Gram-negative organisms include Klebsiella spp., Proteus spp., *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa* and Gram-positive organisms such as Enterococci, coagulase-negative staphylococci, and *Staphylococcus aureus*. Moreover, less virulent organisms that are not commonly pathogenic in the setting of uncomplicated UTIs can cause severe and invasive disease in the setting of cUTIs. |
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 advance in the replacement of other classes of drugs with toxicities and limited spectra of activity against key pathogens. In the current era of increased resistance to extended spectrum cephalosporins, carbapenem antimicrobial agents are frequently the antibiotics of “last defense” for the most resistant pathogens in serious infections, including those found in cUTIs. The recent dissemination of serine carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemase [KPC]) in *Enterobacteriaceae* in many US hospitals and other hospitals worldwide now poses a considerable threat to the carbapenem and other members of the beta-lactam class of antimicrobial agents.

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. Meropenem is approved in many countries around the world at doses up to 2 grams every 8 hours (q8h).

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

Carbavance™, the combination of meropenem and RPX7009 administered as a fixed combination by IV infusion, is being developed to treat serious Gram-negative infections, such as cUTIs, including those infections caused by bacteria resistant to currently available carbapenems.

**Study Design**

This study is a prospective, multi-center, double-blind, double-dummy, randomized, parallel-group study to determine the efficacy, safety, and tolerability of Carbavance (meropenem/RPX7009) compared to piperacillin/tazobactam in the treatment of adults with cUTI or AP.

Approximately 500 subjects who have a clinical diagnosis of cUTI or AP, meet all inclusion/exclusion criteria, and have clinical severity of illness to warrant the use of IV antibiotics for at least 5 days will be enrolled. Subjects will be randomly assigned in a 1:1 ratio to receive either Carbavance (2 g meropenem/2 g RPX7009) in 250 mL infused intravenously as a 3-hour infusion q8h or piperacillin/tazobactam 4.5 g (4 g piperacillin/0.5 g tazobactam) in 100 mL infused intravenously as a 30-minute infusion q8h. After a minimum of 15 doses of IV therapy, subjects may be switched to oral levofloxacin (500 mg once every 24 hours [q24h]) to complete a total treatment course (IV plus oral) of 10 days. Treatment may be up to 14 days if clinically indicated in subjects with concurrent bacteremia. Dose adjustments will be required for subjects with renal insufficiency (See Section 11.2.1).

In view of the different infusion volumes and times, and to maintain the blind, a double-blind, double-dummy methodology will be used. At each IV dose, subjects will receive both a 250 mL infusion given over 3 hours and a 100 mL infusion delivered over 30 minutes. Every 8 hours, subjects randomized to Carbavance (meropenem/RPX7009) will receive 2 g meropenem/2 g RPX7009 in
250 mL of normal saline (NS) infused over 3 hours and an infusion of 100 mL of NS infused over 30 minutes. Every 8 hours, subjects randomized to piperacillin/tazobactam will receive 4 g piperacillin/0.5 g tazobactam in 100 mL of NS infused over 30 minutes and an infusion of 250 mL of NS infused over 3 hours.

Investigators will make daily assessments of signs and symptoms while the subject is on IV therapy, and continuation of IV study drug (Carbavance [meropenem/RPX7009] or piperacillin/tazobactam) or a possible switch to step-down oral therapy will be based on these clinical assessments.

Criteria for switching to oral levofloxacin therapy are as follows: the baseline organism(s) is not known to be resistant to levofloxacin, the subject is afebrile (oral or tympanic temperature <38°C [<100.4°F] or rectal/core temperature <38.3°C [<100.9°F]) for at least 24 hours without the use of antipyretics, signs and symptoms of cUTI or AP present at baseline are absent or have improved (with no new symptoms), any leukocytosis present at baseline has improved or resolved, ≥1 urine culture is negative for growth at 24 hours or exhibits growth with a colony count <10⁴ colony-forming units (CFU)/mL, the subject is able to tolerate and absorb oral medications, the subject has no contraindications for levofloxacin in the opinion of the Investigator, and if the subject has concurrent bacteremia, must have confirmed sterilization of the blood.

In the event it is determined that an increased dose (750 mg dose q24h) of levofloxacin is required due to concerns with resistance, the medical monitor should be contacted for approval.

For subjects who are unable to receive levofloxacin based on prescribing information or have baseline urinary pathogen(s) resistant to levofloxacin and cannot remain in the hospital for a total of 10 days of IV treatment, with Medical Monitor approval, one of the following oral antibiotics can be selected: trimethoprim/sulfamethoxazole, cefdinir, cefixime or cefpodoxime. The urinary pathogen(s) must have documented susceptibility to the selected oral agent. For subjects with bacteremia, if the baseline pathogen is resistant to levofloxacin, subjects should remain in the hospital for 10 to 14 days of IV treatment and cannot be switched to another oral therapy.

Assessments of clinical outcome will be performed on Day 3 of study treatment, on the last day of IV therapy (i.e., the End of IV Treatment [EOIVT]), on the last day of total therapy (i.e., End of Treatment [EOT]), at the Test-of-Cure (TOC) visit, and at the Late Follow-up (LFU) visit. For subjects who do not switch to oral step-down therapy, EOIVT and EOT visit activities will be combined. If a subject withdraws from the study early, study assessments will be performed at an early termination visit.

An independent Data Safety Monitoring Board (DSMB) will review accumulated safety data for this study and Rempex-506 when the enrollment reaches approximately 40% and 75%. The DSMB will review serious adverse events on an ongoing basis and will make recommendations to the Sponsor based on the safety data. Further details regarding data safety monitoring guidelines will be included in the DSMB Charter.
## Duration of Participation for Subjects

The average duration of study participation for each subject will be approximately 25 days (1 day for screening + 10 days of therapy + 14 days follow-up), with a potential maximum duration of study participation of 31 days (1 day for screening + 14 days of therapy + 16 days follow-up).

## Inclusion Criteria

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

1. A signed informed consent form, the ability to understand the study conduct and tasks that are required for study participation, and a willingness to cooperate with all tasks, tests, and examinations as required by the protocol.
2. Male or female ≥18 years of age.
3. Weight ≤185 kg.
4. Expectation, in the judgment of the Investigator, that the subject’s cUTI or AP requires initial treatment with at least 5 days of IV antibiotics.
5. Documented or suspected cUTI or AP as defined below:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Signs or symptoms evidenced by at least TWO of the following:</th>
<th>Pyuria evidenced by ONE of the following:</th>
<th>At least ONE of the following associated risks:</th>
</tr>
</thead>
<tbody>
<tr>
<td>cUTI</td>
<td>• Chills, rigors, or fever (Fever must be documented within 24 hours of the screening visit (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); observed and documented by a health care provider); • Elevated white blood cell count (&gt;10,000/mm³) or left shift (&gt;15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Lower abdominal pain or pelvic pain</td>
<td>• Positive LCE on urinalysis; • White blood cell count ≥10 cells/mm³ in unspun urine; • White blood cell count ≥10 cells/hpf in urine sediment</td>
<td>• 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</td>
</tr>
</tbody>
</table>
6. 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.

7. Expectation, in the judgment of the Investigator, that the subject will survive with effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study.

8. Women of childbearing potential must have a negative pregnancy test before randomization and be willing to use a highly effective method of contraception between randomization and for 7 days after the completion of the study. A highly effective method of contraception includes two of the following: hormonal implants/patch, injectable hormones, oral hormonal contraceptives, prior bilateral oophorectomy, prior hysterectomy, prior bilateral tubal ligation, intra-uterine device, approved cervical ring, condom, true abstinence (if approved by the Investigator), or a vasectomized partner.

9. Willingness to comply with all the study procedures, whether in the hospital or after discharge, for the duration of the study.

### Exclusion Criteria

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

1. Presence of any of the following conditions:
   a. Perinephric abscess;
   b. Renal corticomedullary abscess;
   c. Uncomplicated UTI;

   - Positive LCE on urinalysis;
   - White blood cell count ≥10 cells/mm³ in unspun urine;
   - White blood cell count ≥10 cells/hpf in urine sediment

   AP = acute pyelonephritis; cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; N/A = not applicable; PMN = polymorphonuclear leukocyte.
d. Polycystic kidney disease;
e. Chronic vesicoureteral reflux;
f. Previous or planned renal transplantation;
g. Subjects receiving hemodialysis;
h. Previous or planned cystectomy or ileal loop surgery; or
i. Known candiduria.

2. Presence of suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination.

3. Gross hematuria requiring intervention other than administration of study drug.

4. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy).

5. Renal function at screening as estimated by creatinine clearance <30 mL/min using the Cockcroft-Gault formula.

6. Known non-renal source of infection such as endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to randomization.

7. Any of the following signs of severe sepsis:
   a. Shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline (if known) that is not responsive to fluid challenge;
   b. Hypothermia (oral or tympanic temperature <35.6°C [<96.1°F] or rectal/core temperature <35.9°C [<96.6°F]); or
   c. Disseminated intravascular coagulation as evidenced by prothrombin time or partial thromboplastin time ≥2 × the upper limit of normal (ULN) or platelets <50% of the lower limit of normal.

8. Pregnant or breastfeeding women.

9. History of epilepsy or known seizure disorder requiring current treatment with anti-seizure medication.

10. Treatment within 30 days prior to enrollment with valproic acid.

11. Treatment within 30 days prior to enrollment with probenecid.

12. Treatment within 30 days prior to enrollment with any cancer chemotherapy, immunosuppressive medications for transplantation, or medications for rejection of transplantation.

13. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy.

14. Aspartate aminotransferase or alanine aminotransferase >3 × ULN, or total bilirubin >1.5 × ULN.
15. Receipt of any investigational medication or investigational device during the last 30 days prior to randomization.

16. Prior exposure to RPX7009 alone or in combination with another product.

17. Receipt of any potentially therapeutic antibiotic agent within 48 hours before randomization.

**EXCEPTIONS:**

- Subjects who received a single dose of a short-acting oral or IV antibiotic (an antibiotic that is typically dosed q4h, q6h or q8h in a subject with normal renal function). No more than 25% of subjects will be enrolled who meet this criterion.

- Subjects who received >48 hours of prior systemic antibiotic therapy for the current episode of cUTI with unequivocal clinical evidence of treatment failure (i.e., worsening signs and symptoms).

- Subjects who develop signs and symptoms of cUTI or AP while on antibiotics for another indication.

18. Requirement at time of enrollment for any reason for additional systemic antibiotic therapy (other than study drug) or antifungal therapy. Topical antifungal or a single oral dose of any antifungal treatment for vaginal candidiasis will be allowed.

19. Likely to require the use of an antibiotic for cUTI prophylaxis during the subject’s participation in the study (from enrollment through the LFU visit).

20. Known history of human immunodeficiency virus infection with a CD4 count <200/mm$^3$.

21. Presence of immunodeficiency or an immunocompromised condition including hematologic malignancy, bone marrow transplant, or receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (equivalent to ≥20 mg a day of prednisone or systemic equivalent, for ≥2 weeks).

22. Presence of neutropenia (<1,000 polymorphonuclear leukocytes [PMNs]/mm$^3$).

23. Presence of thrombocytopenia (<60,000 platelets/mm$^3$).

24. A corrected QT (Frdericia) (QTc,F) >480 msec.

25. History of significant hypersensitivity or allergic reaction to Carbavance (Meropenem/RPX7009), piperacillin/tazobactam, any of the excipients used in the respective formulations, or any beta-lactam antibiotics (e.g., cephalosporins, penicillins, carbapenems, or monobactams).

26. Known hypersensitivity or inability to tolerate all of the following: fluoroquinolones (including levofloxacin), trimethoprim/ sulfamethoxazole, cefdinir, cefixime, or cefpodoxime, based on prescribing
information.

27. Unable or unwilling, in the judgment of the Investigator, to comply with the protocol.

28. An employee of the Investigator or study center with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, or a family member of the employee or the Investigator.

29. Acute Physiology and Chronic Health Evaluation (APACHE) II score >30. *An APACHE II score is only required if calculated.*

30. Inability to tolerate intravenous fluids, due to medical reasons, of 1050 ml per day required for study drug administration.

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

<table>
<thead>
<tr>
<th>Microbiology Assessments</th>
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| A urine sample taken as part of the patient’s standard of care in order to support a diagnosis or treat a medical condition within 48 hours prior to first dose of study drug can be used for the baseline microbiological assessments and to assess eligibility. A repeat urine sample for culture must be obtained before the start of study drug therapy for any subjects enrolled after receiving a single dose of a short-acting antibiotic or for subjects who failed preceding antimicrobial therapy. This sample should be taken as close to randomization as possible (preferably within 2 hours prior to enrollment).

Up to 2 isolated pathogens will be allowed per urine culture (at concentrations of $\geq 10^5$ CFU/mL of urine). 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.

Prior to randomization, urine samples submitted for culture must have a microscopic evaluation (e.g., Gram stain) and a dipstick analysis performed by the local laboratory.

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 (urine culture only), and susceptibility testing. All 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.

Prior to randomization, only pathogens at concentrations of $\geq 10^5$ CFU/mL of urine will be sent to the central laboratory, unless the same organism grows in urine and blood, in which case these pathogens should be sent to the Central Lab regardless of CFU/mL. 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.

For instances where susceptibility testing indicates resistance to the study drug but the subject is clinically improving, the subject should remain on the study drug at the Investigator’s discretion.

For instances when a subject grows only a gram-positive organism resistant to piperacillin-tazobactam, the subject should discontinue study drug but should
remain in the study to complete all study assessments.

Samples for microbiologic testing will be collected as follows:

- Urine culture samples: Urine samples should be collected by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration. The baseline (pre-dose) urine sample must have a microscopic evaluation (i.e. gram stain) and a dipstick analysis performed by the local laboratory.

- Urine samples will be obtained prior to randomization (baseline), during treatment (Day 3, EOIVT, EOT), at the TOC visit, at the LFU visit if clinically indicated, and at early termination if the subject withdraws from the study early.

- Blood culture samples: Two sets of samples from 2 separate venipuncture sites will be obtained prior to randomization for baseline blood cultures. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). Additional blood cultures will be collected at the Investigator’s discretion. For subjects with fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) during the trial, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and susceptibility testing.

- Other culture samples: If a tissue sample (i.e., kidney biopsy) is collected, it should be obtained prior to randomization. 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 pathogen. The isolated pathogen should be shipped to the central laboratory (MRL) for confirmation and susceptibility testing.

| Investigational Treatments (Including Comparator, Oral Step-down, and Dummy Placebo) | Intravenous study drug will be administered in a double-blind, double-dummy manner. The following drugs will be provided by the Sponsor and administered in this study:
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>• Carbavance™ (Meropenem/RPX7009) for IV injection, administered as a 2 g/2 g dose diluted in NS to a volume of 250 mL and infused over 3 hours q8h;</td>
</tr>
<tr>
<td></td>
<td>• Piperacillin/tazobactam for IV injection, administered as a 4.5 g (4 g piperacillin/0.5 g tazobactam) dose diluted in NS to a volume of 100 mL and infused over 30 minutes q8h; and</td>
</tr>
<tr>
<td></td>
<td>• Levofloxacin oral tablets administered as a 500 mg dose q24h after a minimum of 15 doses of IV therapy, if clinically indicated, and the subject meets all required criteria for oral step-down therapy. In order to ensure continuation of treatment, subjects should be instructed to take the first levofloxacin dose within 8 hours of the start of the last IV infusion. Levofloxacin oral tablets administered as a 250 mg dose q24h will be provided for subjects with renal insufficiency (See Section 11.2.1) If it is determined that an increased dose (750 mg dose q24h) of levofloxacin is required due to resistance concerns, the medical monitor should be contacted for approval.</td>
</tr>
</tbody>
</table>
In addition, subjects will receive the following dummy placebo treatments based on randomization:

- Subjects randomized to Carabavance (meropenem/RPX7009) will receive a 100 mL infusion of NS administered over 30 minutes q8h;
- Subjects randomized to piperacillin/tazobactam will receive a 250 mL infusion of NS administered over 3 hours q8h; and

Study drug (IV and oral) may be administered in an inpatient or outpatient setting, at the discretion of the Investigator.

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.

### Rationale for Comparator

Piperacillin/tazobactam is approved in most countries for the treatment of cUTI/AP. Although piperacillin/tazobactam is not approved in the United States for cUTI, it is widely used to treat serious Gram-negative infections including those involving the urinary tract, and piperacillin alone is approved for the treatment of cUTI. Piperacillin/tazobactam has bactericidal activity against primary pathogens that cause cUTI/AP, particularly *Enterobacteriaceae*. As a comparator to Carabavance (meropenem/RPX7009), it shares many similar properties such as time-dependent killing of bacteria, three times per day dosing, and achievement of high urinary concentrations. The dose chosen for this study to treat cUTI and AP is 4.5 g (4 g piperacillin/0.5 g tazobactam) q8h.

### Stratification and Enrollment

To ensure balance among treatment arms, the randomization will be stratified by type of infection (AP vs. cUTI with removable source of infection [e.g., Foley catheter] vs. cUTI with non-removable source of infection [e.g., neurogenic bladder]) and geographic region (North America, Europe, Asia Pacific, Rest of World).

Enrollment of subjects who have received a single dose of a short-acting oral or IV antibacterial agent for cUTI within 24 hours prior to randomization will be limited to 25% of subjects.

In order to enroll at least 30% of subjects with acute pyelonephritis, enrollment will continue until at least 150 subjects are enrolled with AP.

### Analysis Populations

- The Intent-to-Treat (ITT) Population will include all subjects screened and randomized to study drug (Carabavance [meropenem/RPX7009] or piperacillin/tazobactam).
- The Modified Intent-to-Treat (MITT) Population will include subjects who meet the ITT criteria and receive at least one 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 actual treatment received.
- The PK Population will include subjects who meet the MITT criteria and have at least one plasma PK sample drawn.
- The Microbiologic Modified Intent-to-Treat (m-MITT) Population will include
subjects who meet the MITT criteria and have a baseline bacterial pathogen(s) of $\geq 10^5$ CFU/mL of urine at baseline urine culture for evaluation or the same bacterial pathogen present in concurrent blood and urine cultures. Subjects who only have an identified Gram positive pathogen in the urine and have received $>48$ hours of an antibiotic with only Gram-positive coverage will not be included in the m-MITT population.

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

- Have no key inclusion or exclusion violations;
- Obtain a clinical outcome (Cure, Improvement, or Failure) at EOIVT, unless criteria for Failure were met at an earlier time point;
- Receive $\geq 80\%$ 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 $\geq 6$ doses of study drug if classified as a Failure on clinical outcome, or receive $\geq 9$ doses of study drug if classified as a Cure on clinical outcome.

The Microbiologic Evaluable (ME) Population will include subjects who meet the MITT criteria as well as the following criteria:

- Have a bacterial pathogen(s) of $\geq 10^5$ CFU/mL of urine at baseline urine culture for evaluation or have the same bacterial pathogen present in concurrent blood and urine cultures;
- Have no key inclusion or exclusion violations;
- Obtain a clinical outcome (Cure, Improvement, or Failure) and microbiologic outcome (Eradication or Persistence) at EOIVT, unless criteria for Failure were met at an earlier time point;
- Receive $\geq 80\%$ 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 $\geq 6$ doses of study drug if classified as a Failure on overall outcome, or receive $\geq 9$ doses of study drug if classified as a Cure on overall outcome.
- Subjects who only have an identified Gram positive pathogen in the urine and have received $>48$ hours of an antibiotic with only Gram-positive coverage will not be included in the ME population.

<table>
<thead>
<tr>
<th>Efficacy Assessments</th>
<th>Primary Endpoint for FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The primary efficacy endpoint for this study for the Food and Drug Administration (FDA) will be the proportion of subjects in the m-MITT Population who achieve overall success at the EOIVT visit.</td>
</tr>
<tr>
<td></td>
<td>Overall success is achieved with a clinical outcome of Cure or Improvement and microbiologic outcome of Eradication at EOIVT. A clinical outcome of Cure at the EOIVT visit is defined as the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. A clinical outcome of</td>
</tr>
</tbody>
</table>
Improvement at the EOIVT visit is defined as lessening, incomplete resolution, or no worsening of the baseline signs and symptoms of cUTI or AP. A microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^4$ CFU/mL of urine.

**Primary Endpoint for EMA**

The primary efficacy endpoint for this study for the European Medicines Agency (EMA) will be the proportion of subjects in the co-primary m-MITT and ME Populations who achieve a microbiologic outcome of Eradication at the TOC visit.

A microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^3$ CFU/mL of urine.

**Secondary Endpoints**

The secondary endpoints for this study are the following:

- Proportion of subjects in the m-MITT Population with overall success at both the EOIVT and TOC visits;
- Proportion of subjects in the m-MITT and ME Populations with a microbiologic outcome of Eradication to $<10^4$ CFU/mL of urine for FDA and $<10^3$ CFU/mL of urine for EMA at Day 3, EOIVT, EOT, TOC, and LFU;
- Proportion of subjects with a clinical outcome of Cure in the m-MITT, CE, and ME Populations at Day 3, EOIVT, EOT, TOC, and LFU;
- Per-pathogen outcome in the m-MITT and ME Populations at Day 3, EOIVT, EOT, TOC, and LFU;
- Pharmacokinetic characterization of plasma exposure of meropenem and RPX7009; and
- Safety and tolerability profile of Carbavance (meropenem/RPX7009) by incidence and severity of adverse events and serious adverse events, vital signs, clinical laboratory tests, electrocardiograms (ECGs), and physical examinations in the Safety Population.

**Safety Assessments**

Safety assessments will include adverse events, clinical laboratory evaluations, vital signs, physical examinations, and ECGs.

**Pharmacokinetic Assessments**

**Plasma PK Assessments**

Pharmacokinetic plasma samples will be used to estimate PK parameters, such as area under the concentration-time curve (AUC), maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), drug clearance (CL), half-life ($t_{1/2}$), minimum plasma concentration ($C_{min}$), and steady-state volume of distribution ($V_{ss}$) for meropenem and RPX7009 using a structural population PK model.

Pharmacokinetic characterization and evaluation of plasma exposures of meropenem and RPX7009 in cUTI and AP subjects will be performed using both non-compartmental and modeling methods. Using a sparse sampling approach, PK samples on Day 1, Day 3, and EOIVT will be obtained from all subjects around the 3-hour infusions as specified in the Schedule of Procedures. The PK
samples will be collected from both treatment groups to maintain the blind. Only PK samples obtained from the Carbavance (meropenem/RPX7009) group will be analyzed (using a validated assay) by the central bioanalytical laboratory.

<table>
<thead>
<tr>
<th>Statistics</th>
<th><strong>Efficacy Analysis</strong></th>
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<tr>
<td></td>
<td>Descriptive statistics will be provided for each treatment group (Carbavance [meropenem/RPX7009] and piperacillin/tazobactam). Statistical tests and/or confidence intervals (CIs) will be used to compare treatment groups. All tests will be conducted using two-sided tests at the alpha = 0.05 level of significance. Analyses of efficacy variables will be performed separately for the MITT, m-MITT, CE, and ME Populations. Non-inferiority Analysis: The primary statistical objective of this study is to determine whether Carbavance (meropenem/RPX7009) is non-inferior to piperacillin/tazobactam in adult subjects with cUTI or AP. The primary endpoint for the FDA will be the proportion of subjects in the m-MITT Population with overall success at the EOI VT visit (Cure or Improvement + Eradication at EOI VT). The primary endpoint for the EMA will be the proportion of subjects in the m-MITT and ME Populations (co-primary) who achieve a microbiologic outcome of Eradication at the TOC visit. The non-inferiority margin will be a difference of 15 percentage points. The non-inferiority assessment will be based on the two-sided 95% CI for the difference in the proportions of subjects, based on the FDA and EMA endpoints, calculated as the rate in the Carbavance (meropenem/RPX7009) group minus that of the piperacillin/tazobactam group. Non-inferiority will be concluded if the lower limit of the two-sided 95% CI is &gt;-15%. If non-inferiority is demonstrated, an assessment for superiority will be performed. Other analyses Descriptive statistics will be provided for secondary endpoints. Treatment differences and associated 95% CIs will also be presented.</td>
</tr>
<tr>
<td><strong>Assuming that, of the approximately 500 subjects enrolled, 60% of subjects will be in the m-MITT Population, this sample size will provide 90% power to demonstrate the non-inferiority of Carbavance (meropenem/RPX7009) to piperacillin/tazobactam in the m-MITT Population, if the overall success rate is 80% in both groups and the non-inferiority margin is 15 percentage points.</strong></td>
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<tr>
<td><strong>Assuming 50% of enrolled subjects will meet criteria for inclusion in the ME Population, with 500 subjects, the study will have 84% power to demonstrate the non-inferiority of Carbavance (meropenem/RPX7009) to piperacillin/tazobactam in the ME Population.</strong></td>
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<td><strong>An overall blinded efficacy evaluation will be conducted along with the evaluability rate of the m-MITT and ME Populations when approximately 60% of subjects are enrolled in the study. Based on this assessment, the sample size may be adjusted accordingly.</strong></td>
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<tr>
<td>Assessment/Procedure</td>
<td>Screening</td>
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</tr>
<tr>
<td>Assessment of adverse events</td>
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</tbody>
</table>

Footnotes appear on the following page.
a. Screening 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.

b. If IOT and EOIVT occur on Day 10, visit activities will be combined. Subjects with concurrent bacteremia may receive up to 14 days of treatment.

c. The TOC visit will occur between Day 15 and Day 19. For subjects with bacteremia, the TOC visit window is Day 15 to Day 23.

d. The LFU visit will occur between Day 22 and Day 26. For subjects with bacteremia, the LFU visit window is Day 22 to Day 30.

e. Subjects are expected to complete all study visits. In circumstances where a subject discontinues the study early, an early termination visit will be performed.

f. Demographic data will be collected, including name, sex, age, race, ethnicity, BMI, alcohol use, and nicotine use.

g. 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. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

i. Assessment of signs and symptoms will include assessments to classify the following as new onset, continuing (increased, decreased, no change), or resolved (returned to pre-infection baseline or pre-infection condition): fever (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]), urinary frequency, urinary urgency, dysuria, nausea, vomiting, abdominal pain, supra-pubic pain or discomfort, flank pain, and costo-vertebral angle tenderness on examination (See Appendix 2).

j. At Screening, a urine pregnancy test will be performed locally and on Day 1 (Pre-dose) a serum pregnancy test will be performed at the central lab on women of childbearing potential only. A urine and serum pregnancy test will be performed at EOT for women of childbearing potential. If a subject discontinues the study early, a urine and serum pregnancy test will be performed if the woman is of childbearing potential.

k. Screening laboratory tests will include AST, ALT, creatinine, WBC count with differentials, platelet count, and LCE in urine. All screening laboratories will be performed at the local laboratory.

l. Hematology parameters include complete blood count (red blood cell count, WBC count with manual differentials, platelet count, hemoglobin, and hematocrit).

m. Serum chemistry parameters include at a minimum: creatinine, creatinine clearance, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, lipase, creatine kinase, amylase, albumin, lactate dehydrogenase, total protein, carbon dioxide, glucose, sodium, potassium, chloride, calcium, and phosphorus.

n. Urinalysis includes dipstick analysis of protein, glucose, ketones, bilirubin, blood, nitrates, and urobilinogen; microscopic evaluation for red blood cells, WBCs, bacteria, and casts; specific gravity; leukocyte esterase and pH.

o. Pharmacokinetic blood samples on Day 1 will be taken 3 to 3.5 hours and 5 to 6 hours after the START of the first 3-hour IV study drug infusion. Pharmacokinetic blood samples on Day 3 and EOIVT will be taken 3 to 3.5 hours after the START of one of that day’s 3-hour IV study drug infusions. Samples will not be collected around the 30-minute infusions. Pharmacokinetic sampling and triplicate 12-lead ECGs should be performed around the same 3-hour infusion.

p. All subjects will have triplicate 12-lead ECGs performed at screening and on Day 1, Day 3, and EOIVT at pre-dose and 15 minutes (±15 minutes) after the completion of one of that day’s 3-hour infusions. Pharmacokinetic sampling and triplicate 12-lead ECGs should be performed around the same 3-hour infusion. If the early termination visit occurs prior to EOIVT, triplicate ECGs should be performed.

q. Two sets of samples from 2 separate venipuncture sites will be obtained prior to randomization for baseline blood cultures. For those where a pathogen is identified, susceptibility testing will be performed. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, subsequent, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). Additional blood cultures will be collected at the Investigator’s discretion. For subjects with fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]), additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and susceptibility testing, and any isolates will be frozen and sent to the central laboratory (MRL) for confirmation.

r. Urine samples should be collected by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration at the specified time points. An additional urine culture should be obtained at the LFU visit, if clinically indicated. The baseline urine sample submitted for culture must have a microscopic evaluation (e.g., Gram stain) and a dipstick analysis performed by the local laboratory. Specimens will be sent to the local laboratory for culture and susceptibility testing and any pathogens will be frozen and sent to the central laboratory (MRL) for confirmation. A repeat urine sample for culture must be obtained before the start of study drug therapy for subjects enrolled after receiving a single dose of a short-acting antibiotic or for subjects who failed preceding antimicrobial therapy.

s. If clinically indicated, a tissue sample (i.e., kidney biopsy) will be collected prior to randomization. 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 pathogen. The isolated pathogen should be shipped to the central laboratory (MRL) for confirmation and susceptibility testing.

t. As specified in Section 11.2.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; ECG = electrocardiogram; EOI VT = End of Intravenous Treatment; EOT = End of Treatment; IV = intravenous; LCE = Leukocyte esterase; LFU = Late Follow-up; MRL = Medpace Reference Laboratory; TOC = Test-of-Cure; WBC = white blood cell.
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AP</td>
<td>Acute pyelonephritis</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the concentration-time curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CD4</td>
<td>Cluster of differentiation 4</td>
</tr>
<tr>
<td>CE</td>
<td>Clinical Evaluable</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony-forming unit</td>
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<td>Confidence interval</td>
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<tr>
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<td>Drug Clearance</td>
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<td>$C_{\text{max}}$</td>
<td>Maximum plasma concentration</td>
</tr>
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<td>$C_{\text{min}}$</td>
<td>Minimum plasma concentration</td>
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<tr>
<td>EOIVT</td>
<td>End of Intravenous Treatment</td>
</tr>
<tr>
<td>EOT</td>
<td>End of Treatment</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>HHS</td>
<td>US Department of Health and Human Services</td>
</tr>
<tr>
<td>hpf</td>
<td>High-powered field</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
</tr>
<tr>
<td>KPC</td>
<td><em>Klebsiella pneumoniae</em> carbapenemase</td>
</tr>
<tr>
<td>LCE</td>
<td>Leukocyte esterase</td>
</tr>
<tr>
<td>LFU</td>
<td>Late Follow-up</td>
</tr>
<tr>
<td>m-MITT</td>
<td>Microbiologic Modified Intent-to-Treat</td>
</tr>
<tr>
<td>ME</td>
<td>Microbiologic Evaluable</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimal inhibitory concentration</td>
</tr>
<tr>
<td>MITT</td>
<td>Modified Intent-to-Treat</td>
</tr>
<tr>
<td>MRL</td>
<td>Medpace Reference Laboratory</td>
</tr>
<tr>
<td>NCI-CTCAE</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>NS</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic(s)</td>
</tr>
<tr>
<td>PMN</td>
<td>Polymorphonuclear leukocyte</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>q8h</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>q24h</td>
<td>Every 24 hours</td>
</tr>
<tr>
<td>QT,F</td>
<td>Corrected QT (Fridericia)</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of product characteristics</td>
</tr>
<tr>
<td>t½</td>
<td>Half-life</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse event</td>
</tr>
<tr>
<td>T max</td>
<td>Time to maximum plasma concentration</td>
</tr>
<tr>
<td>TOC</td>
<td>Test-of-Cure</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>V ss</td>
<td>Steady-state volume of distribution</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>w/</td>
<td>With</td>
</tr>
</tbody>
</table>
7 INTRODUCTION

This study will compare the efficacy, safety, and tolerability of Carbavance™ (meropenem/RPX7009) to that of piperacillin/tazobactam in the treatment of complicated urinary tract infections (cUTIs), including acute pyelonephritis (AP).

Urinary tract infections (UTIs) are a major cause of hospital admissions and are associated with significant morbidity and mortality, as well as a high economic burden. The majority of UTIs are those acquired in the community setting (57.4%), whereas 35.6% are healthcare associated and 7% are nosocomial. Urinary tract infections can be classified according to the anatomic site of infection, such as cystitis or pyelonephritis, and are further classified into complicated or uncomplicated, irrespective of the site and severity of the infection. Complicated UTIs occur in subjects with anatomic or functional abnormalities of the urinary tract or in those with significant medical or surgical co-morbidities. The microbiology of cUTIs is characterized by a greater variety of organisms and an increased likelihood of antimicrobial resistance as compared with uncomplicated UTIs.

*Escherichia coli* is the most common etiologic agent of cUTIs, causing approximately 60% to 80% of community-acquired UTIs and approximately 50% of hospital-acquired UTIs. Other frequently identified Gram-negative organisms include Klebsiella spp., Proteus spp., *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa* and Gram-positive organisms such as Enterococci, coagulase-negative staphylococci, and *Staphylococcus aureus*. Moreover, less virulent organisms that are not commonly pathogenic in the setting of uncomplicated UTIs can cause severe and invasive disease in the setting of cUTIs.

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 advance in the replacement of other classes of drugs with toxicities and limited spectra of activity against key pathogens. In the current era of increased resistance to extended spectrum cephalosporins, carbapenem antimicrobial agents are frequently the antibiotics of “last defense” for the most resistant pathogens in serious infections, including those found in cUTIs. The recent dissemination of serine carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemase [KPC]) in *Enterobacteriaceae* in many United States (US) hospitals and other hospitals worldwide now poses a considerable threat to the carbapenem and other members of the beta-lactam class of antimicrobial agents.

7.1 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 intravenous (IV) administration for the treatment of subjects with serious Gram-negative infections, such as cUTIs, including those infections caused by bacteria resistant to currently available carbapenems.

Meropenem is a broad-spectrum injectable carbapenem antibiotic active against Gram-positive and Gram-negative bacteria, including the *Enterobacteriaceae* (the most frequently occurring pathogens in both the community and hospital settings) and other key pathogens associated with hospital-acquired infections, such as *Pseudomonas aeruginosa*, *Acinetobacter* sp. and anaerobes.
Meropenem is approved in most countries in the developed world. In many countries, meropenem is approved for treatment of both UTI and cUTI. In the US, meropenem is marketed under the proprietary name of Merrem® IV, and is indicated for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and bacterial meningitis. Approved dosing regimens for meropenem in adults include 500 mg, 1000 mg, and 2000 mg administered as 15- to 30-minute infusions every 8 hours (q8h). 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.

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. Its pharmacologic properties 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 carbapenem-resistant Enterobacteriaceae.

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

7.2 Microbiology

7.2.1 Susceptibility Testing
Carbavance (meropenem/RPX7009) has primary activity against Gram-negative organisms. The potency and minimum inhibitory concentrations 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.5

7.3 Nonclinical Pharmacology and Toxicology
A toxicology and safety assessment program to support clinical studies 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, elastogenic, and genotoxic effects for in vivo and in vitro Good Laboratory Practice genotoxicity studies. See the Investigator’s Brochure.5

7.3.1 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.5

7.3.2 Metabolism and Excretion
There was 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 showed no inhibition of key renal transporters, nor does it appear to be a substrate of them. See the Investigator’s Brochure.

7.4 Overview of Clinical Pharmacology

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 2000 mg. 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 a 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 2. 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 3.

In both clinical studies, RPX7009 exposure in subjects (maximum plasma concentration \([C_{\text{max}}]\) and area under the concentration-time curve \([\text{AUC}]\)) increased with increasing dose. The mean \(C_{\text{max}}\) 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 2. Comparison Across Clinical Pharmacology Studies of RPX7009 Pharmacokinetic Parameters (Mean ±SD) Following Single- and Multiple-Dose Administration of RPX7009 2 g Alone and in Combination with Meropenem (Preliminary Data)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study 402 Alone (N=8)</th>
<th>Rempex-501 Alone (N=7)</th>
<th>w/ Meropenem 1 g (N=8)</th>
<th>w/ Meropenem 2 g (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single&lt;sup&gt;a&lt;/sup&gt;</td>
<td>First&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Last&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41.6 ± 4.75</td>
<td>41.44 ± 4.38</td>
<td>34.93 ± 3.96</td>
<td>51.44 ± 16.16</td>
</tr>
<tr>
<td></td>
<td>40.9 ± 4.68</td>
<td>41.44 ± 4.38</td>
<td>34.93 ± 3.96</td>
<td>51.66 ± 7.26</td>
</tr>
<tr>
<td></td>
<td>41.44 ± 4.38</td>
<td>34.93 ± 3.96</td>
<td>51.44 ± 16.16</td>
<td>55.61 ± 10.96</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (mg·h/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>144 ± 13.9</td>
<td>133.26 ± 20.89</td>
<td>141.02 ± 21.35</td>
<td>112.31 ± 8.56</td>
</tr>
<tr>
<td></td>
<td>145 ± 15.8</td>
<td>133.26 ± 20.89</td>
<td>141.02 ± 21.35</td>
<td>112.31 ± 8.56</td>
</tr>
<tr>
<td></td>
<td>144 ± 13.9</td>
<td>133.26 ± 20.89</td>
<td>141.02 ± 21.35</td>
<td>112.31 ± 8.56</td>
</tr>
<tr>
<td></td>
<td>145 ± 15.8</td>
<td>133.26 ± 20.89</td>
<td>141.02 ± 21.35</td>
<td>112.31 ± 8.56</td>
</tr>
<tr>
<td>Half-Life (h)</td>
<td>1.51 ± 0.08</td>
<td>1.31 ± 0.22</td>
<td>1.39 ± 0.20</td>
<td>1.98 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>1.66 ± 0.10</td>
<td>1.43 ± 0.22</td>
<td>1.39 ± 0.20</td>
<td>1.98 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>1.66 ± 0.10</td>
<td>1.43 ± 0.22</td>
<td>1.39 ± 0.20</td>
<td>1.98 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>1.66 ± 0.10</td>
<td>1.43 ± 0.22</td>
<td>1.39 ± 0.20</td>
<td>1.98 ± 0.24</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (L)</td>
<td>18.6 ± 9.30</td>
<td>22.02 ± 2.24</td>
<td>21.37 ± 3.33</td>
<td>21.84 ± 3.50</td>
</tr>
<tr>
<td></td>
<td>20.9 ± 2.77</td>
<td>22.43 ± 2.00</td>
<td>24.95 ± 2.63</td>
<td>17.50 ± 1.99</td>
</tr>
<tr>
<td></td>
<td>18.6 ± 9.30</td>
<td>22.02 ± 2.24</td>
<td>21.37 ± 3.33</td>
<td>21.84 ± 3.50</td>
</tr>
<tr>
<td></td>
<td>20.9 ± 2.77</td>
<td>22.43 ± 2.00</td>
<td>24.95 ± 2.63</td>
<td>17.50 ± 1.99</td>
</tr>
<tr>
<td>Plasma Clearance (L/h)</td>
<td>11.6 ± 5.88</td>
<td>15.32 ± 2.33</td>
<td>13.43 ± 3.23</td>
<td>12.08 ± 2.09</td>
</tr>
<tr>
<td></td>
<td>13.5 ± 1.71</td>
<td>14.44 ± 1.97</td>
<td>14.44 ± 1.97</td>
<td>10.42 ± 1.85</td>
</tr>
<tr>
<td></td>
<td>13.5 ± 1.71</td>
<td>14.44 ± 1.97</td>
<td>14.44 ± 1.97</td>
<td>10.42 ± 1.85</td>
</tr>
<tr>
<td></td>
<td>13.5 ± 1.71</td>
<td>14.44 ± 1.97</td>
<td>14.44 ± 1.97</td>
<td>10.42 ± 1.85</td>
</tr>
<tr>
<td></td>
<td>13.5 ± 1.71</td>
<td>14.44 ± 1.97</td>
<td>14.44 ± 1.97</td>
<td>10.42 ± 1.85</td>
</tr>
</tbody>
</table>

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<sub>(0-24)</sub> values are provided for single doses and AUC<sub>(0-TLast)</sub> values are provided for the last day of multiple dosing.

AUC<sub>(0-∞)</sub> = area under the concentration-time curve from time 0 to infinity; AUC<sub>(0-TLast)</sub> = area under the concentration-time curve from time 0 to the last recorded measurement; C<sub>max</sub> = maximum plasma concentration; SD = standard deviation; V<sub>ss</sub> = steady-state volume of distribution; w/ = with.
### Table 3. 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 Rempex-501

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meropenem 1 g</th>
<th>Meropenem 2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alone w/ RPX7009</td>
<td>Alone w/ RPX7009</td>
</tr>
<tr>
<td></td>
<td>1 g (N=9)</td>
<td>2 g (N=14)</td>
</tr>
<tr>
<td></td>
<td>1 g (N=5)</td>
<td>2 g (N=8)</td>
</tr>
<tr>
<td></td>
<td>1 g (N=5)</td>
<td>2 g (N=8)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</strong></td>
<td>18.93 ±3.65</td>
<td>17.31 ±2.45</td>
</tr>
<tr>
<td></td>
<td>20.16 ±3.97</td>
<td>18.21 ±2.06</td>
</tr>
<tr>
<td></td>
<td>17.04 ±1.65</td>
<td>15.81 ±1.29</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;c&lt;/sub&gt; (mg·h/L)</strong></td>
<td>59.77 ±12.09</td>
<td>53.78 ±8.11</td>
</tr>
<tr>
<td></td>
<td>65.88 ±15.33</td>
<td>58.69 ±9.91</td>
</tr>
<tr>
<td></td>
<td>54.52 ±6.96</td>
<td>48.06 ±2.01</td>
</tr>
<tr>
<td><strong>Half-Life (h)</strong></td>
<td>0.96 ±0.11</td>
<td>0.96 ±0.09</td>
</tr>
<tr>
<td></td>
<td>1.15 ±0.21</td>
<td>1.01 ±0.30</td>
</tr>
<tr>
<td></td>
<td>0.94 ±0.03</td>
<td>1.08 ±0.15</td>
</tr>
<tr>
<td><strong>V&lt;sub&gt;ss&lt;/sub&gt; (L)</strong></td>
<td>21.59 ±3.21</td>
<td>23.46 ±2.34</td>
</tr>
<tr>
<td></td>
<td>21.06 ±4.50</td>
<td>22.36 ±2.53</td>
</tr>
<tr>
<td></td>
<td>21.19 ±2.43</td>
<td>24.97 ±2.89</td>
</tr>
<tr>
<td><strong>Plasma Clearance (L/h)</strong></td>
<td>17.39 ±3.71</td>
<td>19.11 ±3.44</td>
</tr>
<tr>
<td></td>
<td>15.84 ±3.57</td>
<td>17.39 ±2.41</td>
</tr>
<tr>
<td></td>
<td>18.4 ±2.24</td>
<td>20.65 ±0.84</td>
</tr>
<tr>
<td></td>
<td>14.9 ±3.33</td>
<td>14.49 ±2.67</td>
</tr>
<tr>
<td></td>
<td>14.77 ±2.84</td>
<td>14.77 ±2.84</td>
</tr>
</tbody>
</table>

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<sub>(0-<infty>)</sub> values are provided for single doses and AUC<sub>(0-T<sup>last</sup>)</sub> values are provided for the last day of multiple dosing.

AUC<sub>(0-<infty>)</sub> = area under the concentration-time curve from time 0 to infinity; AUC<sub>(0-T<sup>last</sup>)</sub> = area under the concentration-time curve from time 0 to the last recorded measurement; C<sub>max</sub> = maximum plasma concentration; V<sub>ss</sub> = steady-state volume of distribution; w/ = with.

#### 7.4.1 Justification of Carbavance (Meropenem/RPX7009) 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 (PD) parameter for efficacy of meropenem is free drug time above the minimal inhibitory concentration (MIC), and the magnitude of this parameter necessary to achieve maximal efficacy is free drug above the MIC for 30% - 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% - 50% of the dosage interval. This meropenem dosage regimen, as a part of Carbavance (meropenem/RPX7009), has been chosen for this study and the Registration Clinical Development Program.

For RPX7009, both in vitro and in vivo studies 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 target minimum AUC (8 mg/L·24 h = 192 mg·h/L) in
animal and *in vitro* PD 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. This RPX7009 dosage regimen, as a part of Carbavance (meropenem/RPX7009), 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 animal and *in vitro* PD models of infection against *Enterobacteriaceae* and *P. aeruginosa* strains with Carbavance (meropenem/RPX7009) 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 (meropenem/RPX7009) 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-PD 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.

### 7.5 Overview of Clinical Safety

There have been four clinical pharmacology studies conducted with RPX7009 alone or in combination with meropenem (Table 4).

<table>
<thead>
<tr>
<th>STUDY</th>
<th>402</th>
<th>501</th>
<th>503</th>
<th>504</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Ascending Single-Dose Study of the Safety, Tolerability, Pharmacokinetics of Intravenous RPX7009 in Healthy Adult Subjects</td>
<td>A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single- and Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Intravenous RPX2014 and RPX7009 Alone and in Combination in Healthy Adult Subjects</td>
<td>A Phase 1, Randomized, Open-Label, Trial Evaluating the Plasma, Epithelial Lining Fluid, and Alveolar Macrophage Concentrations of Intravenous Carbavance™ (RPX2014/RPX7009) in Subjects with Renal Insufficiency</td>
<td>A Phase 1, Open-Label, Single-Dose Study to Determine The Safety and Pharmacokinetics of Carbavance™ (RPX2014/RPX7009) in Subjects with Renal Insufficiency</td>
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<tr>
<td><strong>Number of Subjects</strong></td>
<td>80 subjects</td>
<td>94 subjects</td>
<td>26 subjects</td>
<td>41 subjects</td>
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</table>

There have been no safety signals identified in the clinical pharmacology studies conducted. In Studies 402 and 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 alone, meropenem alone, 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 501. With the exception of one 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 one 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 Rempex-501 study had asymptomatic elevations in their alanine aminotransferase (ALT) levels to $>3 \times$ upper limit of normal (ULN), which were thought to be study drug-related by the Investigator. One subject was in the meropenem 1 g cohort and the other subject 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.

A Phase I open-label, single-dose study (Rempex 504) was conducted to assess the safety, tolerability, and PK of intravenous (IV) meropenem and RPX7009 given in combination to adults with varying degrees of renal insufficiency and in adult subjects receiving HD therapy as compared to subjects with normal renal function. Additionally, the clearance of IV meropenem and RPX7009 was determined both before and after dialysis. A single, 3-hour infusion of Carbavance, containing 1 g meropenem and 1 g RPX7009, was safe and well tolerated in subjects with mild, moderate, severe, and normal renal function, and there was no evidence of increasing incidence or severity of AEs with decreasing renal function.

In subjects with End-stage Renal Disease (ESRD), the same dose of Carbavance was safe and well tolerated whether administered before or after hemodialysis therapy; however, a greater number of AEs were observed when Carbavance was administered after dialysis (Period 2) as opposed to when Carbavance was administered prior to dialysis during Period 1 (62.5% versus 22.5%). The AEs occurring during Period 2 were mostly mild in severity and were associated with increased meropenem and RPX7009 exposures. Two SAEs were reported in the ESRD
group (diarrhoea haemorrhagic [determined related to study drug by the PI] and prostate cancer metastatic [determined not related to study drug by the PI]) with the later event preventing the subject from receiving the scheduled second dose of study drug. Overall Carbavance was well tolerated across all levels of renal insufficiency, including in subjects with mild and moderate renal insufficiency to be studied in this trial.

Study 503 was a randomized (randomized to timing of bronchoalveolar lavage [BAL]), open-label, clinical study to assess the multiple-dose pharmacokinetics (PK) of Carbavance (meropenem/RPX7009) in healthy adult male and female subjects at 1 site in the United States. The study included an up to 28-day Screening Period, a 2-day Treatment Period, and an End-of-Study Assessment occurring immediately after completion of the Treatment Period. Subjects were administered three IV doses of Carbavance (2 g meropenem/2 g RPX7009).

Twenty six subjects were enrolled. Only 2 subjects experienced adverse events with one of these subjects experiencing adverse events of chest discomfort (2 events), dizziness (2 events), and dyspnoea, which were considered by the Investigator to be possibly related to study drug; an adverse event of chest discomfort resulted in discontinuation of study drug and discontinuation from the study. No subjects had an SAE. No meaningful laboratory, vital sign, ECG, or physical examination findings were observed during the study. Overall, Carbavance (meropenem/RPX7009) was well tolerated in this study.

### 7.6 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 moderate renal insufficiency in this study.
8 STUDY OBJECTIVES

The objectives of the study are the following:

- To assess the efficacy of Carbavance (meropenem/RPX7009) administered by IV infusion in subjects with cUTI or AP;
- To assess the safety and tolerability of Carbavance (meropenem/RPX7009) administered by IV infusion in subjects with cUTI or AP; and
- To assess the population PK of meropenem and RPX7009 in subjects with cUTI or AP.
9 OVERALL STUDY DESIGN

9.1 Study Design

This study is a prospective, multi-center, double-blind, double-dummy, randomized, parallel-group study to determine the efficacy, safety, and tolerability of Carbavance (meropenem/RPX7009) compared to piperacillin/tazobactam in the treatment of adults with cUTI or AP. See Appendix 3 for a flow diagram of the study.

Approximately 500 subjects who have a clinical diagnosis of cUTI or AP, meet all inclusion/exclusion criteria, and have clinical severity of illness to warrant the use of IV antibiotics for at least 5 days will be enrolled. Subjects will be randomly assigned in a 1:1 ratio to receive either Carbavance (2 g meropenem/2 g RPX7009) in 250 mL infused intravenously as a 3-hour infusion q8h or piperacillin/tazobactam 4.5 g (4 g piperacillin/0.5 g tazobactam) in 100 mL infused intravenously as a 30-minute infusion q8h. After a minimum of 15 doses of IV therapy, subjects may be switched to oral levofloxacin (500 mg once every 24 hours [q24h]) to complete a total treatment course (IV plus oral) of 10 days. Treatment may be up to 14 days if clinically indicated in subjects with concurrent bacteremia. Dose adjustments will be required for subjects with renal insufficiency (See Section 11.2.1).

In view of the different infusion volumes and times, and to maintain the blind, a double-blind, double-dummy methodology will be used. At each IV dose, subjects will receive both a 250 mL infusion given over 3 hours and a 100 mL infusion delivered over 30 minutes. Every 8 hours, subjects randomized to Carbavance (meropenem/RPX7009) will receive 2 g meropenem/2 g RPX7009 in 250 mL of normal saline (NS) infused over 3 hours and an infusion of 100 mL of NS infused over 30 minutes. Every 8 hours, subjects randomized to piperacillin/tazobactam will receive 4 g piperacillin/0.5 g tazobactam in 100 mL of NS infused over 30 minutes and an infusion of 250 mL of NS infused over 3 hours.

Investigators will make daily assessments of signs and symptoms while the subject is on IV therapy, and continuation of IV study drug (Carbavance [meropenem/RPX7009] or piperacillin/tazobactam) or a possible switch to step-down oral therapy will be based on these clinical assessments.

Criteria for switching to oral therapy are as follows: the baseline organism(s) is not known to be resistant to levofloxacin, the subject is afebrile (oral or tympanic temperature <38°C [<100.4°F] or rectal/core temperature <38.3°C [<100.9°F]) for at least 24 hours without the use of antipyretics, signs and symptoms of cUTI or AP present at baseline are absent or have improved (with no new symptoms), any leukocytosis present at baseline has improved or resolved, ≥1 urine culture is negative for growth at 24 hours or exhibits growth with a colony count <10⁴ colony-forming units (CFU)/mL, the subject is able to tolerate and absorb oral medications, the subject has no contraindications for levofloxacin in the opinion of the Investigator, and if the subject has concurrent bacteremia, must have confirmed sterilization of the blood.

In the event it is determined that an increased dose (750 mg dose q24h) of levofloxacin is required due to concerns with resistance, the medical monitor should be contacted for approval.

For subjects who are unable to receive levofloxacin based on prescribing information or have baseline urinary pathogen(s) resistant to levofloxacin and cannot remain in the hospital for a total
of 10 days of IV treatment, with Medical Monitor approval, one of the following oral antibiotics can be selected: trimethoprim/sulfamethoxazole, cefdinir, cefixime or cefpodoxime. The urinary pathogen(s) must have documented susceptibility to the selected oral agent. For subjects with bacteremia, if the baseline pathogen is resistant to levofloxacin, subjects should remain in the hospital for 10 to 14 days of IV treatment and cannot be switched to another oral therapy.

Assessments of clinical outcome will be performed on Day 3 of study treatment, on the last day of IV therapy (i.e., the End of IV Treatment [EOIVT]), on the last day of total therapy (i.e., End of Treatment [EOT]), at the Test-of-Cure (TOC) visit, and at the Late Follow-up (LFU) visit. For subjects who do not switch to oral step-down therapy, EOIVT and EOT visit activities will be combined. If a subject withdraws from the study early, study assessments will be performed at an early termination visit.

The average duration of study participation for each subject will be approximately 25 days (1 day for screening + 10 days of therapy + 14 days follow-up), with a potential maximum duration of study participation of 31 days (1 day for screening + 14 days of therapy + 16 days follow-up).

### 9.1.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review accumulated safety data for this study and Rempex-506 when the enrollment reaches approximately 40% and 75%. The DSMB will review serious adverse events on an ongoing basis and will make recommendations to the Sponsor based on the safety data. Further details regarding data safety monitoring guidelines will be included in the DSMB Charter.

### 9.2 Rationale for Study Design

A double-blind, double-dummy design was chosen to minimize potential bias resulting from differences in management, treatment, and assessment of subjects, or interpretation of results that could arise as a result of a subject’s or Investigator’s knowledge of the assigned treatment.

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

Piperacillin/tazobactam is approved in most countries for the treatment of cUTI/AP. Although piperacillin/tazobactam is not approved in the US for cUTI, it is widely used to treat serious Gram-negative infections including those involving the urinary tract, and piperacillin alone is approved for the treatment of cUTI. Piperacillin/tazobactam has bactericidal activity against primary pathogens that cause cUTI/AP, particularly Enterobacteriaceae. As a comparator to Carbavance (meropenem/RPX7009), it shares many similar properties such as time-dependent killing of bacteria, three times per day dosing, and achievement of high urinary concentrations. The dose chosen for this study to treat cUTI and AP is 4.5 g (4 g piperacillin/0.5 g tazobactam) q8h, as stated in the Summary of Product Characteristics (SmPC) for piperacillin/tazobactam. 1
10 SELECTION OF STUDY POPULATION

To be eligible for enrollment, the subject must meet all of the inclusion criteria, and prior to any study-related activities, the subject must be given the opportunity to have any questions answered and be given a copy of the informed consent document. 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, that all inclusion criteria were met, and that all exclusion criteria were absent. The subject cannot be randomized until the Investigator has confirmed that these conditions have been met.

Approximately 500 subjects who have a clinical diagnosis of cUTI or AP, meet all inclusion/exclusion criteria, and have clinical severity of illness to warrant the use of IV antibiotics for at least 5 days will be enrolled.

10.1 Inclusion Criteria

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

1. A signed informed consent form, the ability to understand the study conduct and tasks that are required for study participation, and a willingness to cooperate with all tasks, tests, and examinations as required by the protocol.

2. Male or female ≥18 years of age.

3. Weight ≤185 kg.

4. Expectation, in the judgment of the Investigator, that the subject’s cUTI or AP requires initial treatment with at least 5 days of IV antibiotics.
### Indication

<table>
<thead>
<tr>
<th>Signs or symptoms evidenced by at least TWO of the following:</th>
<th>Pyuria evidenced by ONE of the following:</th>
<th>At least ONE of the following associated risks:</th>
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</thead>
<tbody>
<tr>
<td><strong>cUTI</strong></td>
<td>- Positive LCE on urinalysis;</td>
<td>• Indwelling urinary catheter;</td>
</tr>
<tr>
<td>• Chills, rigors, or fever (Fever must be documented within 24 hours of the screening visit (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); observed and documented by a health care provider);</td>
<td>- White blood cell count ≥10 cells/mm³ in unspun urine;</td>
<td>• Neurogenic bladder with presence or history of urine residual volume of ≥100 mL;</td>
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<td>• Elevated white blood cell count (&gt;10,000/mm³) or left shift (&gt;15% immature PMNs);</td>
<td>- White blood cell count ≥10 cells/hpf in urine sediment</td>
<td>• Obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 hours post-randomization;</td>
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<tr>
<td>• Nausea or vomiting;</td>
<td></td>
<td>• Azotemia due to intrinsic renal disease;</td>
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<tr>
<td>• Dysuria, increased urinary frequency, or urine urgency;</td>
<td></td>
<td>• Urinary retention in men due to previously diagnosed benign prostatic hypertrophy</td>
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<tr>
<td>• Lower abdominal pain or pelvic pain</td>
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<p>| <strong>AP</strong>                                                      |                                          | N/A                                           |
| • Chills, rigors, or fever (Fever must be documented within 24 hours of the screening visit (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); observed and documented by a health care provider); | - Positive LCE on urinalysis;            |                                               |
| • Elevated white blood cell count (&gt;10,000/mm³), or left shift (&gt;15% immature PMNs); | - White blood cell count ≥10 cells/mm³ in unspun urine; |                                               |
| • Nausea or vomiting;                                       | - White blood cell count ≥10 cells/hpf in urine sediment |                                               |
| • Dysuria, increased urinary frequency, or                  |                                          |                                               |</p>
<table>
<thead>
<tr>
<th>urinary urgency;</th>
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</thead>
<tbody>
<tr>
<td>● Flank pain;</td>
</tr>
<tr>
<td>● Costo-vertebral angle tenderness on physical examination</td>
</tr>
</tbody>
</table>

AP = acute pyelonephritis; cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; N/A = not applicable; PMN = polymorphonuclear leukocyte.

6. 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.

7. Expectation, in the judgment of the Investigator, that the subject will survive with effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study.

8. Women of childbearing potential must have a negative pregnancy test before randomization, and be willing to use a highly effective method of contraception between randomization and for 7 days after the completion of the study. A highly effective method of contraception includes two of the following: hormonal implants/patch, injectable hormones, oral hormonal contraceptives, prior bilateral oophorectomy, prior hysterectomy, prior bilateral tubal ligation, intra-uterine device, approved cervical ring, condom, true abstinence (if approved by the Investigator), or a vasectomized partner.

9. Willingness to comply with all the study procedures, whether in the hospital or after discharge, for the duration of the study.

10.2 Exclusion Criteria

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

1. Presence of any of the following conditions:
   
   a. Perinephric abscess;
   
   b. Renal corticomedullary abscess;
   
   c. Uncomplicated UTI;
   
   d. Polycystic kidney disease;
   
   e. Chronic vesicoureteral reflux;
   
   f. Previous or planned renal transplantation;
   
   g. Subjects receiving hemodialysis;
   
   h. Previous or planned cystectomy or ileal loop surgery; or
   
   i. Known candiduria.

2. Presence of suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination.

3. Gross hematuria requiring intervention other than administration of study drug.
4. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy).

5. Renal function at screening as estimated by creatinine clearance <30 mL/min using the Cockcroft-Gault formula.

6. Known non-renal source of infection such as endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to randomization.

7. Any of the following signs of severe sepsis:
   a. Shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline (if known) that is not responsive to fluid challenge;
   b. Hypothermia (oral or tympanic temperature <35.6°C [<96.1°F] or rectal/core temperature <35.9°C [<96.6°F]); or
   c. Disseminated intravascular coagulation as evidenced by prothrombin time or partial thromboplastin time ≥2 × ULN or platelets <50% of the lower limit of normal.

8. Pregnant or breastfeeding women.

9. History of epilepsy or known seizure disorder requiring current treatment with anti-seizure medication.

10. Treatment within 30 days prior to enrollment with valproic acid.

11. Treatment within 30 days prior to enrollment with probenecid.

12. Treatment within 30 days prior to enrollment with any cancer chemotherapy, immunosuppressive medications for transplantation, or medications for rejection of transplantation.

13. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy.

14. Aspartate aminotransferase (AST) or ALT >3 × ULN, or total bilirubin >1.5 × ULN.

15. Receipt of any investigational medication or investigational device during the last 30 days prior to randomization.

16. Prior exposure to RPX7009 alone or in combination with another product.

17. Receipt of any potentially therapeutic antibiotic agent within 48 hours before randomization.

**EXCEPTIONS:**

- Subjects who received a single dose of a short-acting oral or IV antibiotic (an antibiotic that is typically dosed q4h, q6h or q8h in a subject with normal renal function). No more than 25% of subjects will be enrolled who meet this criterion.

- Subjects who received >48 hours of prior systemic antibiotic therapy for the current episode of cUTI with unequivocal clinical evidence of treatment failure (i.e., worsening signs and symptoms).
• Subjects who develop signs and symptoms of cUTI or AP while on antibiotics for another indication.

18. Requirement at time of enrollment for any reason for additional systemic antibiotic therapy (other than study drug) or antifungal therapy. Topical antifungal or a single oral dose of any antifungal treatment for vaginal candidiasis will be allowed.

19. Likely to require the use of an antibiotic for cUTI prophylaxis during the subject’s participation in the study (from enrollment through the LFU visit).

20. Known history of human immunodeficiency virus infection with a CD4 count <200/mm³.

21. Presence of immunodeficiency or an immunocompromised condition including hematologic malignancy, bone marrow transplant, or receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (equivalent to ≥20 mg a day of prednisone or systemic equivalent, for ≥2 weeks).

22. Presence of neutropenia (<1,000 polymorphonuclear leukocytes [PMNs]/mm³).

23. Presence of thrombocytopenia (<60,000 platelets/mm³).

24. A corrected QT (Fridericia) (QTcF) >480 msec.

25. History of significant hypersensitivity or allergic reaction to Carbavance (meropenem/RPX7009), piperacillin/tazobactam, any of the excipients used in the respective formulations, or any beta-lactam antibiotics (e.g., cephalosporins, penicillins, carbapenems, or monobactams).

26. Known hypersensitivity or inability to tolerate all of the following: fluoroquinolones (including levofloxacin), trimethoprim/sulfamethoxazole, cefdinir, cefixime or cefpodoxime, based on prescribing information.

27. Unable or unwilling, in the judgment of the Investigator, to comply with the protocol.

28. An employee of the Investigator or study center with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, or a family member of the employee or the Investigator.

29. Acute Physiology and Chronic Health Evaluation (APACHE) II score >30. *An APACHE II score is only required if calculated.*

30. Inability to tolerate intravenous fluids, due to medical reasons, of 1050 ml per day required for study drug administration.

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

10.3 Prior and Concomitant Medications and Treatments

Reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, and vitamin supplements, supportive therapies, and concomitant non-pharmacologic treatments) received by the subject within 14 days before administration of study drug and during the study, which will be recorded in the electronic Case Report Form (eCRF). The medication name, route of administration, dose, frequency, indication, and duration of the treatment/procedure (start and
stop dates) will be recorded. Concomitant treatments (non-pharmacologic treatments) include any surgical or diagnostic procedures.

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**
Additional or adjunctive non-study-specified antibiotic therapy administered with the intent of treatment of cUTI, AP, or other infection is NOT permitted under this protocol.

However, subjects in whom a resistant Gram positive organism is suspected or identified may receive empiric coverage for gram-positive organisms, as deemed necessary by the Investigator, using an antibiotic with only gram-positive coverage (e.g. vancomycin, daptomycin or linezolid).

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. Topical antifungal treatment or a single oral dose of any antifungal treatment of vaginal candidiasis will be allowed.

10.3.4 **Concomitant Medication Precautions and Exclusions**
Concomitant treatment with probenecid, valproic acid, vecuronium, and/or methotrexate is excluded. Efficacy of aminoglycosides may be reduced if the subject is also treated with piperacillin/tazobactam.¹

10.4 **Randomization and Treatment Group Assignment**
Subjects will be randomized to receive either Carbavance™ (meropenem/RPX7009) or piperacillin/tazobactam through a centralized Interactive Web Response System (IWRS). The subject will 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 type of infection (AP vs. cUTI with removable source of infection [e.g., Foley catheter] vs. cUTI with non-removable source of infection [e.g., neurogenic bladder]) and geographic region (North America, Europe, Asia Pacific, Rest of World).

Enrollment of subjects who have received a single dose of a short-acting oral or IV antibacterial agent for cUTI within 24 hours prior to randomization will be limited to 25% of subjects.

In order to enroll at least 30% of subjects with acute pyelonephritis, enrollment will continue until at least 150 subjects are enrolled with AP.

After fulfillment of all study entry criteria, subjects will be assigned a treatment assignment number via the IWRS. In a randomization notification addressed only to the unblinded pharmacist (or appropriately qualified unblinded designee) at the study site, the treatment assignment number and corresponding treatment assignment will be specified. Subjects will be
randomized in a 1:1 ratio. A blinded randomization notification will be sent to the appropriate blinded site personnel.

10.5 Blinding

The Investigator, site personnel, Sponsor, and the Sponsor’s designees involved in blinded monitoring, data management, or other aspects of the study will be blinded to treatment assignment. The site pharmacist or qualified designee who will prepare the IV infusion solution will be unblinded so that he/she may obtain the assigned drug and prepare the IV dosing solutions. The drug supply itself will not be blinded. The infusion bag containing the reconstituted study drug will be identified with the subject’s identification number, but will not identify the specific drug product. An amber IV bag cover will be placed over the 250ml infusion bag for every subject to aid in maintaining the blind. Coverage of the 100 mL infusion bag is not required. Refer to the Pharmacy Manual for further instruction on maintaining the blind during the trial.

Unblinding by request of an Investigator should occur only in the event of an emergency or adverse event for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. If the Investigator must identify the treatment assignment to an individual subject, an Investigator or qualified designee should request the medication information from the IWRS. They should not attempt to get this information from the site’s unblinded pharmacist or qualified designee. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner so as not to unblind the treatment assignment to other site or Sponsor personnel. The Investigator is also advised not to reveal the study treatment assignment to other site or Sponsor personnel.

Prior to unblinding, and if the situation allows it, the Investigator should try to contact the site monitor or the Sponsor’s medical monitor in order to get additional information about the investigational product. If this is impractical, the Investigator must notify the site monitor or the Sponsor’s medical monitor as soon as possible, without revealing the treatment assignment of the unblinded subject. The Investigator must document the subject identification and the date and time for breaking the blind and must clearly explain the reasons for breaking the code.

For subjects who are unblinded and withdrawn from the study, EOT procedures should be completed.
11 STUDY DRUG

Intravenous study drug will be administered in a double-blind, double-dummy manner. The following drugs will be provided by the Sponsor and administered in this study:

- Carabavance (meropenem/RPX7009) for IV injection, administered as a 2 g/2 g dose diluted in NS to a volume of 250 mL and infused over 3 hours q8h;
- Piperacillin/tazobactam for IV injection, administered as a 4.5 g (4 g piperacillin/0.5 g tazobactam) dose diluted in NS to a volume of 100 mL and infused over 30 minutes q8h; and
- Levofloxacin oral tablets administered as a 500 mg dose q24h after a minimum of 15 doses of IV therapy, if clinically indicated, and the subject meets all required criteria for oral step-down therapy. In order to ensure continuation of treatment, subjects should be instructed to take the first levofloxacin dose within 8 hours of the start of the last IV infusion. Levofloxacin oral tablets administered as a 250 mg dose q24h will be provided for subjects with renal insufficiency (See Section 11.2.1).

In addition, subjects will receive the following dummy placebo treatments based on randomization:

- Subjects randomized to Carabavance (meropenem/RPX7009) will receive a 100 mL infusion of NS administered over 30 minutes q8h; and
- Subjects randomized to piperacillin/tazobactam will receive a 250 mL infusion of NS administered over 3 hours q8h.

Infusions of IV study drug will occur q8h for 5 to 10 days (and up to 14 days in subjects with bacteremia). If clinically indicated, after ≥15 doses of IV treatment, the subject may be switched to oral levofloxacin 500 mg q24h to complete a treatment course of 10 days of total therapy (i.e., time on IV therapy + time on oral therapy). Treatment may be up to 14 days if clinically indicated in subjects with concurrent bacteremia.

Criteria for switching to levofloxacin are:

- The baseline organism(s) is not known to be resistant to levofloxacin;
- The subject is afebrile (oral or tympanic temperature <38°C [<100.4°F] or rectal/core temperature <38.3°C [<100.9°F]) for at least 24 hours without use of antipyretics;
- Signs and symptoms of cUTI or AP present at baseline are absent or have improved (with no new symptoms);
- Any leukocytosis present at baseline has improved or resolved;
- At least 1 urine culture is negative for growth at 24 hours or exhibits growth with a colony count <10^4 CFU/mL;
- The subject is able to tolerate and absorb oral medications;
- The subject has no contraindications for levofloxacin in the opinion of the Investigator; and
- If the subject has concurrent bacteremia, must have confirmed sterilization of the blood.
In the event it is determined that an increased dose (750 mg dose q24h) of levofloxacin is required due to concerns with resistance, the medical monitor should be contacted for approval.

For subjects who are unable to receive levofloxacin based on prescribing information or have baseline urinary pathogen(s) resistant to levofloxacin and cannot remain in the hospital for a total of 10 days of IV treatment, with Medical Monitor approval, one of the following oral antibiotics can be selected: trimethoprim/sulfamethoxazole, cefdinir, cefixime or cefpodoxime. The urinary pathogen(s) must have documented susceptibility to the selected oral agent. For subjects with bacteremia, if the baseline pathogen is resistant to levofloxacin, subjects should remain in the hospital for 10 to 14 days of IV treatment and cannot be switched to another oral therapy.

Study drug (IV and oral) may be administered in an inpatient or outpatient setting, at the discretion of the Investigator.

11.1 Description of Study Drugs

11.1.1 Carbavance (Meropenem/RPX7009)

Meropenem is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. When constituted 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 vial contains enough RPX7009 to deliver either 500 mg or 1000 mg RPX7009 when reconstituted and prepared according to instructions provided in the Pharmacy Manual. Once reconstituted, it is a clear, colorless to yellow solution. Each vial is reconstituted with the appropriate volume of diluent (NS) and introduced to an appropriately sized IV bag, whereupon it is further diluted to the appropriate concentration for delivery.

11.1.2 Piperacillin/Tazobactam

Piperacillin/tazobactam for injection is a white to off-white powder consisting of piperacillin and tazobactam as their sodium salts packaged in vials.

Each piperacillin/tazobactam 4.5 g (4 g piperacillin/0.5 g tazobactam) single-dose vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam.

11.1.3 Levofloxacin

Levofloxacin will be provided to sites as film-coated 500 mg and 250 mg tablets.

11.2 Study Drug Administration

An unblinded pharmacist (or designee) will be responsible for providing study drug to the blinded study personnel for administration. The study drug will be provided to blinded study personnel or nurse ready for IV infusion. Subjects will receive treatment based on randomization. Subjects randomized to Carbavance (meropenem/RPX7009) will receive the following infusions q8h: Carbavance (meropenem/ RPX7009) 2 g/2 g diluted in NS to a volume of 250 mL infused over 3 hours and 100 mL NS infused over 30 minutes. Subjects randomized to piperacillin/tazobactam will receive the following infusions q8h: piperacillin/tazobactam 4.5 g (4 g piperacillin/0.5 g tazobactam) diluted in NS to a volume of 100 mL infused over 30 minutes
and 250 mL NS infused over 3 hours. Levoﬂoxacin 500 mg oral tablets will be administered q24h, instead of piperacillin/tazobactam or Carbavance (meropenem/RPX7009), if a subject meets all step-down criteria and has received a minimum of 15 doses of study drug.

Each subject will receive 3-hour infusions and 30-minute infusions by programmable infusion pump while seated or semi-recumbent in bed. The time at which each infusion is started and stopped must be recorded. The two infusions should be given simultaneously and if this is not possible, they can be administered consecutively. 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 the 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 Pharmacy Manual.

11.2.1 Dosing in Subjects with Renal Insufﬁciency

The RempeX-504 study is an open-label single dose study evaluating the safety and PK of RPX7009 in combination with meropenem in subjects with renal insufﬁciency; 41 subjects with normal, mild, moderate, or severe renal dysfunction were enrolled in the study. All subjects were given a single 1 g dose of meropenem in combination with 1 g of RPX7009 administered as 3-hour constant rate intravenous infusion.

Meropenem and RPX7009 plasma clearance decreased to a similar extent in subjects with decreasing renal function. This similar decrease of plasma clearance allows the ratio of meropenem and RPX7009 to be maintained for dose adjustment in subjects with reduced renal function.

Based on the preliminary data from this trial and data obtained with meropenem alone using a similar 3-hour infusion and dosage regimen, the following dosage regimens for Carbavance (meropenem/RPX7009) are recommended for subjects with reduced renal function. The dose reductions for piperacillin/tazobactam and levoﬂoxacin follow the recommendations as per the respective SmPC.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Carbavance (Meropenem/RPX7009)</th>
<th>Piperacillin/tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>2 g/2 g q8h</td>
<td>4.5 g q8h</td>
</tr>
<tr>
<td>≥30-49</td>
<td>1 g/1 g q8h</td>
<td>4.5 g q8h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Levoﬂoxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥40</td>
<td>500 mg qd</td>
</tr>
<tr>
<td>≥30-39</td>
<td>250 mg qd</td>
</tr>
</tbody>
</table>

CrCL = Creatinine clearance; q8h = every 8 hours.

11.3 Study Drug Labeling and Packaging

The Sponsor or the Sponsor’s designee will package study drug. Study drug will be labeled and supplied according to the Pharmacy Manual.
11.4 Study Drug Storage Conditions

The unblinded Pharmacist or designated unblinded study personnel will ensure that all study drugs are stored in a locked secured area (with access limited to appropriate study personnel) under recommended storage conditions and in accordance with the protocol. All Study Drug (vials/bottles/blisters) should be stored at room temperature, per the labels. Meropenem and piperacillin/tazobactam should be stored at 20°C to 25°C (68°F to 77°F). RPX7009 and levofloxacin should be stored at 15°C to 30°C (59°F to 86°F).

Refer to the Pharmacy Manual for storage conditions of reconstituted Carbavance (meropenem and RPX7009) and piperacillin/tazobactam.

11.5 Receipt of Supplies

Upon receipt of the study drug(s), the pharmacist or designated unblinded study site personnel will visually inspect the shipment and verify the drug information, quantity, and condition of the kits received. Receipt of shipment must be confirmed 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 unblinded monitor.

11.7 Study Drug Handling and Return

Upon the completion or termination of the study, the Sponsor or the Sponsor’s representative will provide disposition instructions for all unused and/or partially used study drugs 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 the study drugs 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 the first dose of study drug. Screening procedures may only be performed after informed consent has been obtained. All screening procedures must be completed prior to randomization and the first dose of study drug. Screening assessments will include the following:

- Obtain signed informed consent;
- Review of all inclusion and exclusion criteria (See Section 10.1 and Section 10.2, respectively);
- Record significant medical/surgical history including past and present illnesses and relevant non-pharmacologic procedures (See Section 12.4.2);
- Record all prior and concomitant medications taken within the previous 14 days and all current drugs taken (including non-prescription medications, vitamins, dietary supplements, and herbal products) and non-pharmacologic treatments (See Section 12.4.3);
- Record demographic information including name, sex, age, race, ethnicity, body mass index (BMI), alcohol use, and nicotine use (See Section 12.4.4);
- Record height and weight (See Section 12.4.4);
- Perform complete physical examination (See Section 12.4.4);
- Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);
- Perform urine pregnancy test (for women of childbearing potential only) (See Section 12.4.9);
- Perform triplicate 12-lead ECGs (See Section 12.4.7);
- Collect urine sample for screening laboratories processed at local lab (See Section 12.4.9); and
- Collect blood samples for screening laboratories processed at local lab (See Section 12.4.9).
12.2 Treatment Period (Day 1 to Day 10) (Up to Day 14 for Subjects with Bacteremia)

Subjects will receive daily q8h IV treatment for 5 to 10 days (subjects with bacteremia may receive up to 14 days of treatment). If clinically indicated after 5 days of treatment and if the criteria for switching to step-down therapy are met, the subject may be switched to oral levofloxacin 500 mg q24h to complete treatment course of 10 days (up to 14 days in subjects with bacteremia) of total therapy (i.e., time on IV therapy + time on oral therapy). The following procedures will be performed each day during the IV Treatment Period:

- Continue to administer routine care according to local standard;
- Assess adverse events (See Section 14.1);
- Record concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (See Section 12.4.3);
- Continue IV study drug or oral therapy and record start and stop time of study drug administration; and
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6).

Subjects who are managed as outpatients after completing IV therapy will have adverse events, concomitant medications, and clinical signs/symptoms collected at the EOT, TOC, LFU, and Early Termination visits.

12.2.1 Study Day 1 Pre-Dose

Study Day 1 may be the same day as screening. The following procedures will be performed on Day 1 before administration of study drug (in addition to any screening procedures that are 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 all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (See Section 12.4.3);
- Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5). Screening vital signs may be used if collected within 4 hours of the first dose of IV study drug;
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6). Screening clinical signs and symptoms may be used if collected within 4 hours of the first dose of IV study drug;
- Perform triplicate 12-lead ECGs. Screening ECGs may be used if collected within 8 hours prior to the first dose of IV study drug (See Section 12.4.7);
- Collect urine sample by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and culture.
(See Section 12.4.9 and Section 12.4.10). This sample may be collected within 48 hours prior to the first dose of IV study drug;

- Collect blood samples for serum chemistry, hematology, serum pregnancy (if applicable), and culture to be sent to the Central Laboratory (See Section 12.4.9 and Section 12.4.10). This sample may be collected within 8 hours prior to the first dose of IV study drug;
- Collect additional tissue culture (i.e., kidney biopsy) if clinically indicated (See Section 12.4.10). This sample may be collected within 24 hours prior to the first dose of IV study drug and
- Obtain randomized treatment assignment via the IWRS (See Section 10.4).

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 (See Section 11.2);
- Assess adverse events (See Section 14.1);
- Perform triplicate 12-lead ECGs 15 minutes (±15 minutes) after the first 3-hour IV study drug infusion (See Section 12.4.7); and
- Collect PK blood samples 3 to 3.5 hours and 5 to 6 hours after the start of the first 3-hour IV study drug infusion (See Section 12.4.8).

12.2.3 Study Day 3

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

- Administer IV study drug at appropriate times and record start and stop time of study drug administration (See Section 11.2);
- Assess adverse events (See Section 14.1);
- Record all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (See Section 12.4.3);
- Perform limited, symptom-based, physical examination (If a subject does not display symptoms, no limited physical examination needs to be performed) (See Section 12.4.4);
- Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);
- Record assessment of clinical outcome (See Section 15.2.1);
- Perform triplicate 12-lead ECGs pre-dose and at 15 minutes (±15 minutes) after the completion of one of that day’s 3-hour IV study drug infusions (See Section 12.4.7);
- Collect PK blood samples 3 to 3.5 hours after the start of one of that day’s 3-hour IV study drug infusions (See Section 12.4.8). Pharmacokinetic samples and the ECG should be completed around the same IV study drug infusion;
- Collect urine samples by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and culture (See Section 12.4.9 and Section 12.4.10); The urine sample that is collected for the Central Lab urinalysis, may be collected within a ± 1 day window.
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9). These blood samples that are collected for the Central Lab may be collected within a ± 1 day window; and
- Collect blood samples for culture if baseline sample was positive and if needed, repeat sample until negative (See Section 12.4.10).

12.2.4 End of Treatment

Subjects will be assessed on the last day of IV treatment and on the last day of total treatment. Subjects who switch to oral step-down therapy will have an EOIVT visit on the last day of IV treatment (+1 day) and an EOT visit on the last day of oral treatment (+1 day). For subjects who receive only IV treatment, the last day of IV treatment will be the same as the last day of total treatment, and visit activities will be combined.

12.2.4.1 End of Intravenous Treatment (EOIVT) Visit (for Subjects Switching to Oral Step-Down Therapy Only)

An EOIVT visit will be required for subjects switching to oral step-down therapy (See Section 11). If subjects do not switch to oral step-down therapy, EOIVT and EOT will occur on the same day and visit activities will be combined. The following procedures will be performed at the EOIVT visit:
- Assess adverse events (See Section 14.1);
- Record all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (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);
- Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);
- Record assessment of clinical outcome (See Section 15.2.1);
- Administer IV study drug and record start and stop time of study drug administration (See Section 11.2);
- Perform triplicate 12-lead ECGs pre-dose and at 15 minutes (±15 minutes) after the completion of one of that day’s 3-hour IV study drug infusions (See Section 12.4.7);
• Collect PK blood samples 3 to 3.5 hours after the start of one of that day’s 3-hour IV study drug infusions (See Section 12.4.8). Pharmacokinetic samples and the ECG should be completed around the same IV study drug infusion;

• Collect urine samples by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and culture (See Section 12.4.9 and Section 12.4.10);

• Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9); and

• Collect blood samples for culture if baseline sample was positive and if needed, repeat sample until negative (See Section 12.4.10).

12.2.4.2 **End of Treatment (EOT) Visit**

All subjects will be assessed on the last day of study treatment (Day 10; up to Day 14 for subjects with bacteremia). For subjects who did not switch to oral step-down therapy, EOT and EOT will be the same day and visit activities will be combined. The following procedures will be performed at the EOT visit:

• Administer study drug at appropriate times and record start and stop time of study drug administration (See Section 11.2);

• For subjects who have switched to oral step-down treatment, the start and stop date as well as the dose, frequency and number of doses taken will be recorded.;

• Assess adverse events (See Section 14.1);

• Record all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (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);

• Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);

• Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);

• Record assessment of clinical outcome (See Section 15.2.1);

• Perform urine pregnancy test (for women of childbearing potential only) (See Section 12.4.8);

• Collect urine samples by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and culture (See Section 12.4.9 and Section 12.4.10);

• Collect blood samples for serum chemistry and hematology analyses and serum pregnancy (if applicable) (See Section 12.4.9); and

• Collect blood sample for culture if baseline sample was positive and if needed, repeat sample until negative (See Section 12.4.10).
12.3 Follow-up Period

12.3.1 Test-of-Cure (TOC)
The following assessments for TOC will be performed 7 days (±2 days) post-EOT (Day 15 to Day 19) for subjects without bacteremia. Test-of-Cure assessments will be performed 7 days (±2 days) post-EOT (Day 15 to Day 23) for subjects with bacteremia. The following procedures will be performed at the TOC visit:

- Assess adverse events (See Section 14.1);
- Record all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (See Section 12.4.3);
- Perform complete physical examination (If a subject does not display symptoms, no physical examination needs to be performed) (See Section 12.4.4);
- Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);
- Record assessment of clinical outcome (See Section 15.2.1);
- Collect urine samples by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and culture (See Section 12.4.9 and Section 12.4.10); and
- Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9).

12.3.2 Late Follow-up (LFU)
The following assessments for LFU will be performed 14 days (±2 days) post-EOT (Day 22 to Day 26) for subjects without bacteremia. Late Follow-up assessments will be performed 14 days (±2 days) post-EOT (Day 22 to Day 30) for subjects with bacteremia. The following procedures will be performed at the LFU visit:

- Assess adverse events (See Section 14.1);
- Record all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (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);
- Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);
- Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);
- Record assessment of clinical outcome (See Section 15.2.1);
- Collect urine samples by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and if clinically indicated culture (See Section 12.4.9 and Section 12.4.10); and
• Collect blood samples for serum chemistry and hematology analyses (See Section 12.4.9).

### 12.3.3 Early Termination

Subjects who withdraw from the study for any reason prior to the completion of the study 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 all concomitant medications (including non-prescription medications, vitamins, dietary supplements, and herbal products) (See Section 12.4.3);
• Perform complete physical examination (See Section 12.4.4);
• Obtain vital sign measurements, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (See Section 12.4.5);
• Assess clinical signs/symptoms (See Appendix 2 and Section 12.4.6);
• Record assessment of clinical outcome (See Section 15.2.1);
• Perform triplicate 12-lead ECGs if early termination occurs prior to EOIVT (See Section 12.4.7);
• Perform a urine pregnancy test (women of childbearing potential only) (See Section 12.4.9);
• Collect urine samples by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration for urinalysis and culture (See Section 12.4.9 and Section 12.4.10); and
• Collect blood samples for serum chemistry and hematology analyses and serum pregnancy (if applicable) (See Section 12.4.9).

### 12.4 Study Interventions/Procedures

#### 12.4.1 Informed Consent

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 Investigators(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. The rights and welfare of the subjects will be protected by emphasizing to them 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

Medical history and details regarding all clinically significant illnesses and allergies, date(s) of onset, and current status of conditions will be collected at screening. Additional information to be collected includes significant past surgical and medical procedures as well as non-pharmacologic procedures. Presence or history of the components of the Charlson Comorbidity Index will also be collected at Baseline.

12.4.3 Prior and Concomitant Medications

All 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. 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 measured only at screening. Demographic data including name, sex, age, race, ethnicity, BMI, alcohol use, and nicotine 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.

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

All physical examinations may be performed by physicians, physician’s assistants, or nurse practitioners.

12.4.5 Vital Signs

Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature, and will be measured at the indicated visits.

Body temperature may be taken per the site’s preferred method. Method of measuring body temperature will be recorded in the appropriate eCRF. The same method of measuring a subject’s body temperature should be used throughout the study. Vitals signs should be collected at the same time as assessments of signs and symptoms.

Subjects should be resting in a semi-recumbent position for at least 5 minutes prior to and during measurement of vital signs.

12.4.6 Assessment of Signs and Symptoms

Signs and symptoms will be assessed daily during IV treatment, as well as at scheduled visits per the Schedule of Procedures (See Table 1). When possible, the same study personnel should complete the assessments and record them at the same time each day. Each sign/symptom in the following list will be assigned a classification of new onset, continuing (increased, decreased, no change), or resolved (returned to pre-infection baseline or pre-infection condition):
• 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;
• Urinary frequency;
• Urinary urgency;
• Dysuria;
• Nausea;
• Vomiting;
• Abdominal pain;
• Supra-pubic pain or discomfort;
• Flank pain; and
• Costo-vertebral angle tenderness.

12.4.7 12-Lead ECG

All 12-lead ECGs will be performed at study visits as specified by the Schedule of Procedures (Table 1) and sent to a central ECG reader. All 12-lead ECGs will be performed pre-dose and 15 minutes (±15 minutes) after the completion of the 3-hour IV study drug infusions. Triplicate 12-lead ECGs and PK sampling should be performed around the same 3-hour IV study drug infusion. The Sponsor provided ECG machine should be used for pre-dose and post-dose readings. Twelve-lead ECGs will be performed in triplicate, at least 1 minute apart, after the subject has been in the supine position for at least 10 minutes. The average value at screening will be utilized for assessing the QTcF exclusion criterion. The ECG will include all 12 standard leads and will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be recorded:

• Heart rate;
• QRS interval;
• PR Interval;
• RR interval;
• QT interval; and
• QTc interval.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities. Electrocardiograms will be interpreted, signed, and dated by the Investigator or qualified designee. The ECGs will be classified as normal, having a not clinically significant abnormality, or having a clinically significant abnormality.
12.4.8 **Pharmacokinetic Sampling**

Pharmacokinetic blood samples on Day 1 will be taken 3 to 3.5 hours and 5 to 6 hours after the start of the first 3-hour IV study drug infusion. Pharmacokinetic blood samples on Day 3 and EOIVT will be taken 3 to 3.5 hours after the START of one of that day’s 3-hour IV study drug infusions. Samples will not be collected around the 30-minute infusions. Pharmacokinetic sampling and triplicate 12-lead ECGs should be performed around the same 3-hour infusion.

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

12.4.9 **Clinical Laboratory Assessments**

Blood samples for chemistry and hematology analyses will be collected as specified by the Schedule of Procedures (Table 1). Laboratory tests that are clinically significantly abnormal will be repeated. The chemistry, hematology, and urinalysis parameters assessed in this study include the following:

- Chemistry: creatinine, creatinine clearance, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, lipase, creatine kinase, amylase, albumin, lactate dehydrogenase, total protein, carbon dioxide, glucose, sodium, potassium, chloride, 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, leukocyte esterase and urobilinogen; microscopic evaluation for red blood cells, WBCs, bacteria, and casts; specific gravity; and pH.

Screening laboratory tests will include, at a minimum, AST, ALT, creatinine, WBC count with differentials, platelet count, and leukocyte esterase (LCE) in urine. All screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 24 hours prior to Randomization.

If the urine sample is obtained within 48 hours as part of the subject’s standard of care in order to support a diagnosis or treat a medical condition, the result may be used for study eligibility.

For women of childbearing potential, a serum and urine pregnancy test will be performed before the first dose of study drug. A urine and serum pregnancy test will be performed at EOT or early termination.

12.4.10 **Microbiology Assessments**

A urine sample taken as part of the subject’s standard of care in order to support a diagnosis or treat a medical condition within 48 hours prior to first dose of study drug can be used for the baseline microbiological assessments and to assess eligibility. A repeat urine sample for culture must be obtained before the start of study drug therapy for any subjects enrolled after receiving a single dose of a short-acting antibiotic or for subjects who failed preceding antimicrobial therapy. This sample should be taken as close to randomization as possible (preferably within 2 hours prior to enrollment).
Up to 2 isolated pathogens will be allowed per urine culture (at concentrations of $\geq 10^5$ CFU/mL of urine). 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.

Prior to randomization, urine samples submitted for culture must have a microscopic evaluation (e.g., Gram stain) and a dipstick analysis performed by the local laboratory.

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 (urine culture only), and susceptibility testing. All 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.

Prior to randomization, only pathogens at concentrations of $\geq 10^5$ CFU/mL of urine will be sent to the central laboratory, unless the same organism grows in urine and blood, in which case these pathogens should be sent to the Central Lab regardless of CFU/mL.

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.

For instances where susceptibility testing indicates resistance to the study drug, but the subject is clinically improving, the subject should remain on the study drug at the Investigator’s discretion.

For instances when a subject grows only a gram-positive organism resistant to piperacillin-tazobactam, the subject should discontinue study drug but should remain in the study to complete all study assessments.

Samples for microbiologic testing will be collected as follows:

- **Urine culture samples**: Urine samples should be collected by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration. The baseline (pre-dose) urine samples must have a microscopic evaluation (i.e. gram stain) and a dipstick analysis performed by the local laboratory.

- **Urine samples** will be obtained prior to randomization (baseline), during treatment (Day 3, EOIVT, EOT), at the TOC visit, at the LFU visit if clinically indicated, and at early termination if the subject withdraws from the study early.

- **Blood culture samples**: Two sets of samples from 2 separate venipuncture sites will be obtained prior to randomization for baseline blood cultures. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). Additional blood cultures will be collected at the Investigator’s discretion. For subjects with fever spikes (oral or tympanic temperature $\geq 38^\circ$C [≥100.4°F] or rectal/core temperature $\geq 38.3^\circ$C [≥100.9°F]) during the trial, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and susceptibility testing.

- **Other culture samples**: If a tissue sample (i.e., kidney biopsy) is collected, it should be obtained prior to randomization. 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 pathogen. The isolated pathogen should be shipped to the central laboratory (MRL) for confirmation and susceptibility testing.

12.4.11 Hospitalization Assessments

Hospital admissions, transfers and discharge 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 Intensive Care Unit (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.).
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 the 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 fail to meet the inclusion and meet exclusion criteria will be defined as screen failures. A screening log that 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 recorded in the 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 for a 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.

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 (CRO), 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 abnormal, clinically significant laboratory test variables, will be monitored and documented from the time of informed consent until study participation is completed. Treatment-emergent adverse events (TEAEs), which include clinical laboratory test variables that are reported as adverse events, 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 an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF. It is expected that the Investigator will provide or arrange appropriate supportive care for subjects if necessary. In the case that a subject is lost to follow-up, every effort should be made to contact the subject.

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. Clinical Signs or Symptoms (See Section 12.4.6) associated with the index infection (cUTI or AP) 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, 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 reporting 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. Reference safety information for piperacillin/tazobactam and levofloxacin is available in the referenced summaries of product characteristics (SmPC). An expectedness list is included in the Carbavance (meropenem/RPX7009) Investigator’s Brochure.

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), detail of which can be found in Appendix 4. 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**
- Event could be explained by subject’s clinical state or other factors.

**Probable**
- 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 one 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.
- 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 electronic data capture (EDC) system for the study. When the form is completed, Medpace 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 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 Reporting – USA, Latin America, Asia:
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 Reporting – 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 of delivery, 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.

All other suspected unexpected serious adverse reactions 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.

A list of expected adverse reactions associated with administration of Carbavance (meropenem/RPX7009) is provided in the Investigator’s Brochure. A list of expected adverse reactions associated with administration of piperacillin/tazobactam and levofloxacin is available in the referenced SmPC.
15 EFFICACY EVALUATION

15.1 Study Endpoints

15.1.1 Primary Endpoint for Food and Drug Administration

The primary efficacy endpoint for this study for the FDA will be the proportion of subjects in the Microbiologic Evaluable Modified Intent-to-Treat (m-MITT) Population who achieve overall success at the EOIVT visit.

Overall success is achieved with a clinical outcome of Cure or Improvement and microbiologic outcome of Eradication at EOIVT. A clinical outcome of Cure at the EOIVT visit is defined as the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. A clinical outcome of Improvement at the EOIVT visit is defined as lessening, incomplete resolution, or no worsening of the baseline signs and symptoms of cUTI or AP. A microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to <10^4 CFU/mL of urine.

15.1.2 Primary Endpoint for European Medicines Agency

The primary efficacy endpoint for this study for the European Medicines Agency (EMA) will be the proportion of subjects in the co-primary m-MITT and Microbiologic Evaluable (ME) Populations who achieve a microbiologic outcome of Eradication at the TOC visit.

A microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to <10^3 CFU/mL of urine.

15.1.3 Secondary Endpoints

The secondary endpoints for this study are the following:

- Proportion of subjects in the m-MITT Population with overall success at both the EOIVT and TOC visits;
- Proportion of subjects in the m-MITT and ME Populations with a microbiologic outcome of Eradication to <10^4 CFU/mL of urine for FDA and <10^3 CFU/mL of urine for EMA at Day 3, EOIVT, EOT, TOC, and LFU;
- Proportion of subjects with a clinical outcome of Cure in the m-MITT, Clinical Evaluable (CE), and ME Populations at Day 3, EOIVT, EOT, TOC, and LFU;
- Per-pathogen microbiologic outcome in the m-MITT and ME Populations at Day 3, EOIVT, EOT, TOC, and LFU;
- Pharmacokinetic characterization of plasma exposure of meropenem and RPX7009; and
- Safety and tolerability profile of Carbavance (meropenem/RPX7009) by incidence and severity of adverse events and SAEs, vital signs, clinical laboratory tests, ECGs, and physical examinations in the Safety Population.
15.1.4 Exploratory Endpoints

The exploratory endpoints for this study are the following:

- Incidence of treatment-emergent new infections;
- Length of hospital stay;
- Length of intensive care unit (ICU) stay;
- Proportion of subjects with infection-related ICU re-admission;
- Length of ICU stay for subjects with infection-related ICU re-admission;
- All-cause mortality;
- Time to oral switch (if clinically indicated);
- 30-day all-cause and infection-related hospital re-admission;
- Relapse/recurrence rates of cUTI or AP at the LFU visit; and
- Subject disposition (discharge status).

15.2 Efficacy Assessments

15.2.1 Clinical Outcome

The Investigator will be provided with a choice of clinical outcomes based on the assessment of signs and symptoms of the subject at the Day 3, EOIVT, EOT, TOC, and LFU visits.

At EOIVT, if all symptoms present at baseline are classified as mostly resolved or continuing (decreased), with no new onset symptoms, the subject will have a clinical outcome of Cure. At the EOT, TOC, and LFU visits, if all symptoms present at baseline are classified as mostly resolved or continuing (decreased), with no new onset symptoms, such that no further antimicrobial therapy is warranted, the subject will have a clinical outcome of Cure. At Day 3 and EOIVT, subjects with lessening, incomplete resolution, or no worsening of the symptoms present at baseline (i.e., continuing [decreased or no change] and resolved), who still warrant antimicrobial therapy, will have a clinical outcome of Improvement. Subjects with worsening of symptoms and new onset symptoms in addition to any of the criteria in Table 5 will have a clinical outcome of Failure.

The Investigator will assign a clinical outcome as defined in Table 5.
### Table 5. Criteria for Clinical Outcome

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>At EOIVT, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. At EOT, TOC, and LFU, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy is warranted. Symptom resolution does not necessarily include baseline symptoms associated with anatomic abnormalities that predispose to cUTI such as symptoms associated with the presence of an indwelling urinary catheter. <strong>This outcome category will be used only at EOIVT, EOT, TOC, and LFU visits.</strong></td>
</tr>
<tr>
<td>Improvement</td>
<td>Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms of cUTI or AP, but continued IV therapy is warranted. <strong>This outcome category will be used only at Day 3 and EOIVT visits.</strong></td>
</tr>
</tbody>
</table>
| Failure    | Subjects who experience any one of the following:  
- At any study visit, worsening of baseline clinical signs and symptoms of cUTI or AP or the development of new clinical signs and symptoms of infection, sufficient to stop study drug and initiate non-study antimicrobial;  
- At EOT, 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.                                                                                                                                                                                                                                                                                                      |

AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOIVT = End of Intravenous Treatment; EOT = End of Treatment; IV = intravenous; LFU = Late Follow-up; TOC = Test-of-Cure.

### 15.2.2 Microbiologic Outcome

The microbiologic outcome of Eradication in the m-MITT and ME Populations at the TOC visit will be used as the primary endpoint for the EMA for this study. The criteria for microbiologic outcome are defined in **Table 6.**
### Table 6. Criteria for Microbiologic Outcome

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| 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 for an organism that is identified as a uropathogen (if repeated after positive at baseline blood culture). |
| Persistence| - Persistence is the demonstration that one or more of the bacterial pathogen(s) found at baseline remains continuously present at $\geq 10^4$ CFU/mL on urine culture for FDA or $\geq 10^3$ CFU/mL for EMA;  
- OR a continuously positive blood culture with an organism that is identified as a uropathogen. |
| 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 urine culture or the urine culture cannot be interpreted for any reason. |

CFU = colony-forming units; EMA = European Medicines Agency; FDA = Food and Drug Administration.

To determine the per-pathogen outcome, the Sponsor will classify each baseline organism as a pathogen or a non-pathogen. Each baseline pathogen will be assigned a microbiologic outcome at the TOC visit and the results of the urine or blood culture at TOC documented. Multiple pathogens identified in cultured samples from the same subject will be assigned separate outcomes. The categories for pathogen microbiologic outcome are the same as those listed in Table 6.

#### 15.2.3 Overall Response

Overall success rate at EOIVT in the m-MITT Population will be used as the primary endpoint for the study for the FDA. Overall success rate at EOIVT and TOC in the m-MITT Population will be evaluated as a secondary endpoint for the study. This efficacy measure is derived from a composite of the clinical outcome and the microbiologic outcome.

The algorithm for overall response at the EOIVT visit is summarized in Table 7.
Table 7. Overall Response at End of Intravenous Treatment (EOIVT) Visit

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Microbiologic Outcome</th>
<th>Eradication</th>
<th>Persistence</th>
<th>Recurrence a</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>Success</td>
<td>Failure</td>
<td>Failure</td>
<td>Success based on presumed eradication</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>Success</td>
<td>Failure</td>
<td>Failure</td>
<td>Success based on presumed eradication</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>Failure</td>
<td>Failure</td>
<td>Failure</td>
<td>Failure based on presumed persistence</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Failed if clinical outcome at Day 3 = Indeterminate</td>
<td>Failure</td>
<td>Failure</td>
<td>Failed if clinical outcome at Day 3 = Indeterminate</td>
<td></td>
</tr>
</tbody>
</table>

a. For an outcome of Recurrence, subjects must have documented prior eradication (i.e., Day 3).

The algorithm for overall response at the TOC visit is summarized in Table 8.

Table 8. Overall Response at Test-of-Cure (TOC) Visit

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Microbiologic Outcome</th>
<th>Eradication</th>
<th>Persistence</th>
<th>Recurrence a</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>Success</td>
<td>Failure</td>
<td>Failure</td>
<td>Success based on presumed eradication</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>Failure</td>
<td>Failure</td>
<td>Failure</td>
<td>Failure based on presumed persistence</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Failed if clinical outcome at any earlier visit is failed; Otherwise = Indeterminate</td>
<td>Failure</td>
<td>Failure</td>
<td>Failed if clinical outcome at any earlier visit is failed; Otherwise = Indeterminate</td>
<td></td>
</tr>
</tbody>
</table>

a. For an outcome of Recurrence, subjects must have documented eradication at any prior time point.
16 PHARMACOKINETIC ASSESSMENTS

The PK plasma samples will be used to estimate PK parameters, such as area under the concentration-time curve (AUC), maximum plasma concentration (C<sub>max</sub>), time to maximum plasma concentration (T<sub>max</sub>), drug clearance (CL), half-life (t<sub>1/2</sub>), minimum plasma concentration (C<sub>min</sub>), and steady-state volume of distribution (V<sub>ss</sub>) for meropenem and RPX7009 using a structural population PK model.

Pharmacokinetic characterization and evaluation of plasma exposures of meropenem and RPX7009 in cUTI and AP subjects will be performed using both non-compartmental and modeling methods. Using a sparse sampling approach, PK samples on Day 1, Day 3, and EOIVT will be obtained from all subjects around the 3-hour infusions as specified in Table 1. The PK samples will be collected from both treatment groups to maintain the blind. Only PK samples obtained from the Caravance (meropenem/RPX7009) group will be analyzed (using a validated assay) by the central bioanalytical laboratory. While the PK analysis will be ongoing during the study, the Sponsor and all study personnel will remain blinded to the results.
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 CRO 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 summarizing 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 piperacillin/tazobactam).

The MITT Population will include subjects who meet the ITT criteria and receive at least one 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 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 bacterial pathogen(s) of ≥10^5 CFU/mL of urine at baseline urine culture for evaluation or the same bacterial pathogen present in concurrent blood and urine cultures. Subjects who only have an identified Gram positive pathogen in the urine and have received > 48 hours of an antibiotic with only Gram-positive coverage will not be included in the m-MITT population.

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 EOIVT, 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 ≥6 doses of study drug if classified as a Failure on clinical outcome, or receive ≥9 doses of study drug if classified as a Cure on clinical outcome.

The ME Population will include subjects who meet the MITT criteria as well as the following criteria:

- Have a bacterial pathogen(s) of ≥10^5 CFU/mL of urine at baseline urine culture for evaluation or have the same bacterial pathogen present in concurrent blood and urine cultures;
- Have no key inclusion or exclusion violations;
- Obtain a clinical outcome (Cure, Improvement, or Failure) and microbiologic outcome (Eradication or Persistence) at EOIVT, 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 ≥6 doses of study drug if classified as a Failure on overall outcome, or receive ≥9 doses of study drug if classified as a Cure on overall outcome.

• Subjects who only have an identified Gram positive pathogen in the urine and have received > 48 hours of an antibiotic with only Gram-positive coverage will not be included in the ME population.

18.2 Disposition, Demographics, Baseline Characteristics, and Exposure

The number of subjects randomized, treated, completed, and discontinued early from study drug and the 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

Descriptive statistics will be provided for each treatment group (Carbavance [meropenem/RPX7009] and piperacillin/tazobactam). Statistical tests and/or confidence intervals (CIs) will be used to compare treatment groups. All tests will be conducted using two-sided tests at the alpha = 0.05 level of significance.

Analyses of efficacy variables will be performed separately for the MITT, m-MITT, CE, and ME Populations.

Non-inferiority Analysis: The primary statistical objective of this study is to determine whether Carbavance (meropenem/RPX7009) is non-inferior to piperacillin/tazobactam in adult subjects with eUTI or AP. The primary endpoint for the FDA will be the proportion of subjects in the m-MITT Population with overall success at the EOIVT visit (Cure or Improvement + Eradication at EOIVT). The primary endpoint for the EMA will be the proportion of subjects in the m-MITT and ME Populations (co-primary) who achieve a microbiologic outcome of Eradication at the test-of-cure (TOC) visit. The non-inferiority margin will be a difference of 15 percentage points. The non-inferiority assessment will be based on the two-sided 95% CI for the difference in the proportions of subjects, based on the FDA and EMA endpoints, calculated as the rate in the Carbavance (meropenem/RPX7009) group minus that of the piperacillin/tazobactam group. Non-inferiority will be concluded if the lower limit of the two-sided 95% CI is >=-15%. If non-inferiority is demonstrated, an assessment for superiority will be performed.

Other analyses

Descriptive statistics will be provided for secondary endpoints. Treatment differences and associated 95% CIs will also be presented.

18.4 Safety Analysis

All subjects who receive at least one dose of study drug (i.e. the MITT population) will be included in the safety analyses and analyzed based on the treatment received. Adverse events will be collected throughout the study duration. Safety will be evaluated by presenting summaries of TEAEs, routine clinical laboratory evaluations, ECGs, vital signs, and physical examination findings for each treatment group.
A TEAE is defined as an adverse event with a start date and time on or after the first dose of study drug. The number and percentage of subjects with TEAEs will be tabulated by system organ class and preferred term for each treatment group and by severity and relationship to treatment. Adverse events leading to discontinuation from study drug and SAEs will be summarized by treatment group.

Clinical laboratory parameters and vital signs will be summarized at each scheduled evaluation using descriptive statistics. The changes in clinical laboratory parameters and vital signs from baseline to each scheduled evaluation and to the worst overall post-baseline value will also be summarized using descriptive statistics. The numbers and percentages of subjects with treatment-emergent potentially clinically significant laboratory and vital sign values will be tabulated for each treatment group. Other safety data (e.g., ECGs) will be summarized as appropriate.

All safety analyses will be performed using the Safety Population.

18.5 Pharmacokinetic Analysis
Plasma concentrations and PK parameters for meropenem and RPX7009 will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Derived plasma PK parameters will be summarized using descriptive statistics (n, arithmetic and geometric means, coefficient of variation, standard deviation of the arithmetic mean, median, minimum, and maximum).

All PK analyses will be performed using the PK Population.

18.6 Sample Size Justification
Assuming that of the approximately 500 subjects enrolled, 60% of subjects will be in the m-MITT Population, this sample size will provide 90% power to demonstrate the non-inferiority of Carbavance (meropenem/RPX7009) to piperacillin/tazobactam in the m-MITT Population, if the overall success rate is 80% in both groups and the non-inferiority margin is 15 percentage points.

Assuming 50% of enrolled subjects will meet criteria for inclusion in the ME Population, with 500 subjects, the study will have 84% power to demonstrate the non-inferiority of Carbavance (meropenem/RPX7009) to piperacillin/tazobactam in the ME Population.

An overall blinded efficacy evaluation will be conducted along with the evaluability rate of the m-MITT and ME Populations when approximately 60% of subjects are enrolled in the study. Based on this assessment, the sample size may be adjusted accordingly.
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 Good Clinical Practice (GCP), including ICH guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

19.2 Institutional Review Board/Independent Ethics Committee

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 responsible for notifying the IRB/IEC of all unanticipated problems involving risks to subjects or others 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

In compliance with GCP requirements, written informed consent will be obtained from all subjects. The informed consent form approved by a regional IRB/IEC 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). A copy of the signed/dated informed consent form must be provided to the subject. 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, and 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 CRO (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 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 Electronic Case Report Forms

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 Principal Investigator or a sub-investigator. It is the responsibility of the Principal Investigator 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 and site that will include the per subject eCRF in an individual subject profile.

19.8 Data Quality Assurance

Standard operating procedures will be available for all activities performed at the site as relevant to the quality of this study. Designated personnel at the site will be responsible for maintaining quality assurance and quality control to ensure that the study is conducted, and that data are generated, documented and reported, in compliance with the study protocol, GCP, and Good Laboratory Practice (GLP) requirements as well as applicable regulatory requirements. The Sponsor will also perform quality assurance audits of clinical sites and participating vendors.

All activities performed will be reported and a quality assurance certificate will be included in the study report issued by the Sponsor.

All clinical data will undergo a 100% quality control check (blinded) prior to clinical database lock. Edit checks will be performed for appropriate databases as a validation routine using SAS® (statistical analysis system) to check for missing data, data inconsistencies, data ranges, etc. Corrections will be made prior to statistical database lock.

Each eCRF will be reviewed and signed off by the Investigator.

19.9 Source Document Maintenance

Source documents are the records on which clinical observations and activities of a clinical investigation are first recorded. Source documents may include, but are not limited to, clinician
notes, medical records, printouts of 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 Sponsor representatives, the FDA and EMA, or other regulatory authorities.

19.10 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 review the source against the eCRF at regular intervals throughout the study, to verify the adherence to the protocol, and the completeness, consistency and accuracy of the data 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 (i.e., Quality Assurance [QA] Auditor), the FDA and EMA, and/or respective health authorities to inspect facilities and records relevant to this study.

19.11 Study File Management

It will be the responsibility of the Investigator(s) to assure that subject case histories and essential study documents are maintained at the site. 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 with 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.

19.12 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 Principal Investigator (an IRB/IEC summary letter is acceptable).

19.13 Audits

During the course of the study, or after completion of the study, study sites will be selected for an audit by a QA Auditor from the Sponsor (or an auditor appointed by the Sponsor or its authorized representative) and/or an inspector from the FDA, EMA, Department of Health and Human Services (HHS) and/or other regulatory authority.
19.14 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 Case Report Forms, consent forms, laboratory test results, and medication inventory records be kept on file by the Principal Investigator 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. The ICH 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.

19.15 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, EMA, 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.

19.16 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.

19.17 Publication Policy

The publication policy is outlined in more detail in the Clinical Trial Agreement.

All unpublished information given to the site by the Sponsor shall not be published or disclosed to a third party without prior written consent from the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon the Sponsor’s written consent to publish the article.
20 REFERENCES


APPENDIX 1: STATISTICAL ANALYSIS POPULATIONS

### Screened Population

- Screen failure

### Intent-to-Treat Population

- Drop no-med subjects

### Modified Intent-to-Treat (MITT) Population

- Have at least one plasma PK sample drawn

### Pharmacokinetic (PK) Population

- Receive ≥1 dose of Study Drug

### Microbiologic Modified Intent-to-Treat (m-MITT) Population

- Baseline bacterial pathogen(s) ≥10^5 CFU/mL or same bacterial pathogen in concurrent blood and urine cultures.
- Subjects who only have an identified Gram positive pathogen in the urine and have received > 48 hours of an antibiotic with only Gram-positive coverage will not be included.

### Clinical Evaluable (CE) Population

- Meet Evaluability Criteria:
  - Have no key inclusion/exclusion violations
  - Clinical outcome of (C/I/F) at EOIVT unless Failure at earlier time point
  - Receive ≥80% of expected IV doses
  - Miss no more than 1 IV dose in 1st 48 hours of treatment
  - Miss no more than 2 consecutive IV doses overall
  - ≥6 doses for Failure, ≥9 doses for Cure

### Microbiologic Evaluable (ME) Population

- Meets all m-MITT evaluability criteria and:
  - Have no key inclusion/exclusion violations
  - Clinical outcome of (C/I/F) and microbiologic outcome of (E/P) at EOIVT, unless Failure at earlier time point
  - Receive ≥80% of expected IV doses
  - Miss no more than 1 IV dose in 1st 48 hours of treatment
  - Miss no more than 2 consecutive IV doses
  - ≥6 doses for Failure, ≥9 doses for Cure

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C = Cure; CFU = colony-forming units; E = Eradication; EOIVT = End of Intravenous Treatment; F = Failure; I = Improvement; IV = intravenous; P = Persistence; PK = pharmacokinetic.

Safety population consists of the same patients as in the MITT population, except that the analyses on the safety population will be performed based on actual treatment received.
APPENDIX 2: SIGNS AND SYMPTOMS

The following signs and symptoms will be used to determine subject eligibility for step-down therapy, as well as to assess clinical outcome:

- Fever (oral or tympanic temperature $\geq 38^\circ\text{C} \geq 100.4^\circ\text{F}$ or rectal/core temperature $\geq 38.3^\circ\text{C} \geq 100.9^\circ\text{F}$)
- Urinary frequency
- Urinary urgency
- Dysuria
- Nausea
- Vomiting
- Abdominal pain
- Supra-pubic pain or discomfort
- Flank pain
- Costo-vertebral angle tenderness

All those listed above will be assessed as:

- New Onset
- Continuing (increased, decreased, no change)
- Resolved (returned to a pre-infection baseline or pre-infection condition)
REMPIEX 505 Carbavance (Meropenem/RPX7009)

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF CARBAVANCE (MEROPENEM/RPX7009) COMPARED TO PIPERACILLIN-TAZOBACTAM IN THE TREATMENT OF COMPLICATED URINARY TRACT INFECTIONS, INCLUDING ACUTE PYELONEPHRITIS, IN ADULTS

APPENDIX 3: STUDY SCHEMA

Subjects with cUTI or AP with or without bacteremia Requiring more than 5 days of IV treatment

Randomization

Carbavance (meropenem/RPX7009) 2 g/2 g q8h via IV infusion over 3 hours AND 100 mL NS via IV infusion over 30 minutes

Piperacillin/tazobactam 4.5 g (4 g piperacillin/0.5 g tazobactam) q8h via IV infusion over 30 minutes AND 250 mL NS via IV infusion over 3 hours

Screening Day -1 to Day 1

Treatment with IV Study Drug Day 1 through Day 5 (up to Day 10**)

EOIVT* ≥15 doses (Day 5 up to Day 10**)
FDA primary endpoint

EOT* Day 10**

Follow-up*** Day 15 up to Day 26

TOC*** Day 15 up to Day 19 EMA Primary Endpoint

LFU*** Day 22 up to Day 26

≥15 doses of IV Study Drug Transition to oral step-down therapy** if clinically indicated and criteria met

Objectives

To assess the efficacy of Carbavance (meropenem/RPX7009) administered by intravenous (IV) infusion in subjects with cUTI or AP.

To assess the safety and tolerability of Carbavance (meropenem/RPX7009) administered by IV infusion in subjects with cUTI or AP.

To assess the population PK of meropenem and RPX7009 in subjects with cUTI or AP.

EOIVT* = End of Intravenous Treatment; EOT* = End of Treatment (IV + oral); FDA = Food and Drug Administration; IV = intravenous; LFU = Late Follow-up; NS = normal saline; PK = pharmacokinetic; q8h = Every 8 hours; TOC = Test-of-Cure

*If EOIVT and EOT occur on the same day, visit activities will be combined.

**Subjects who are unable to receive levofloxacin based on prescribing information or have baseline urinary pathogen(s) resistant to levofloxacin and cannot remain in the hospital for a total of 10 days of IV treatment, with Medical Monitor approval, one of the following oral antibiotics can be selected: trimethoprim/sulfamethoxazole, cefdinir, cefixime or cefpodoxime.

***Subjects with bacteremia may receive treatment up to 14 days. For subjects with bacteremia, the visit window for the TOC visit is Day 15 to Day 23 and the visit window for the LFU visit is Day 22 to Day 30.

AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EMA = European Medicines Agency; EOIVT = End of Intravenous Treatment; EOT = End of Treatment (IV + oral); FDA = Food and Drug Administration; IV = intravenous; LFU = Late Follow-up; NS = normal saline; PK = pharmacokinetic; q8h = Every 8 hours; TOC = Test-of-Cure
APPENDIX 4: COMMON TOXICITY CRITERIA TABLE

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


The quick reference guide is available online at: