Official Protocol Title:	A Phase III Non-randomized, Non-controlled, Open Label Clinical Trial to Study the Safety and Efficacy of Imipenem/Cilastatin/ Relebactam (IMI/REL [MK-7655A]) in Japanese Subjects with Complicated Intra-Abdominal Infection (cIAI) or Complicated Urinary Tract Infection (cUTI)
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TITLE:

A Phase III Non-randomized, Non-controlled, Open Label Clinical Trial to Study the Safety and Efficacy of Imipenem/Cilastatin/Relebactam (IMI/REL [MK-7655A]) in Japanese Subjects with Complicated Intra-Abdominal Infection (cIAI) or Complicated Urinary Tract Infection (cUTI)

EudraCT NUMBER: Not Applicable

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1.0 TRIAL SUMMARY

Abbreviated Title	IMI/REL (MK-7655A) in Japanese Subjects with Complicated Intra-Abdominal Infection (cIAI) or Complicated Urinary Tract Infection (cUTI)
Sponsor Product Identifiers	MK-7655A Imipenem/Cilastatin/Relebactam (IMI/REL)
Trial Phase	Phase III
Clinical Indication	Treatment of complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	IMI/REL (MK-7655A)
Number of trial subjects	Approximately 80 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 14.5 months [54 weeks of enrollment + up to 14 days (2 weeks) of IV study therapy + 14 days (2 weeks) of follow up =58 weeks] from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 3 to 4 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After ≤ 24 hours of screening visit, each subject will be receiving IMI/REL for 5 to up to 14 days. After the end of IV therapy, each subject will be followed for at least 14 days. The total duration for each subject in the study will be up to 29 days.

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

Relebactam (REL; also known as MK-7655) is being developed as a fixed dose combination (FDC) with imipenem/cilastatin (IMI), a beta-lactam antibiotic of the carbapenem class. Throughout this protocol the combination of imipenem/cilastatin/relebactam (also known as MK-7655A) will be referred to as IMI/REL and imipenem/cilastatin will be referred to as IMI.

This is a nonrandomized, non-controlled, multi-site, open-label trial of IMI/REL in Japanese subjects with complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI).

Approximately 80 Japanese subjects with cIAI or cUTI as a primary infection site will be enrolled into this study. The number of subjects with either of infection types enrolled in this study should not exceed 50. Subjects with bloodstream infections (bacteremia) secondary to cIAI, or cUTI are eligible for enrollment. Of those, subjects who meet the criteria for sepsis will be evaluated for the efficacy on sepsis in addition to their infection at primary site. After a maximum 24-hour screening period, eligible subjects will receive a minimum of 5 days to up to a maximum of 14 days of IV study therapy. While on study therapy, study visits will be

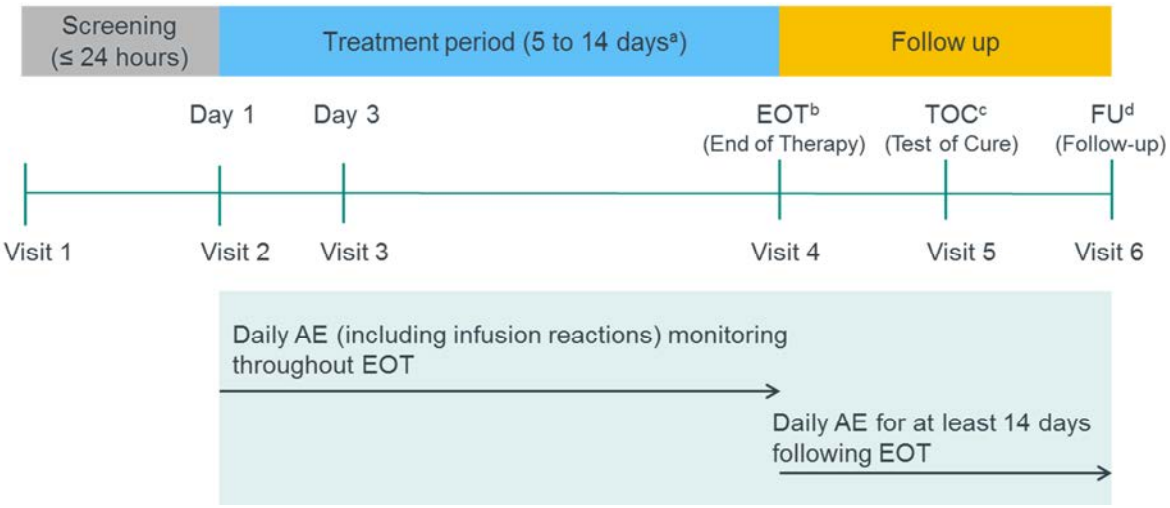
performed on Day 1 (initiation of IV study drug), Day 3 (on therapy visit), and at end of therapy (EOT). Following the completion of IV study therapy, all subjects will be evaluated 5 to 9 days following completion of therapy (at test of cure, TOC visit). In addition, a Follow up (FU) visit will be performed in all subjects at 14 days after completion of IV study therapy. All subjects will remain in the study for a total of up to 29 days.

Safety and tolerability will be carefully monitored throughout the study by the Sponsor in accordance with standard procedures.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted Figure 1.



a. Subjects will receive a minimum of 5 days to up to a maximum of 14 days of IV study therapy.
b. The EOT visit must occur ≤24 hours after the last dose of IV therapy.
c. 5 to 9 days following EOT.
d. Follow up visit will occur 14 days following completion of IV study therapy.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male/female Japanese subjects who are at least 18 years of age and have been diagnosed with complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI):

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** For the subjects with cIAI or cUTI, to evaluate the safety and tolerability profile of IMI/REL.

(2) **Objective:** To estimate the proportion of subjects with favorable response to IMI/REL by infection type.

The response for each infection type will be estimated based on the following:

(a) Clinical response at End of Therapy (EOT) visit for subjects with cIAI.

(b) Microbiological response at EOT visit for subjects with cUTI.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: For subjects with cIAI, to estimate the proportion of subjects with favorable clinical response to IMI/REL at test of cure (TOC) visit.

(2) **Objective**: For subjects with cUTI, to estimate the proportion of subjects with favorable microbiological response to IMI/REL at TOC visit.

3.3 Exploratory Objective

(1) **Objective:** For subjects with cIAI, to estimate the proportion of subjects with favorable microbiological response to IMI/REL at EOT and TOC visit.

(2) **Objective:** For subjects with cUTI, to estimate the proportion of subjects with a favorable clinical response to IMI/REL at EOT and TOC visit.

(3) **Objective:** For subjects with cUTI, to summarize the proportion of subjects with favorable composite clinical and microbiological response to IMI/REL at EOT and TOC visit.

(4) **Objective:** For subjects with cIAI or cUTI who meet the criteria for sepsis, to describe the composite clinical and microbiological response to IMI/REL at EOT and TOC visit.

(5) **Objective:** To provide the plasma concentrations of REL, imipenem, and cilastatin.

(6) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-7655A.

4.1.1 Pharmaceutical and Therapeutic Background

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

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

IMI, a potent broad spectrum β-lactam antibacterial agent from the carbapenem class, has been used clinically for the treatment of serious infections since 1985. The bactericidal activity of imipenem results from inhibition of cell wall synthesis. Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I, resulting in relatively low levels in the urine. Cilastatin sodium is an inhibitor of this enzyme and effectively prevents renal metabolism of imipenem so that, when given together, adequate serum antibacterial levels of imipenem are achieved. Imipenem is active against a broad range of Gram-positive and Gram-negative organisms and is approved for use in a variety of infections, including lower respiratory tract infections, urinary tract infections (complicated and uncomplicated), intra-abdominal infections, gynecologic infections, bacterial septicemia, bone and joint infections, skin and skin structure infections, endocarditis, and polymicrobial infections. REL represents a new generation of BLIs to combat evolving clinical resistance and to maintain the usefulness of the β-lactam class of antibiotics. REL is a dual Ambler Class A/Class C BLI that is highly potent against AmpC, a common Class C β-lactamase encountered in many bacteria, most predominantly *Pseudomonas aeruginosa*. REL is also active against the Class A β-lactamases, including the *Klebsiella pneumoniae* carbapenemase (KPC) present in some Enterobacteriaceae, including Klebsiella strains. REL has no activity against the Class B metallo-β-lactamases (including NDM-1, IMP, or VIM-containing strains) or Class D β-lactamases (including OXA-producing strains).

4.1.2 Pre-clinical and Clinical Trials

Preclinical data, including *in vitro* microbiological studies with imipenem-resistant clinical isolates of *P. aeruginosa* and KPC-producing organisms, as well as *in vivo* infection models with imipenem-resistant *P. aeruginosa* and *K. pneumoniae*, suggest that REL, in combination with IMI, has the potential to fulfill a significant and growing medical need by providing a next-generation BLI to combat severe Gram-negative bacterial infections.

Preclinical toxicity studies in rats and monkeys have demonstrated that REL is generally well-tolerated. There was no evidence of adverse effects of REL as a single agent on cardiovascular, central nervous system, and respiratory function in well-characterized preclinical safety pharmacology models. Toxicity of REL in combination with IMI has been evaluated for up to one month and 3 months in monkeys. Evidence of renal toxicity was

observed at levels 0.6 times the target human exposure; however, no clinically relevant findings associated with renal function have been identified in the Phase I studies or in the completed Phase II study in humans.

To date, REL has been evaluated in approximately 218 individuals who have received at least one dose of REL across six completed Phase I studies (PN001, PN002, PN005, PN007, PN009 and PN012). Healthy young and elderly male and female adults as well as subjects with varying degrees of renal insufficiency have been studied, including subjects with end stage renal disease (ESRD) on hemodialysis.

Unblinded safety data from the Phase I studies have demonstrated that single and multiple intravenous doses of REL have been generally safe and well tolerated throughout the dose ranges tested and across the various subject populations. In PN009 (a standard thorough QTc study evaluating the effect of REL on the QTc interval), a supratherapeutic dose of REL did not prolong the QTc interval to a clinically meaningful extent and no risk of cardiac repolarization prolongation was identified.

In PN001, generally mild elevations in hepatic transaminases above the upper limit of normal range (ULN) have been observed in the multiple-dose treatment arms in which REL was coadministered with IMI. Elevations were also seen in subjects receiving IMI alone. None of the liver transaminase elevations in these subjects were associated with clinical findings. The elevations were not dose related and were reversible after discontinuation of dosing.

Generally mild elevations in hepatic transaminases were also observed in Japanese subjects receiving multiple doses of REL in PN012. Similar to observations in PN001, the increases in ALT/AST resolved after completion of dosing. Elevations have not been observed in subjects administered single or multiple doses in PN002, PN005, PN007 or single doses in PN009.

The PK of REL, imipenem, and cilastatin (CIL) were evaluated following single and multiple doses of REL in combination with 500 mg IMI, administered every 6 hours for 7 to 14 days in PN001 and PN002. Data from these studies demonstrated that REL exposures increase proportionally with dose, with doses at 125 mg and above exceeding the identified REL PK target of $AUC_{0-\infty} \geq 37.5$ μM-hr. PN012 showed that the pharmacokinetic profiles of REL, imipenem and cilastatin in healthy Japanese subjects were similar to historical data obtained from non-Japanese subjects in PN001. The PK of REL, imipenem, and CIL were also evaluated in renally impaired subjects (PN005). PK data from PN005 were consistent with expectations given that REL, imipenem, and CIL are cleared almost entirely renally in healthy subjects. The plasma clearance (CL_{plasma}), terminal half-life ($t_{1/2}$) and area under the concentration time curve ($AUC_{0-\infty}$) were significantly and similarly altered for each of these three analytes when comparing subjects with renal impairment to their healthy matched subjects. Based on this data, the dose adjustment for subjects with renal impairment was considered and included in this protocol (refer to the section 4.2.2.1 and 5.2.1.1 for the details). These data are consistent with the expected change in magnitude of glomerular filtration rate (GFR). In addition, in subjects with ESRD, REL, imipenem, and CIL were efficiently removed by hemodialysis. The PK of REL was also studied in healthy volunteers in an intrapulmonary lung penetration study (PN007). In PN007, the intrapulmonary PK profiles of REL and imipenem were assessed after administration of REL and IMI administered every 6 hours over 5 doses. Data in these subjects showed penetration of both

REL and imipenem into the extracellular (epithelial lung fluid [ELF]) and intracellular (alveolar cells [AC]) spaces. In PN009, the pharmacokinetics of REL were assessed to confirm that supratherapeutic levels were achieved for the evaluation of the effect of REL on the QTc interval A single 1150 mg dose of REL in PN009 achieved $AUC_{0-\infty}$ and a C_{eoi} that were ~4-fold higher than those observed following a single dose of 250 mg and similar to exposures observed after an identical dose in PN001.

Additional details regarding the preclinical and Phase I clinical studies completed to date are summarized in the Investigator's Brochure for MK-7655A.

PN004 was a randomized, double-blind, multicenter, comparative study evaluating the safety, tolerability, and efficacy of IMI + REL versus IMI alone in adults with cIAI. A total of 351 subjects with cIAI were randomized in a 1:1:1 ratio to one of 3 treatment groups (1) IMI + REL (250 mg), (2) IMI + REL (125 mg), or (3) IMI + placebo to REL. The primary efficacy endpoint was the proportion of subjects with favorable clinical response at discontinuation of IV study therapy (DCIV). The primary analysis population was the microbiologically evaluable (ME) population. The primary efficacy analysis indicates that treatment with either 250 mg or 125 mg of IMI + REL is at least as effective as IMI alone. Specifically, at DCIV in the ME population, the proportion of subjects with a favorable clinical response was 96.3 % (78/81) in subjects who received IMI + REL (250 mg), 98.8 % (85/86) in subjects who received IMI + REL (125 mg), and 95.2 % (79/83) in subjects who received IMI + placebo to REL.

The incidence rate of adverse experiences observed in subjects who received either dose of IMI + REL (either the 125 mg or the 250 mg dose of REL) was generally comparable to that observed in subjects who received IMI + placebo to REL. No evidence of significant renal toxicity or hepatotoxicity was observed. Given the findings from PN001, close monitoring for transaminase elevations was included in PN004. As part of this monitoring, there were 2 pre-specified events of clinical interest (ECI) that triggered staged evaluation and monitoring of subjects with these elevations. The events of clinical interest included: 1) confirmed AST or ALT $\geq$ 5 X ULN and 2) ALT or AST $\geq$ 3 X ULN and total bilirubin $\geq$ 2 X ULN and, at the same time, alkaline phosphatase < 2 X ULN. A total of 2 (1.7%) subjects who received IMI + REL (250 mg), 0 subjects who received IMI + REL (125 mg) and 2 (1.8%) subjects who received IMI + placebo to REL experienced ECI #1. The two subjects with ECI #1 in the IMI + REL (250 mg) group were due to elevations in the subject's ALT, while the two subjects in the IMI + placebo to REL met criteria for ECI #1 based on elevations in AST. There were no statistically significant differences between either of the two IMI + REL groups versus the IMI + placebo to REL in the percentage of subjects meeting the definition of ECI #1.

There was 1 subject who received IMI + REL (250 mg) who met the criteria for ECI #2. On the second day of IV therapy, the subject developed elevated ALT/AST during treatment with IV study therapy, which normalized with continued therapy. The subject subsequently completed study therapy and was considered a cure. In the investigator's opinion, the elevations were not related to study therapy and could be due to concurrent septic shock or history of cholelithiasis. There were no statistically significant differences between either of the two REL groups vs the IMI + placebo to REL group in the percentage of subjects meeting the ECI #2 definition.

PN003 was a randomized, double-blind, multicenter, comparative study evaluating the safety, tolerability, and efficacy of IMI + REL versus IMI alone (IMI + placebo to REL) in adults ≥18 years of age with cUTI. A total of 302 subjects with cUTI (including pyelonephritis) were randomized in a 1:1:1 ratio to one of 3 treatment groups (1) IMI + REL (250 mg), (2) IMI + REL (125 mg), or (3) IMI alone. The primary efficacy endpoint was the proportion of subjects with favorable microbiological response at discontinuation of IV study therapy (DCIV). The primary analysis population was the microbiologically evaluable (ME) population. The primary efficacy analysis indicates that treatment with IMI plus either 250 mg or 125 mg of REL is at least as effective as IMI alone for the treatment of cUTI. Specifically, at DCIV in the ME population, the proportion of subjects with a favorable microbiological response was 95.5 % (64 /67) in subjects who received IMI + REL (250 mg), 98.6 % (70/71) in subjects who received IMI + REL (125 mg), and 98.7 % (74/75) in subjects who received IMI + placebo.

The incidence rate of AEs observed in subjects who received either dose of IMI + REL (either the 125 mg or the 250 mg dose of REL) was generally comparable to that observed in subjects who received IMI alone. No evidence of significant renal toxicity or hepatotoxicity was observed. Close monitoring for transaminase elevations was included in PN003 in the same fashion as in PN004. One (1.0%) subject who received IMI + REL 250 mg, 1 (1.0%) subject who received IMI + REL 125 mg and 0 subjects who received IMI + placebo experienced ECI #1 (confirmed AST or ALT ≥ 5 X ULN). There were no statistically significant differences in the percentage of subjects meeting the definition of ECI #1 between either of the two IMI + REL groups versus the IMI + placebo group. No subjects met the criteria for ECI #2 (ALT or AST ≥ 3 X ULN and total bilirubin ≥ 2 X ULN and, at the same time, alkaline phosphatase < 2 X ULN).

Additional details regarding the Phase II clinical studies are summarized in the Investigator's Brochure for MK-7655A.

4.1.3 Ongoing Clinical Trials

Two Phase III studies to evaluate safety and efficacy of MK-7655A are ongoing (Protocol 013 [PN013] and Protocol 014 [PN014]). Japan is currently participating in both studies. PN013 is a Phase III randomized, double-blind, comparator-controlled study to estimate the safety and efficacy of IMI/REL versus colistin as colistimethate sodium (CMS) + IMI in subjects with imipenem-resistant bacterial infection, including hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), cIAI, or cUTI. Subjects are randomized in a 2:1 ratio to receive 1 of 2 of the following treatments for a minimum of 5 or 7 days (depending on primary site of infection) to a maximum of 21 days, administered q6h: 1) IMI/REL (500 mg/250 mg) + placebo to CMS; 2) IMI (500 mg) + CMS. PN013 also includes a third, open label treatment arm in subjects with imipenem- and colistin-resistant infection who will receive IMI/REL as a fixed-dose combination. PN014 is a Phase III randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and efficacy of IMI/REL versus piperacillin/tazobactam in hospitalized subjects with HABP/VABP. Approximately 536 subjects will be randomized in a 1:1 ratio to one of the following treatment groups: 1) IMI/REL (500 mg/250 mg) administered IV as a fixed-dose combination, or 2) piperacillin/tazobactam (4000 mg/500 mg) administered IV as a fixed dose combination.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

As previously mentioned, IMI/REL has the potential to fulfill a significant and growing unmet medical need by providing a next generation BL/BLI with which to combat severe Gram-negative bacterial infections including imipenem-resistant infection.

The current epidemic of multi-drug resistant (MDR) bacterial infections is a critical challenge in healthcare today. The organisms known as "ESKAPE" pathogens (*Enterococus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *A. baumanni*, *P. aeruginosa*, and Enterobacter species) predominate in the resistance epidemic and have become a significant problem in hospital-acquired infections [1]. The ESKAPE organisms currently cause a substantial proportion of U.S. hospital infections and are responsible for increasing numbers of outbreaks in healthcare facilities around the world [2-11]. Over the last decade, the emergence of several highly resistant Gram-negative pathogens, including Carbapenem-Resistant (CR) *P. aeruginosa* and CR Enterobacteriaceae (predominantly KPC), had posed a particularly troubling, and escalating, global health issue [3, 12]. Multi-drug resistance (MDR) severely limits the utility of currently available antibiotics. Due to the absence of effective and tolerable antibiotics, infections caused by CR Gram-negative organisms have a high mortality rate. Even with treatment using last-resort therapies such as colistin, mortality rates in critically ill patients with MDR pathogens, including CR pathogens, range from 16% up to as high as 60% [13-20]. Thus, there is an urgent need for new, well-tolerated drugs with activity against these emerging antibiotic-resistant bacteria.

Some of the most common sites of infection in patients with MDR, including CR, Gram-negative infections are the lungs, the abdomen and the urinary tract [13-20]. These are also of the most common sites of healthcare-associated infections.

Based on the above situation, subjects with certain CR, Gram-negative infections (CR *P. aeruginosa* and KPC) at several prevalent infection sites, including HABP/VABP, cIAI, and cUTI are enrolled in PN013. In addition to PN013 study, PN014 study which evaluate the efficacy and safety of IMI/REL in subjects with HABP/VABP, regardless of pathogen susceptibility. Approximately 40 Japanese subjects will be enrolled into this study. Half of subjects who enrolled into the PN014 study will be treated with IMI/REL. However, there is a need for additional data which supports the safety and efficacy for Japanese subjects treated with IMI/REL, especially for infections other than HABP/VABP which are evaluated in PN014. Although the safety and efficacy of IMI + REL has been evaluated in 2 Phase II studies (PN003 in subjects with cUTI, and PN004 in subjects with cIAI) in order to establish clinical proof-of concept and to identify the optimal dose for REL for subsequent studies, comparable data in Japanese subjects are not yet available. The current proposed study will enroll subjects with cIAI and cUTI, and all of them will be treated with open-label IMI/REL. Subjects with bloodstream infections (bacteremia) secondary to cIAI, or cUTI are also eligible for enrollment. If there are subjects enrolled who meet the criteria of sepsis

predefined in this protocol (refer to section 5.1.2, inclusion criteria #2) are enrolled, those subjects will be evaluated for efficacy of sepsis treatment in addition to the efficacy of treatment of their primary infections.

A hundred (100) subjects are considered as a targeted number in evaluation of safety for Japanese subjects. Approximately 20 subjects will be enrolled and treated in the ongoing PN014 study, and an additional 80 subjects will need to be enrolled in this study (PN017). Considering the limitation of total number of subjects enrolled in this study, and the two different types of infection are to be enrolled in one study, the number of subjects for each infection is not defined in the protocol. However, the number of subjects with either of infection types enrolled in this study should not exceed 50.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Dose selected for IMI/REL

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

Both a 125 mg and 250 mg dose of REL have been evaluated in the Phase II clinical studies (PN003 and PN004). The 250 mg dose was selected for this study to achieve exposures above the PK target that may be required for the treatment of highly resistant organisms. This dose has been evaluated in the ongoing Phase III studies (PN013 and PN014) in which Japan is participating.

4.2.2.2 Rationale for Dose Modification of IMI/REL

As previously discussed, REL, imipenem, and CIL are primarily renally excreted, with similar increases observed for each analyte in a Phase I renal insufficiency study (PN005). Thus, dose adjustments can be made in the same proportion for both REL and IMI, and all can be dosed in a fixed ratio. IMI and REL will be provided together in a single vial as a fixed-dose combination product in this study (IMI/REL). Dose adjustment is required in subjects with renal impairment. Depending on the individual subject's renal function (as determined by actual or estimated creatinine clearance), the total daily dose of IMI/REL may be adjusted. PK-based simulation results indicate that in subjects with normal renal function, the dose of 250 mg REL and 500 mg IMI is appropriate. For subjects with mild renal insufficiency, the dose should be reduced to 200 mg REL and 400 mg IMI, for moderate renal insufficiency 150 mg REL and 300 mg IMI, and for severe renal insufficiency 100 mg

REL and 200 mg IMI. The specific dosing guidelines are included in Section 5.2.1.1 (Table 13).

4.2.2.3 Rationale for Duration of Therapy

IV study therapy will be administered for a minimum of 5 days up to a maximum of 14 days.

Subjects with severe infections required hospitalization and IV therapy will be enrolled. Guidelines published by the Japanese Association for Infectious Diseases/the Japanese Society of Chemotherapy (JAID/JSC) [22] recommend at least 3 days of initial treatment for severe cUTI infections and 5 to 7 days of treatment for cIAI for most infections. The guideline also recommends that maximum 14 days for cUTI. The Infectious Diseases Society of America (IDSA) guideline [23, 24] provided similar recommendation; limiting treatment of catheter-associated UTI to less than 2 weeks, limiting treatment of cIAI to less than 1 week for most infections.

Considering the above and the expectation that subjects with infection caused by MDR, including CR which is the target population of PN013 study may also participate in this study since pathogen susceptibility is not confirmed before subjects enrolled into this study, the minimum duration of IV therapy was determined as same as PN013 study, i.e., 5 days, and maximum duration was determined as 14 days based on the current clinical practice recommended by guidelines.

In addition the current data for REL support up to 1 month of administration; REL was studied for toxicity in monkeys and rats up to 3 months with acceptable results. Refer to the Investigator's Brochure (IB) for more detailed information on preclinical toxicity studies for MK-7655A.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

As the primary objective, of this study, the safety and tolerability of IMI/REL will be assessed by clinical evaluation of adverse experiences and inspection of other study parameters including vital signs, physical examinations, and standard laboratory safety tests at time points specified in the Trial Flow Chart. Adverse experiences are graded and recorded according to Section 7.2. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

4.2.3.2 Efficacy Endpoints

The efficacy in clinical studies is typically measured differently for different infection types. As the primary efficacy endpoints, clinical response at End of Therapy (EOT) for subjects with cIAI and the overall (per subject) microbiological response at EOT for subjects with cUTI will be evaluated. Each of these endpoints are selected considering to the efficacy endpoints used in Phase II studies for IMI/REL, i.e., PN003 and PN004 to confirm the efficacy of IMI/REL in the targeted infection types. The primary intention of this study is to evaluate the true impact of IMI/REL for Japanese subjects. Hence, the primary endpoint will focus on the timepoint of EOT in order to evaluate the effect of IMI/REL.

Throughout the study, clinical and microbiological responses will be evaluated at EOT, and at 5 to 9 days after completion of treatment (the Test of Cure, TOC). Evaluation of microbiological and clinical response at these timepoints will provide valuable data to fully characterize the response profile of IMI/REL when administered to Japanese subjects. Those endpoints relevant to the response to IMI/REL and which are not included as primary endpoints will be evaluated secondary or exploratory. For subjects with cUTI, composite clinical and microbiological response will be also evaluated at each timepoint.

In addition, for subjects who meet the criteria of sepsis (refer to section 5.1.2, inclusion criteria #2), the efficacy will be assessed using specified criteria based on composite of clinical and microbiological evaluation, referring to the guideline published in Japan as well as FDA guideline [25, 26]. Because of expectation that the number of subjects with sepsis may be very small, the outcome of sepsis will be described for each subject. These subjects are also included in the general assessment of cIAI or cUTI.

Refer to Table 1 for efficacy endpoints by infection type, and by timing. Details regarding the endpoints are presented in subsequent sections.

Table 1 Summary of Efficacy Endpoints

Infection Type	Endpoints	Timing
cIAI	Clinical response (per subject)	EOT (Primary), TOC
	Microbiological response (per subject)	EOT, TOC
cUTI	Clinical response (per subject)	EOT, TOC
	Microbiological response (per subject)	EOT (Primary), TOC
	Composite clinical and microbiological response	EOT, TOC
Sepsis	Composite clinical and microbiological response	EOT, TOC

4.2.3.2.1 Definition of Efficacy Endpoints

In this study clinical response and microbiological response will be evaluated at the EOT and TOC visits. Refer to the following details of definitions for each efficacy response.

4.2.3.2.1.1 Clinical response

Clinical response will be assessed for all subjects based on evaluation by the investigator at the EOT and TOC visits. Based on comparison to baseline clinical signs and symptoms of the subject's infection(s), the investigator will determine the clinical response rating (and record the response on the appropriate eCRF) at each visit as described in Table 2 (for EOT visit) and Table 3 (for TOC visit).

In support of evaluation of efficacy endpoints that include clinical response, the clinical response rating determined by the investigator at each visit will be categorized as "favorable" or "unfavorable". Details regarding determination of the category of clinical response ("favorable" or "unfavorable") in support of relevant study endpoints are provided in the tables describing clinical response as well as Section 8.4.2.

Table 2 Definitions of the Clinical Response Rating at the EOT Visit

Clinical Response[a]	Response Definition
Cure	All pretherapy signs and symptoms[b] of the index infection(s) have resolved (or returned to "preinfection status") **AND** no additional IV antibiotic therapy is required, **AND**, for cIAI subjects, no unplanned surgical procedures or percutaneous drainage procedures have been performed.
Improved	All or most pretherapy signs and symptoms[b] of the index infection(s) have improved or resolved (or returned to "preinfection status") **AND** no additional IV antibiotic therapy is required, **AND**, for cIAI subjects, no unplanned surgical procedures or percutaneous drainage procedures have been performed.
Failure	No apparent response to IV study therapy in prestudy signs and symptoms[b] of the index infection(s): persistence or progression of most or all pretherapy signs and symptoms.
Indeterminate	Study data are not available for evaluation of clinical response for any reasons at the EOT visit, including: a) Complication related to underlying medical condition; **OR** b) Subject was discontinued for any reason before sufficient data had been obtained to permit evaluation for any reason; **OR** c) Extenuating circumstances preclude classification as "cure", "improved" or "failure" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.
[a] A favorable clinical response at EOT requires an assessment of “cure” or “improved”. [b] Refer to Table 14 in section 7.1.2.6 for a description of disease-specific clinical signs and symptoms.	

Table 3 Definitions of the Clinical Response Rating at the TOC Visit

Clinical Response[a]	Response Definition
Cure	All pretherapy signs and symptoms[b] of the index infection(s) have resolved (or returned to "preinfection status") **AND** no additional IV antibiotic therapy is required, **AND**, for cIAI subjects, no unplanned surgical procedures or percutaneous drainage procedures have been performed.
Failure	No apparent or insufficient response to IV study therapy in prestudy signs and symptoms of the index infection(s): persistence, progression, or improvement (without full resolution) of all pretherapy signs and symptoms[b]
Indeterminate	Study data are not available for evaluation of efficacy for any reasons, including: a) Complication related to underlying medical condition; **OR** b) Subject was discontinued for any reason before sufficient data had been obtained to permit evaluation of clinical response; **OR** c) Extenuating circumstances preclude classification as "cure" or "failure" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.
[a] A favorable clinical response at TOC visit requires an assessment of “cure”. [b] Refer to Table 14 in section 7.1.2.6 for a description of disease-specific clinical signs and symptoms.	

4.2.3.2.1.2 Microbiological Response

Microbiological response will be evaluated separately for each baseline pathogen (i.e., by-pathogen). The by-pathogen response rating will be determined by investigator. Separate criteria for microbiological evaluation will be utilized for cIAI and cUTI. According the following criteria, the by-pathogen microbiological response will be determined at the EOT and TOC visits based on local laboratory results from cultures collected at each of these visits relative to the pathogen(s) isolated at baseline/admission.

In support of evaluation of efficacy endpoints that include microbiological response, the by-pathogen microbiological response rating will be utilized to categorize the overall microbiological response (i.e., overall microbiological response for the subject based on the response of all pathogens present in the baseline culture) as "favorable" or "unfavorable." For subjects from whom only one pathogen is isolated, the overall microbiological response assessment will be based on the microbiological response rating for that pathogen. For subjects from whom more than one baseline pathogen is isolated, the overall microbiological response outcome will be based on microbiological culture results for all baseline pathogens.

Details regarding determination of the category of overall microbiological response outcome ("favorable" or "unfavorable") in support of relevant study endpoints are provided in the tables describing microbiological response as well as in Section 8.4.2.

4.2.3.2.1.2.1 Microbiological Response for cIAI

The following tables are for the definitions of Microbiological Response for cIAI, as described in Table 4 (for the EOT visit) and Table 5 (for the TOC visit). Only subjects with an intra-operative culture positive for the presence of at least 1 gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI will be considered microbiologically evaluable.

Table 4 Definitions of the By-Pathogen Microbiological Response Rating for cIAI at the EOT Visit

Microbiological Response[a,b]	**Response Definition**
Eradication	The follow-up culture at the site of infection taken at the EOT visit (or, if not available, from the last available culture after at least 48 hours of IV study therapy) shows eradication of the pathogen found at study entry.
Presumptive eradication	Absence of material to culture from the site of infection in a subject who had responded clinically to treatment.
Persistence[c]	The follow-up culture at the site of infection taken at the EOT visit (or, if not available, from the last available culture after at least 48 hours of IV study therapy) grows the pathogen found at study entry.
Super infection	The follow-up culture at the site of infection taken at the EOT visit (or, if not available, from the last available culture after at least 48 hours of IV study therapy) grows a pathogen other than a baseline pathogen during the course of IV study therapy OR emergence during IV study therapy of a new pathogen at a distant sterile site along with worsening signs and symptoms of infection.
Indeterminate	a) Entry culture at the site of infection either not obtained or no growth ; **OR** b) Follow-up cultures are not available from the site of infection due to subject death or withdrawal from study; **OR** c) Microbiological data are incomplete; **OR** d) Assessment not possible due to protocol violation; **OR** e) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered "super infection" for any new/emergent pathogen isolated after initiation of IV study therapy.

[b] A favorable overall microbiological response at EOT requires "eradication" or "Presumptive eradication" of all baseline pathogens.

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

Table 5 Definitions of the By-Pathogen Microbiological Response for cIAI at the TOC Visit

Microbiological Response[a,b]	**Response Definition**
Sustained eradication[c]	The follow-up culture at the site of infection taken at TOC visit, shows eradication of the pathogen found at study entry.
Presumptive eradication	Absence of material to culture from the site of infection in a subject who had responded clinically to treatment.
Persistence	The follow-up culture at the site of infection taken at TOC visit grows the pathogen found at study entry. These subjects are carried forward with this status from the EOT visit otherwise it meets the criteria for 'New infection' or 'Recurrence' to those 2 follow up visit.
New Infection	Eradication of the original pathogen from the site of infection followed by replacement (at the same site and after completion of IV study therapy) by a new species or by a new serotype or biotype of the same organism in the presence of signs or symptoms of infection. If a pathogen was isolated from a site distant to the primary infection after IV study therapy has been completed, then this is also designated as a new infection.
Recurrence	The follow-up culture from the site of infection taken anytime after documented eradication at the EOT visit grows the original pathogen.
Indeterminate	a) Follow-up culture is not available at the TOC visit due to subject death or withdrawal from study; **OR** b) Microbiological data are incomplete; **OR** c) Assessment not possible due to protocol violation; **OR** d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered a "new infection" for any new/emergent pathogen isolated after initiation of IV study therapy.

[b.] A favorable overall microbiological response at TOC visit requires "sustained eradication" or "Presumptive eradication" of all baseline pathogens.

[c] A microbiological response of "sustained eradication" at TOC is used when the microbiological response assessment at EOT visit is also "eradication".

4.2.3.2.1.2.2 Microbiological Response for cUTI

The following tables are for the definitions of Microbiological Response for cUTI, as described in Table 6 (for the EOT visit) and Table 7 (for the TOC visit).

Table 6 Definitions of the By-Pathogen Microbiological Response Rating for cUTI at the EOT Visit

Microbiological Response[a,b]	**Response Definition**
Eradication	A urine culture taken at the EOT visit[d] shows eradication of the uropathogen (e.g., $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry.
Persistence[c]	A urine culture taken at the EOT visit[d] grows a uropathogen (at $\geq 10^4$ CFU/mL) found at study entry.
Super infection	An infection-site culture grows a uropathogen (at $\geq 10^5$ CFU/mL) other than a baseline pathogen during the course of IV study therapy **OR** emergence during IV study therapy of a new pathogen at a distant (non-urine), sterile site along with worsening signs and symptoms of infection.
Indeterminate	a) Follow-up urine culture is not available at the EOT visit due to subject death or withdrawal from study; OR b) Microbiological data are incomplete; OR c) Assessment not possible due to protocol violation; OR d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered "super infection" for any new/emergent pathogen isolated after initiation of IV study therapy.

[b] A favorable overall microbiological response at EOT requires "eradication" of all baseline pathogens.

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

[d] If a culture is not available at EOT, an assessment at this visit can be made from the last available urine culture which was collected after at least 48 hours of IV study therapy.

Table 7 Definitions of the By-Pathogen Microbiological Response for cUTI at the TOC Visit

Microbiological Response[a,b]	**Response Definition**
Sustained eradication[c]	A urine culture taken at the TOC visit still shows eradication of the uropathogen (e.g., $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry.
Persistence	A urine culture taken at the TOC visit grows a uropathogen (at $\geq 10^4$ CFU/mL) found at study entry.
New Infection	A uropathogen, other than a microorganism found at baseline is present in the urine (at a level $\geq 10^5$ CFU/mL) any time after IV study therapy is finished; **OR** A pathogen is isolated from a distant (non-urine), sterile after IV study therapy has been completed.
Recurrence	A urine grows a uropathogen (at a level $\geq 10^5$ CFU/mL) taken any time after documented eradication.
Indeterminate	a) Follow-up urine culture is not available at the EFU visit due to subject death or withdrawal from study; **OR** b) Microbiological data are incomplete; **OR** c) Assessment not possible due to protocol violation; **OR** d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered a "new infection" for any new/emergent pathogen isolated after initiation of IV study therapy.
[b.] A favorable overall microbiological response at TOC visit requires "sustained eradication" of all baseline pathogens.
[c] A microbiological response of "sustained eradication" at TOC is used when the microbiological response assessment at EOT visit is also "eradication".

4.2.3.2.1.2.3 Composite Clinical and Microbiological Response (only for cUTI)

Composite clinical and microbiological response at each timepoint will be determined by Sponsor based on the clinical response evaluated by investigator and overall microbiological response (per subject) determined by Sponsor. Only the subject who have favorable outcomes for both of the clinical response and overall microbiological response will be determined as 'favorable' for composite clinical and microbiological response at each timepoint.

Details regarding determination of the category of clinical response and overall microbiological response outcome ("favorable" or "unfavorable") in support of relevant study endpoints are provided in the tables describing clinical response or microbiological response as well as in Section 8.4.2.

4.2.3.2.1.3 Efficacy Criteria for sepsis

4.2.3.2.1.3.1 Clinical Response

Clinical response for sepsis will be assessed for subjects meets the criteria of sepsis (refer to section 5.1.2, inclusion criteria #2) based on evaluation by the investigator at the EOT and TOC visits. Based on comparison to baseline clinical signs and symptoms of sepsis, the investigator will determine the clinical response rating (and record the response on the appropriate eCRF) at each visit as described in Table 8 (for EOT visit) and Table 9 (For TOC visit).

In support of evaluation of efficacy endpoints of composite clinical and microbiological response for sepsis, the clinical response rating determined by the investigator at each visit will be categorized as "favorable" or "unfavorable".

Table 8 Definitions of the Clinical Response Rating for sepsis at the EOT Visit

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

Table 9 Definitions of the Clinical Response Rating for sepsis at the TOC Visit

Clinical Response[a]	Response Definition
Cure	All pretherapy signs and symptoms of the sepsis have resolved (or returned to "preinfection status") **AND** no additional IV antibiotic therapy is required,
Failure	No apparent or insufficient response to IV study therapy in prestudy signs and symptoms of sepsis: persistence, progression, or improvement (without full resolution) of all pretherapy signs and symptoms
Indeterminate	Study data are not available for evaluation of efficacy for any reasons, including: a) Complication related to underlying medical condition; **OR** b) Subject was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical response; **OR** c) Extenuating circumstances preclude classification as "cure" or "failure" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory
[a] A favorable clinical response at TOC requires an assessment of "cure".	

4.2.3.2.1.3.2 Microbiological Response based on blood culture

Microbiological response will be evaluated separately for each baseline pathogen (i.e., by-pathogen). The by-pathogen response rating will be determined by investigator. According the following criteria, the by-pathogen microbiological response will be determined at the EOT and TOC visits based on local laboratory results from blood cultures collected during the study relative to the pathogen(s) isolated at baseline blood culture.

In support of evaluation of efficacy endpoints of composite clinical and microbiological response for sepsis, the by-pathogen microbiological response rating will be utilized to categorize the overall microbiological response (i.e., overall microbiological response for the subject based on the response of all pathogens present in the baseline culture) as "favorable" or "unfavorable." For subjects from whom only one pathogen is isolated, the overall microbiological response assessment will be based on the microbiological response rating for that pathogen. For subjects from whom more than one baseline pathogen is isolated, the overall microbiological response outcome will be based on microbiological culture results for all baseline pathogens.

The following tables are for the definitions of Microbiological Response for sepsis, as described in Table 10 (for the EOT visit) and Table 11 (for the TOC visit).

Table 10 Definitions of the By-Pathogen Microbiological Response Rating at the EOT Visit

Microbiological Response[a,b]	**Response Definition**
Eradication	A blood culture taken at or prior to the EOT visit shows eradication of the pathogen found at study entry.
Persistence[c]	A blood culture taken at EOT visit grows a pathogen found at study entry.
Super infection	A blood culture grows a pathogen other than a baseline pathogen during the course of IV study therapy
Indeterminate	a) Follow-up blood culture is not available at or prior to the EOT visit due to subject death or withdrawal from study; OR b) Microbiological data are incomplete; OR c) Assessment not possible due to protocol violation; OR d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered "super infection" for any new/emergent pathogen isolated after initiation of IV study therapy.
[b] A favorable overall microbiological response at EOT requires "eradication" of all baseline pathogens.
[c] If a subject is discontinued from IV study therapy due to clinical failure (i.e., unfavorable clinical response), but persistence of the admission pathogen is not confirmed by culture results or no culture is obtained at the time of clinical failure, the admission pathogen will be presumed to have persisted.

Table 11 Definitions of the By-Pathogen Microbiological Response at the TOC Visit

Microbiological Response[a,b]	**Response Definition**
Sustained eradication[c]	A blood culture taken at or prior to TOC visit still shows eradication of the pathogen found at study entry. If blood culture taken at or prior to EOT visit shows negative and blood culture at TOC visit is not available because subject's infection is clinically resolved, the result will be carry forward with status at EOT visit to TOC visit
Persistence	A blood culture taken at TOC visit grows a pathogen found at study entry.
New Infection	A pathogen, other than a microorganism found at baseline is present in the blood any time after IV study therapy is finished.
Recurrence	A blood culture grows a pathogen taken any time after documented eradication.
Indeterminate	a) Follow-up blood culture is not available at the TOC visit due to subject death or withdrawal from study; **OR** b) Microbiological data are incomplete; **OR** c) Assessment not possible due to protocol violation; **OR** d) Any other circumstance which makes it impossible to define the microbiological response

[a] A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered a "new infection" for any new/emergent pathogen isolated after initiation of IV study therapy.
[b.] A favorable overall microbiological response at TOC visit requires "sustained eradication" of all baseline pathogens.
[c] A microbiological response of "sustained eradication" at TOC is used when the microbiological response assessment at EOT visit is also "eradication".

4.2.3.2.1.3.3 Composite Clinical and Microbiological Response Outcome for Sepsis

Composite clinical and microbiological response for sepsis at each timepoint will be determined by Sponsor based on the clinical response evaluated by investigator and overall microbiological response (per subject) determined by Sponsor. Only the subject who have favorable outcomes for both of the clinical response and overall microbiological response will be determined as 'favorable' for composite clinical and microbiological response at each timepoint.

4.2.3.3 Pharmacokinetic Endpoints

At the timepoints specified in the Trial Flow Chart (Section 6.0), whole blood samples will be collected for determination of plasma concentration of REL, imipenem, and CIL. These samples will support further evaluation of the PK profiles of these drugs by confirming that subjects achieve expected exposures, and will also aid in further assessment of the clinical relationship between REL plasma concentrations and efficacy against resistant isolates.

4.2.3.4 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response and the molecular basis of disease is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation and/or disease. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding molecular basis of disease and the genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens consented for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects enrolled in this trial are hospitalized subjects with infections requiring treatment with IV therapy. Subjects will receive treatment, in part, with an agent, IMI, recommended and commonly used for the treatment of such infections, and, in addition, subject can potentially benefit from treatment with the investigational agent REL.

Although potentially more frequent than standard of care, the study procedures described in Section 6.0 (Trial Flow Chart) are generally typical procedures performed for this hospitalized subject population. Additional burden may be incurred due to visits following release from the hospital. However, the procedures performed at these visits are generally not likely to lead to significant harm (e.g., blood draws, urine collection, physical exam, vital signs). These procedures are necessary to support a robust evaluation of the safety and efficacy of the investigational drug with potential to support treatment of subjects for whom no or limited alternative therapies are available.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female Japanese subjects who are at least 18 years of age and have been diagnosed with complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. be ≥ 18 years of age on the day of signing informed consent.
2. require hospitalization and treatment with IV antibiotic therapy for complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI)

   NOTE: Subjects have to meet the following diagnostic criteria, including relevant clinical and microbiological evidence for each infection type.

Complicated Intra-Abdominal Infection (cIAI)

A. Definition

Intra-abdominal infection (IAI) is broadly defined as peritoneal inflammation in response to microorganisms, resulting in purulence in the peritoneal cavity. IAI are classified as uncomplicated or complicated based on the extent of infection. Complicated IAI (cIAI) extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis.

B. Diagnostic Guidelines

Subject has clinical evidence on the basis of operative findings and is able to provide the specimen to confirm the microbiological findings at baseline. Procedures include open laparotomy, laparoscopy, and percutaneous drainage of intra-abdominal abscess. Postoperative (or intraoperative) enrollment of subjects is encouraged. If, however, preoperative data are available that strongly suggest an appropriate diagnosis for entry (e.g., intraperitoneal abscess or perforation on computed tomography [CT] scan), then these subjects may be enrolled preoperatively. For preoperative enrollment, subjects must have a surgical intervention performed within 24 hours of the initiation of IV study drug.

1. Clinical

A diagnosis of cIAI should include at least one of the following as evidence of intra-peritoneal infection (or strongly suggested with an appropriate diagnosis confirmed by CT scan):

- Intra-abdominal abscess, including splenic or liver abscess
- Appendicitis complication by perforation or abscess formation
- Diverticulitis complicated by perforation or abscess formation
- Cholecystitis with evidence of perforation or empyema
- Perforation of the large or small intestine with abscess or fecal contamination
- Gastric or duodenal ulcer perforation, only if operated on >24 hours after perforation
- Peritonitis due to perforated viscus, surgical intervention, or other focus of infection. Spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites are not eligible.

AND

At least one of the following clinical signs and symptoms of infection should be present:

- Fever, defined as oral temperature greater than or equal to 38.0°C [or axillary temperature greater than or equal to 37.5°C];
- Hypothermia, defined as core body temperature less than or equal to 35°C;
- Abdominal pain or flank pain, or pain caused by cIAI that is referred to another anatomic area such as back or hip
- Nausea or vomiting
- Elevated white blood cells (WBC; >10,500/mm^3)

2. Microbiological

Purulent material from intra-abdominal space is able to be obtained during a surgical operation or percutaneous drainage at baseline. Specimens from the surgical intervention must be sent for aerobic and anaerobic culture.

Complicated Urinary Tract Infection (cUTI)

A. Definition

A complicated urinary tract infection is an infection of one or more structures in the urinary system in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Pyelonephritis, regardless of underlying abnormalities of the urinary tract, is a type of cUTI that affects one or both kidneys. UTIs are a clinical syndrome characterized by pyuria and a documented microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms of infection.

B. Diagnostic Guidelines

For a diagnosis of cUTI, including pyelonephritis, supportive clinical and microbiological findings should be present.

1. Clinical

Subject has at least two of the following local or systemic signs and symptoms:

- Local signs and symptoms: Dysuria, urinary frequency, suprapubic or pelvic pain, urinary urgency, or flank pain or costovertebral angle (CVA) tenderness on physical examination
- Systemic signs and symptoms: Fever (defined as oral temperature greater than or equal to 38.0°C [or axillary temperature greater than or equal to 37.5°C], chills or rigors (accompanied by fever), nausea or vomiting

AND

Pyuria determined by a midstream clean-catch (MSCC) or catheterized (indwelling or straight catheter) urine specimen with ≥10 white blood cells (WBCs) per high-power field (hpf) on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine.

NOTE: If pyuria cannot be determined by urinalysis in a clinically relevant timeframe, a urine dipstick may be employed as a rapid diagnostic aid. If urine dipstick is used, a positive test for leukocyte esterase is the preferred indicator for the presence of pyuria.

2. Anatomical

Subject has at least one of the following conditions associated with a risk for developing cUTI:

- Indwelling urinary catheter or other urinary bladder instrumentation
- Urinary retention (at least 100 mL of residual urine after voiding)
- Neurogenic bladder
- Obstructive uropathy (nephrolithiasis, fibrosis or prostatic hypertrophy)
- Azotemia

OR,

Subject has pyelonephritis and normal urinary tract anatomy.

3. Microbiological

Subject has a positive urine culture at baseline as defined below:

- $\geq 10^5$ CFU/mL of uropathogen either from a mid-stream clean catch (MSCC) or indwelling catheter urine specimen, OR
- $\geq 10^4$ CFU/mL of uropathogen either from a MSCC or indwelling catheter urine specimen if blood culture is also positive

NOTE: For subjects with an indwelling catheter, samples should be collected following the placement of a new catheter. If the placement of a new catheter is contraindicated or is not feasible, specimens should be collected using aseptic techniques with the urine obtained through a properly disinfected collection port. Urine samples should never be obtained from a collection bag.

NOTE: If more than one pathogen is identified, each should be present at the colony counts noted above to be considered pathogens. In general, if more than 2 bacterial pathogens are identified in an admission urine culture at the predefined colony counts, the sample should be considered contaminated (unless one of the pathogens is also identified in a blood culture).

NOTE: A subject can be enrolled before the urine culture results are available if it is likely to be positive (based on clinical findings and urinalysis).

Sepsis secondary to cIAI or cUTI

The investigator should confirm if the subjects meet the following diagnosis for sepsis upon the study entry in addition to the one of diagnostic criteria for their primary infection. Subjects don't need to meet the criteria for sepsis to be enrolled into this study. However for subjects with sepsis, investigators should also follow the procedures for sepsis as determined in this protocol.

A. Definition

Sepsis is defined as a systemic inflammatory response syndrome induced by infection, with microbiologically documented.

B. Diagnostic Guidelines

Subjects should have clinical signs defined below and meet the following microbiologic criteria;

1. Clinical:

Temperature ≥38.0°C or < 36°C [defined as oral temperature, and ≥37.5°C or < 35.5°C as axillary temperature], with one of the following:

- WBC count >12,000 or <4,000, or with a differential count showing 10% band forms
- Tachycardia: Pulse rate > 100 bpm

- Tachypnea: Respiratory rate > 20 breaths/minute
- Hypotension: Systolic blood pressure < 90 mm Hg

2. Microbiologic criteria:

Subject has positive blood culture at baseline (within 24 hours of initiation IV study therapy)

3. have an infection known or thought to be, in the opinion of the investigator, caused by microorganisms susceptible to the IV study therapy.
4. whose baseline specimen from the primary infection-site for culture could be obtained during the following period;
    - For cIAI: intra-abdominal specimen obtained at operative procedure at screening period.

    NOTE: For cIAI subject who enrolled pre-operatively enrollment, the specimen from the infection site obtained during the interventional procedure should be provided as baseline.

    - For cUTI: Urine specimen within 48 hours prior to initiation of IV study drug.
5. agree to allow any bacterial isolates obtained from protocol-required specimens related to the current infection to be provided the Central Microbiology Reference Laboratory for study-related microbiological testing, long-term storage, and other future testing.
6. understand (or have a legal representative that understands) the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agree to participate by giving written informed consent for the trial. The subject or legally acceptable representative may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
7. meet one of the following categories:

    a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

    b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner from the time of consent through completion of the study by complying with one of the following: (1) practice abstinence from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are:

Single method (one of the following is acceptable):

- non-hormonal intrauterine device (IUD)
- vasectomy of a female subject's male partner

Combination method (requires use of two of the following):

- diaphragm with spermicide
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill)

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. has received any amount of effective antibiotic therapy (defined as therapy known to be active against the identified pathogen) after obtaining the culture for admission to this study (admission culture) and prior to the administration of the first dose of IV study therapy.

   Note: For subjects with cIAI, use of intra-operative antibiotics per each institution's standard procedure is allowed.

2. has received treatment with systemic effective antibiotics for > 24 hours within the 72 hours immediately prior to initiation of study therapy.

   NOTE: For a subject has received >48 hours of systemic antimicrobial therapy, he/she is eligible for this study if there are clear evidence that the subject has failed this regimen or developed the current index infection while on the previous antibiotic regimen. Such evidence would include new or continued fever or persistence or worsening of symptoms related to the index infection and persistent laboratory or radiographic changes (if previously present). In addition, investigators should confirm the evidence of positive cultures which suggests persistent bacterial infection. Culture results do not need to be known before entry; however, the evidence should be obtained as support the presence of bacteria in sample from index infection such as Gram stain. These measures should be confirmed prior to study entry.

3. has a concurrent infection that would interfere with evaluation of response to IMI/REL, including any of the following:
    - endocarditis
    - osteomyelitis
    - meningitis
    - prosthetic joint infection
4. has a cIAI or cUTI due to a confirmed fungal pathogen.

    NOTE: Use of antifungal therapy for treatment of mucocutaneous infections (e.g., vaginal candidiasis or onychomycosis) is allowed (see Section 5.5).
5. has cUTI which meets any of the following:
    - complete obstruction of any portion of the urinary tract (requiring a permanent indwelling urinary catheter or instrumentation)
    - known ileal loop
    - intractable vesico-uretral reflux
    - presence of indwelling urinary catheter which cannot be removed at study entry

    NOTE: All indwelling urinary catheters must be removed prior to the start of IV therapy. Unless medically necessary, it is recommended that an indwelling urinary catheter not be reinserted while on IV study therapy.
6. has cIAI which meets any of the following:
    - Subject has an infection which should be managed by Staged Abdominal Repair (STAR) or open abdomen technique.
    - Infections limited to the hollow viscus, such as simple cholecystitis and simple appendicitis, ischemic bowel disease without perforation, acute suppurative cholangitis and acute necrotizing pancreatitis
7. has a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to any of the following:
    - Any carbapenem, cephalosporin, penicillin, or other β-lactam agent
    - other β-lactamase inhibitors (e.g., tazobactam, sulbactam, clavulanic acid, avibactam)
8. is a female who is pregnant or is expecting to conceive (or is a male partner of a female who is expecting to conceive), is breastfeeding, or plans to breastfeed prior to completion of the study.
9. has a history of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years).

10. is anticipated to be treated with any of the following medications during the course of study therapy:
    - valproic acid (or has used valproic acid in the 2 weeks prior to screening)
    - concomitant IV or oral antimicrobial treatments which is considered effective to the index pathogen, in addition to the study treatments.

    NOTE: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected methicillin-resistant *S. aureus* (MRSA) infection or use of IV linezolid to treat confirmed or suspected vancomycin-resistant *Enterococcus spp.* (VRE) infection is allowed. (Refer to Section 5.5).
11. is currently receiving immunosuppressive therapy, including use of high-dose corticosteroids (i.e., ≥ 40 mg prednisone or prednisone equivalent per day).

    NOTE: Prior short term use (≤ 7 days) of steroid therapy in the 30 days prior to study entry is allowed.
12. has an estimated or actual creatinine clearance of less than 15 mL/min at screening based on the findings of local laboratory values. Creatinine clearance in mL/min may be calculated from serum creatinine concentration by the C-G equation:

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

    Creatinine clearance (Females) = 0.85 X the value obtained using the formula above
13. is currently undergoing hemodialysis or peritoneal dialysis.
14. has any of the following laboratory abnormalities at the time of screening:
    - Alanine aminotransferase (ALT) values ≥ 4 times the upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) values ≥ 4 times ULN
    - ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN and, at the same time, Alkaline phosphatase (ALP) < 2 × ULN
    - Total bilirubin value ≥ 3 times ULN

    NOTE: Subjects with acute hepatic failure or acute decompensation of chronic hepatic failure should also be excluded.
15. has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the investigator, might confound the results of the study, interfere with the subject's participation for the full duration of the study, or pose additional risk in administering the study drugs to the subject.

16. is currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of the presentation or during the previous 30 days prior to screening or is anticipated to participate in such a clinical study during the course of this trial.

17. has previously participated in this study at any time

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

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial is outlined below in Table 12.

Table 12 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Imipenem/cilastatin/ relebactam (IMI/REL)	Imipenem: 500 mg Relebactam:250 mg	Every 6 hours	IV	5 to 14 days	experimental

The first dose of prescribed study therapy should be administered at the Day 1 visit. Subjects will receive a minimum of 5 days to up to a maximum of 14 days of intravenous (IV) study therapy.

Detailed dosing guidelines, including dose selection and timing of dose administration, are outlined in Section 5.2.1 and Section 5.2.2, respectively.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The chosen dose for IMI/REL in subjects with normal renal function is IMI/REL 500mg/250 mg administered IV as an FDC once every 6 hours (q6h). For subjects with renal insufficiency or whose creatinine clearance changes during treatment with study therapy, the dose must be adjusted based upon the degree of renal function impairment, as determined by the estimated or actual creatinine clearance. Subjects should be carefully monitored for renal function during IV treatment. Dose adjustments are included in Table 13.

Table 13 Administration Dosage of IMI/REL According to Renal Function

Creatinine Clearance (mL/min)	IMI/REL[a]
≥ 90	500/250 mg q6h
< 90 to ≥ 60	400/200 mg q6h
< 60 to ≥ 30	300/150 mg q6h
< 30 to ≥ 15	200/100 mg q6h
[a] IMI/REL is provided as a single vial in a fixed-dose combination; therefore, the dose for each component will be adjusted equally during preparation. For example, a subject who has a creatinine clearance of 50 mL/min should receive a 300/150 mg q6h dose of IMI/REL according to the table.	

Creatinine clearance in mL/min may be calculated from serum creatinine concentration by the following equation:

Creatinine clearance: (Males) = (weight in kg) X (140 minus age)

(72) X (creatinine in mg/dL)

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

5.2.2 Timing of Dose Administration

As shown in Table 13, the dose of IMI/REL may need to be adjusted based on the subject's renal function. The frequency of administration will not change. Each infusion should be administered within 60 minutes of the scheduled dose.

IMI/REL should be administered over 30 minutes +/- 5 minutes. The study therapy must NOT be administered simultaneously through the same infusion line/lumen with any other drugs (including IV non-study drugs). If another IV drug is required either prior to or after study drug and only 1 line/lumen is available, an appropriate volume of saline flush must be used between IV infusions.

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

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment using an integrated web response system (IWRS).

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

The following concomitant medications/therapies are not permitted in this study:

1. Valproic acid (during treatment with study drug and the 2 weeks prior to screening)
2. Non-study systemic (IV or oral) antibacterial treatments

   NOTE: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected methicillin-resistant *S. aureus* (MRSA) infection or use of IV linezolid to treat confirmed or suspected vancomycin-resistant *Enterococcus* spp. (VRE) infection is allowed.
3. Systemic (IV or oral) antifungal therapy

   NOTE: Concomitant use of antifungal therapy for treatment of mucocutaneous infections (e.g., vaginal candidiasis, onychomycosis) is allowed.
4. Immunosuppressive therapy, including use of high-dose corticosteroids (i.e., ≥40 mg prednisone or prednisone equivalent per day)

   NOTE: Short-term use (≤7 days) of systemic (Oral or IV) steroid therapy and Topical steroids for the treatment of skin conditions are also allowed.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Any of the following post-baseline elevations in liver transaminase levels:

In subjects without baseline transaminase elevations:

- ALT or AST ≥8 X ULN
- ALT or AST ≥3 X ULN accompanied by total bilirubin > 2 X ULN or INR > 1.5
- ALT or AST ≥3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (defined as oral temperature ≥38.0°C), rash, and/or eosinophilia (>5%)

NOTE: In subjects in whom fatigue, nausea, vomiting, and right upper quadrant pain or tenderness was a part of the subject's presenting illness, the subject may continue on therapy if there is no elevation in transaminases from baseline measurements. In such subjects who experience a return of their original symptoms with accompanying elevations in transaminases it may be difficult to determine the cause, and investigators may discuss subjects in this situation with the Sponsor Clinical Director prior to discontinuation, if desired.

In subjects with preexisting transaminase elevations,

- Further increase in transaminases to ≥8X ULN that is not anticipated from their underlying medical condition.
- ALT or AST ≥3 X ULN [with at least 50% increase from transaminase values collected at Day 1] and new onset of clinical signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (defined as oral temperature ≥38.0°C), rash, and/or eosinophilia (>5%)
- Clinically significant worsening of liver function associated with further transaminase elevations in a subject with abnormal transaminase levels already meeting the above criteria (i.e., ≥8X ULN; ALT or AST ≥3 X ULN [with at least 50% increase from transaminase values collected at Day 1] and new onset of clinical signs and symptoms listed) at baseline.

The subject will discontinue from study therapy, but will continue to participate in the study and will be assessed according to all study planned study procedures through the final study visit and will be evaluated for blood chemistry and hematology (including, at minimum, ALT, AST, alkaline phosphatase, bilirubin (direct + indirect) and creatine phosphokinase) until values return to within normal range. The trial site guidance for assessment and follow up of liver function test (LFT) elevations can be found in the Investigator Trial File Binder.

- A post-baseline decline in estimated or actual creatinine clearance to a value of less than 15 mL/min.
- The subject requires initiation of hemodialysis or peritoneal dialysis.
- The subject has a confirmed positive serum or urine (sensitivity of < 25 million IU/L is required if using urine test) pregnancy test.
- A physician investigator feels it is in best interest of the subject to discontinue for any reason, including, but not limited to, the need for alternative non-study antibacterial therapy.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

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

5.8.2 Withdrawal from the Trial

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

Trial Period:	Screening	IV Study Therapy			Post-Therapy	
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy (OTX)	Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow up (FU)
Scheduled Day:	≤24 hours pre-initiation of study	Day 1	Day 3	Day 5 to Day 14[1]	5 to 9 days following EOT	14 (+2) days following EOT
Administrative Procedures						
Informed Consent	X					
Informed Consent for Future Biomedical Research[2]	X					
Inclusion/Exclusion Criteria	X					
Subject Identification Card	X					
Medical History, including full assessment of details of infection site diagnoses[3]	X					
Concomitant Medication Review	X	X	X	X	X	X
Allocation of treatment assignment[4]		X				
Administration of IV Study Therapy		←	Daily	→		
Clinical Procedures/Assessments						
APACHE II Score (only for subjects with cIAI)[5]	X					
Full Physical Examination		X				
Directed Physical Examination			X	X	X	X
Vital Signs (heart rate, blood pressure, respiratory rate, oral/tympanic temperature) [6]		←	Daily during IV therapy	→	X	X
Height		X				
Weight[7]		X	X			
Adverse Events Monitoring[8]	X	←	Daily during IV therapy	→	X	X
Local infusion tolerability monitoring		←	Daily during IV therapy	→		
Review of clinical signs and symptoms of infection (including primary infection and sepsis if applicable)[9]		←	Daily during IV therapy	→	X	
Infection source control review[10]		X	X	X		
Laboratory Procedures/Assessments						
Blood for hematology[11]		X	X	X	X	X
Blood for chemistry[11]		X	X	X	X	X
Urine for urinalysis[11,12]		X		X		X
Serum β-Human Chorionic Gonadotropin (β-hCG) – if applicable[13]	X					X
Blood for genetic analysis[2]		X				
Infection Site Specimen for Culture						
cIAI[14]	X		X	X	X	
cUTI[15]	X[16]		X	X	X	

Trial Period:	Screening	IV Study Therapy			Post-Therapy	
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy (OTX)	Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow up (FU)
Scheduled Day:	≤24 hours pre-initiation of study	Day 1	Day 3	Day 5 to Day 14[1]	5 to 9 days following EOT	14 (+2) days following EOT
Blood Specimen for Culture[17, 18]		X	As clinically indicated or, if pre-study blood culture was positive, repeat blood culture until confirmed negative.			
Population Pharmacokinetics Analysis						
Whole blood to collect plasma for REL, IMI, and CIL assay[19]	X	X	X			
Efficacy Evaluation						
Clinical Response Assessment (including sepsis if applicable)[20]			X	X	X	
Microbiological Response Rating[21]			X	X	X	

1. IV study therapy should be administered for a minimum of 5 full days. The total duration of IV study therapy should not exceed 14 days.
2. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
3. The details of subject's infection-site diagnoses (cIAI or cUTI) will be documented separately on the appropriate eCRF(s). Details should include the diagnosis and additional diagnostic details associated with the infection site (e.g., characterization of the complicated nature of the cIAI or cUTI).
4. The most recently collected creatinine clearance should be used to support dosage determination. (refer to Table 13 in Section 5.2.1.1). Any local or central laboratory abnormalities in serum creatinine that result in an adverse event or a dose adjustment should be recorded.
5. APACHE II score is calculated at screening only for subjects with cIAI. Please refer to Appendix 12.4 for the parameters and instructions for calculation of APACHE II score.
6. Vital signs should be performed and documented on the appropriate electronic case report forms (eCRFs) at the Day 1 prior to administration of the first dose of study therapy and daily during IV study therapy. Vital signs should also be performed and documented at the additional visits specified.
7. For all subject, weight must be measured at baseline. Enter weight if a clinically significant weight change occurred and resulted in a change in CrCl category.
8. Monitor for adverse events and local infusion tolerability and collect infection-specific clinical signs and symptoms daily during IV study therapy and adverse experiences for 14 days after completion of IV study therapy. Laboratory abnormalities that emerge during IV therapy and are considered adverse experiences by the investigator must be followed until resolved or stabilized. Serious adverse experiences that are considered by the investigator to be related to the investigational product that is brought to the attention of the investigator at any time outside of 14 days post-therapy also must be reported immediately to the Sponsor.
9. Clinical signs and symptoms, radiographic (daily reporting not required for radiographic findings) and laboratory characteristics associated with the primary bacterial infection and with sepsis (see Table 14 in section 7.1.2.6) will be reviewed and documented on the appropriate electronic case report forms (eCRFs) daily during IV study therapy and at the additional visits specified.
10. Includes information regarding infection source control should be documented on the appropriate eCRF. Source control includes the following for each infection site: cUTI - baseline information associated with catheterization (e.g., recent surgery or instrumentation, presence of catheter/stent) as well as any details related to removal and/or replacement of urinary catheters at any time during the study. cIAI: details associated with the qualifying abdominal surgical intervention or any subsequent interventions, including an anonymized narrative of the operative note and/or interventional radiology report.
11. Blood for laboratory safety tests (hematology and chemistry) should be collected for submission to the central safety laboratory at Day 1 prior to administration of the first dose of study therapy, on Day 3 (OTX), and every 3 days thereafter until EOT (including the EOT visit). Blood should also be collected at TOC and FU. Urine for urinalysis

Trial Period:	Screening	IV Study Therapy			Post-Therapy	
Visit Number/Title:	Visit 1 Screening	Visit 2 Initiation of Therapy	Visit 3 On Therapy (OTX)	Visit 4 End of Therapy (EOT)	Visit 5 Test of Cure (TOC)	Visit 6 Follow up (FU)
Scheduled Day:	≤24 hours pre-initiation of study	Day 1	Day 3	Day 5 to Day 14[1]	5 to 9 days following EOT	14 (+2) days following EOT

should be collected for submission to the central safety laboratory at the Day 1 prior to administration of the first dose of study therapy and at EOT and FU.

12. The urinalysis should be performed on mid-stream clean catch urine or catheter urine specimen, if possible.
13. Prior documentation of a negative serum β-HCG within 48 hours of enrollment is acceptable for women of reproductive potential. If documentation is not available, a rapid urine β HCG may be used for screening. To conduct urine testing, sites must have individuals certified in administration and interpretation of test and the urine test utilized must have sensitivity of < 25 million IU/L. If a rapid urine test is performed at screening, a serum β HCG must be collected and sent to the Central Lab for confirmation of the dipstick result. If the serum β HCG test comes back positive from the Central Laboratory, the subject must be discontinued. The sample collected at FU visit should be a serum β-HCG.
14. Obtain sample for culture from infection site prior to initiation of IV study therapy for all subjects with cIAI during the screening period. (For cIAI subject who enrolled pre-operatively enrollment, the specimen from the infection site obtained during the interventional procedure should be provided as baseline.). However, for subjects in which infection site specimen collection is not medically acceptable (e.g., cIAI subject in whom an additional sample would require surgical intervention), additional collection for subsequent visit is not required. Bacterial isolates will be stored for future testing. In addition, the most recently available laboratory data for the suspected causative pathogen(s), including specimen type, and culture ID must be collected on the appropriate eCRF.
15. Urine culture is required at all specified timepoints for all subjects with cUTI. Acceptable methods of collection include mid-stream-clean-catch, indwelling catheter or straight catheter specimen. For subjects with an indwelling catheter, samples should be collected following the placement of a new catheter. If the placement of a new catheter is contraindicated or is not feasible, specimens should be collected using aseptic techniques with the urine obtained through a properly disinfected collection port. Urine samples should never be obtained from a collection bag. Bacterial isolates will be stored for future testing. In addition, the most recently available laboratory data for the suspected causative pathogen(s), including specimen type, culture ID, and colony count must be collected on the appropriate eCRF.
16. Urine samples must be collected within 48 hours prior to initiation of IV study therapy.
17. Two sets of blood cultures, from two separate venipuncture (or 1 venipuncture and 1 catheter) sites are required before study therapy is initiated in all subjects. Subjects with positive blood cultures at screening should have follow-up blood cultures collected until 2 sequential cultures demonstrates no growth. If further testing is required, samples for blood culture collected after screening should be collected immediately prior to subsequent doses. Bacterial isolates will be stored for future testing.
18. For subjects who meet the criteria of sepsis, the blood collection for culture is required at EOT and TOC, unless blood cultures taken at prior to the corresponding visits show negative.
19. Whole blood (4 mL) for attainment of plasma samples for determination of REL, IMI, and CIL plasma concentrations will be collected at screening and on Day 1 and Day 3 at 2 timepoints: (1) at approximately 30 minutes post-start of first IV drug infusion, and (2) at approximately 4 hours post-start of first IV drug infusion. If it is not feasible to collect PK samples post-start of first IV drug infusion on Day 3, samples may be collected with a later infusion within a 24 hour period. Both time points should be collected after the same dose (for example, 30 minutes and 4 hours post Dose #3). Whole blood sample collection procedures are provided in a separate Laboratory Manual. Sample handling, processing and shipment procedures will be provided separately in a Laboratory Manual. Actual whole blood collection date and times are required for these samples.
20. The presence and/or absence of infection-specific clinical signs and symptoms will be evaluated by the investigator at each specified visit compared with baseline signs and symptoms to determine the clinical response assessment. Clinical and other signs and symptoms of each infection type are included in Table 14 in section 7.1.2.6. In addition, investigator should also evaluate the clinical response of sepsis for subjects who meets the criteria for sepsis (refer to 5.1.2)
21. A by-pathogen and overall microbiological response will be determined by the Sponsor based on culture data reported on the appropriate eCRFs..

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

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

Any prior history of bacterial infection must also be recorded. Any history of conditions that may predispose a subject to infection (e.g., malignancies, management of organ transplant, treatment for rheumatologic disease) will also be documented on the appropriate eCRF.

A full evaluation of infection-site diagnoses (cIAI or cUTI) will also be performed. The details of these diagnoses will be documented separately on the appropriate eCRF(s). Details should include the diagnosis and any additional diagnostic details associated with the infection site (e.g., characterization of the complicated nature of the cIAI and/or cUTI).

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 14 days and any antimicrobial medications taken within 30 days before starting the trial.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

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

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified IV study therapy treatment plan of 1) greater than or equal to 2 doses of IV study therapy during the first 5 days of therapy; OR 2) greater than or equal to 4 doses of IV study therapy during days 6 to 14 of therapy require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.9 Study Therapy Administration

Trial treatment is described in Section 5.2. The specific dosage as well as frequency and timing of administration for IMI/REL are provided in Section 5.2.1 and 5.2.2.

All IV study therapy infusions should be administered over 30 minutes +/- 5 minutes. The IV study therapy must NOT be administered simultaneously through the same infusion line/lumen with any other drugs (including IV non-study drugs). If another IV drug is required either prior to or after study drug and only 1 line is available, an appropriate volume of saline flush must be used between IV infusions.

Further details on the preparation, storage, and administration of the intravenous study antibiotics are provided in a separate Pharmacy Binder.

IV study therapy should be administered for a minimum of 5 full days to up to a maximum of 14 days. Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 APACHE II Score

Only for cIAI subjects, severity of illness will be determined by APACHE II score at screening [27].

See Appendix 12.4 for details regarding the calculation of this score. Results of APACHE II score calculations must be entered on the appropriate eCRF(s).

7.1.2.2 Full and Directed Physical Examinations

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

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

After the initial full physical exam, a physical exam targeted to the subject's illness and complaints will be performed at subsequent visits as specified in Section 6.0 (Trial Flow Chart).

7.1.2.3 Vital Signs

Vital signs should be collected daily while on IV study therapy and at other time points/visits as specified in Section 6.0 (Trial Flow Chart). Collection at Day 1 should be performed prior to initiation of IV therapy.

For this study, vital signs include heart rate (HR), blood pressure (BP), respiratory rate (RR), and oral temperature. Subjects should be resting in a seated or semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary methods are acceptable. The method of body temperature should be consistent during the trial.

Any abnormal or clinically significant findings from the physical examinations must be recorded on the appropriate eCRF.

7.1.2.4 Height and Weight

The subject's height and weight should be measured prior to initiation of IV study therapy at Day 1. Weight should be measured and recorded during the study if a clinically significant weight change occurred and resulted in a change in CrCl category.

7.1.2.5 Adverse Event Monitoring and Local Infusion Tolerability Monitoring

Clinical adverse events will be collected daily from the time of initiation of the first dose of IV study therapy to completion of FU visit. All adverse events should be documented on the appropriate eCRF. In general, events that emerge during IV study therapy and are considered as related to IV study therapy by the investigator must be followed until resolved or stabilized. Serious adverse events (SAE) that are considered as related to study drug that is brought to the attention of the investigator at any time outside of the study period also must be reported immediately to the Sponsor.

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

Laboratory adverse events will be based on safety laboratory tests, including hematology and chemistry tests from blood and urinalysis from urine. Please refer to Section 6.0 and Section 7.1.3 for more details on type of tests and timing of collection.

Please refer to Section 7.2 for details regarding assessment and documentation of adverse events.

7.1.2.6 Clinical Signs and Symptoms of Infection

A detailed diagnosis as well as relevant clinical information associated with diagnosis including clinical signs and symptoms, radiographic and laboratory characteristics related to the primary bacterial infections sites will be reviewed and documented on the appropriate eCRFs at timepoints specified in Section 6.0 (Trial Flow Chart).

Presence or absence of specific clinical signs and symptoms relevant for each infection site of interest (Table 14) will be recorded daily during IV study therapy and at visits specified in Section 6.0 (Trial Flow Chart). Intensity of signs and symptoms will also be graded by the investigator as mild, moderate, or severe (See Section 7.2).

Table 14 Infection-Site Specific Clinical Signs and Symptoms

Infection Site	Clinical Signs and Symptoms [a]
cIAI	Body temperature (fever or hypothermia), abdominal pain, flank pain, pain caused by cIAI that is referred to another anatomic area such as back or hip, tenderness to palpation, rebound tenderness, guarding, mass, ascites, ileus, bowel sounds, need for enteral feeding, nausea and vomiting
cUTI	Body temperature (fever), chills or rigors, flank pain, costovertebral angle (CVA) tenderness on physical examination, dysuria, urinary frequency, suprapubic pain, pelvic pain, and urinary urgency, nausea and vomiting

[a] Evaluation of clinical response for infection type may also include resolution of lab abnormalities present at baseline (see inclusion criteria #2 in section 5.1.2 for relevant abnormalities for each infection site).

For Sepsis, if there are systemic sign and symptoms (for example, chills or tremble) in addition to lab abnormalities present at baseline (defined as inclusion criteria #2 in section 5.1.2), those should be evaluated as a part of clinical response for sepsis. Those must be recorded on the appropriate eCRF.

7.1.2.7 Infection Source Control Review

Information related to infection source control must be collected for all subjects in the appropriate eCRFs. Information collected will be specific to the site(s) of bacterial infection.

For subjects with cUTI, baseline information associated with catheterization (e.g., recent surgery or instrumentation, presence of catheter/stent) as well as any details related to removal and/or replacement of urinary catheters at any time during the study must be collected. For subjects with cIAI, details associated with the qualifying abdominal surgical intervention or any subsequent interventions, including an anonymized narrative of the operative note and/or interventional radiology report must be collected.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 15.

Table 15 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Rapid urine β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-hCG
Platelet count	Alanine aminotransferase (ALT)	Protein	
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	
	Bicarbonate	Microscopic exam, if abnormal results are noted	
	Blood Urea Nitrogen		
	Calcium		
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		

Hematology	Chemistry	Urinalysis	Other
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	C-reactive protein (CRP)		

With the exception of the rapid urine β-hCG (dipstick), all blood and urine samples for safety laboratory testing (hematology, chemistry and urinalysis) will be sent to a central safety laboratory for testing. Additional details regarding biological specimen processing, handling, and shipment will be provided by the Sponsor in a separate laboratory manual. Of note is that, following the Day 3 blood sample, blood for safety laboratory testing must be collected every 3 days until EOT (including EOT). Refer to Section 6.0 (Trial Flow Chart) for all specific time points for these laboratory assessments.

Safety laboratory results from the central laboratory will likely not be available in a timely fashion for patient management purposes. Therefore, additional laboratory tests required for adequate medical management of individual study participants should be obtained as indicated by the primary physician and submitted to the local laboratory for testing in the medically appropriate timeframe. Results of these local laboratory tests must be documented in the subject's medical record (or other source document). Laboratory abnormalities resulting in an adverse experience or dose adjustment should also be collected on the appropriate eCRF. Any laboratory test abnormality that emerged during study therapy and was considered by the investigator to be an adverse experience or event of clinical interest should be repeated until the abnormal value has normalized, stabilized, or returned to baseline.

In addition, creatinine values obtained locally which determine the dose of study drug at baseline and/or result in a change in dose of study drug during the treatment period, the data should be entered within the appropriate eCRF.

7.1.3.2 Culture

Culture (aerobic for all infection-site specimens and anaerobic for cIAI specimens) of infection site specimens collected at the study-specified time points (see Section 6.0, Trial Flow Chart) will be performed at the local clinical microbiology laboratory for each site. All Suspected causative bacterial pathogens obtained from infection-site specimens collected from enrolled subjects will be retained by the local clinical microbiology laboratory and sent to the central microbiology reference laboratory. The available data from the culture specimen, including date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRF forms. Additional details regarding bacterial specimen collection, processing, handling, and shipment will be provided by the Sponsor in a separate microbiology laboratory manual.

7.1.3.2.1 Prior Infection-Site Specimens

A specimen will be obtained at baseline for culture from infection site prior to initiation of IV study therapy for all subjects. For cUTI subjects, a previously obtained culture is acceptable if urine specimen was obtained within 48 hours of initiation of IV study drug. For cIAI subjects, intra-abdominal specimen should be obtained at operative procedure at screening period. Culture should be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures. Relevant culture data from these samples should also be recorded on the appropriate eCRFs. Suspected causative bacterial pathogens should also be stored at the local laboratory for possible future testing. Relevant culture data from these samples should also be recorded on the appropriate eCRFs.

7.1.3.2.2 On-Study Infection-Site Specimens

Infection-site specimens for culture should be obtained according to Section 6.0 (Trial Flow Chart).

For subjects with cIAI, collection of specimens from the infection site is preferred; however, for subjects in which infection site specimen collection is not medically acceptable follow up specimen is not required. Additional unscheduled cultures from the infection site should also be collected at the time of any surgical or drainage procedure (if required).

For subjects with cUTI, infection-site specimens for culture are required for all visits specified in Section 6.0 (Trial Flow Chart).

Culture should be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures. Relevant culture data from these samples should also be recorded on the appropriate eCRFs. Suspected causative bacterial pathogens should also be stored at the local laboratory for possible future testing. Relevant culture data from these samples should also be recorded on the appropriate eCRFs.

7.1.3.2.3 Blood Cultures

Two sets of blood cultures, from two separate venipuncture (or 1 venipuncture and 1 catheter) sites are required before study therapy is initiated in all subjects. Subjects with positive blood cultures at screening should have follow-up blood cultures until 2 sequential cultures demonstrate no growth is confirmed. For subjects who meet the criteria of sepsis, the blood collection for culture is required at EOT and TOC, unless blood cultures taken at prior to the corresponding visits show negative. Follow-up up blood cultures in subjects with no evidence of bacteremia (i.e., positive blood cultures) at study entry should also be performed, at the investigator discretion, as clinically indicated.

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

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

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

Whole blood to obtain plasma samples will be collected for pharmacokinetic evaluation of REL, imipenem, and cilastatin concentrations.

As outlined in Section 6.0 (Trial Flow Chart), whole blood (4 mL) should be collected at screening and on Day 1 and Day 3 of IV study therapy at 2 time points: (1) at approximately 30 minutes post-start of first IV drug infusion, and (2) at approximately 4 hours post-start of first IV drug infusion. If it is not feasible to collect PK samples post-start of first IV drug infusion on Day 3, samples may be collected with a later infusion within a 24 hour period. Both time points should be collected after the same dose (e.g., 30 minutes and 4 hours post Dose #3). Actual date and time for the whole blood samples must be recorded in the eCRFs.

Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

7.1.3.4 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

7.1.3.5 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover DNA for genetic analysis

7.1.3.6 Efficacy Evaluation

7.1.3.6.1 Clinical Response

Clinical signs and symptoms of infection (e.g., fever) as well as local signs of infection will be assessed at visits specified in Section 6.0 (Trial Flow Chart) in support of determination of a clinical response rating for each subject. Based on comparison to baseline clinical signs and symptoms of the subject's infection(s), the investigator will determine and record the clinical response rating at each visit as described in Section 4.2.3.2.1.1 (Table 2, and Table 3). In subjects with sepsis, a separate clinical response rating will be determined according to the definition of clinical response for sepsis as described in Section 4.2.3.2.1.3.1 (Table 8, and Table 9). The clinical response for sepsis will be determined in addition to the clinical response for cIAI or cUTI, since those subjects also included in the evaluation population for their primary infection. A detailed list of disease-specific signs and symptoms in support of evaluation of the clinical response rating are included in Section 5.1.2, inclusion criteria #2) and Section 7.1.2.6, Table 14.

7.1.3.6.2 By-Pathogen Microbiological Response

The by-pathogen microbiological response rating will be determined by investigator at the visits specified in Section 6.0 (Trial Flow Chart) based on local laboratory results (per eCRF data provided by the investigator) of infection-site and/or blood cultures collected at each visit relative to the pathogen(s) isolated at baseline/admission.

Separate criteria for microbiological evaluation will be utilized for cIAI and cUTI, as described in Table 4 (for EOT visit) and Table 5 (for TOC visit) in Section 4.2.3.2.1.2.1 for cIAI and Table 6 (for EOT visit) and Table 7 (for TOC visit) in Section 4.2.3.2.1.2.2 for cUTI. In subjects with sepsis, an additional microbiological response rating for sepsis will be determined according to Table 10, and Table 11 in Section 4.2.3.2.1.3.2. The microbiological response for sepsis will be determined in addition to the microbiological response for cIAI or cUTI, since those subjects also included in the evaluation population for their primary infection.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Please also refer to Section 5.8 for details of Subject Withdrawal/Discontinuation Criteria..

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.2 Subject Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

1. Refrigerator

   IV study therapy must be stored in a secure, limited-access location under the storage conditions specified on the label, which may include refrigeration.

2. Freezer

   For specimens or study samples that may require storage at -20°C or -70°C.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Within 24 hours prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated in some circumstances after consultation with the Sponsor.

7.1.5.2 Treatment Period

IV study therapy should be administered for a minimum of 5 full days. This translates to either 20 dose of IMI/REL based on the q6h dosing regimen. The total duration of IV study therapy should not exceed 14 days.

Assessments and procedures while on IV study therapy will be completed at the indicated times and intervals as per the Flow Chart in Section 6.0. All study assessments are recommended to be performed at approximately consistent time of day for the study patient (e.g. every morning) for each calendar day.

The EOT visit will be completed within 24 hours after the last dose of IV study therapy.

7.1.5.3 Post-Therapy (Follow up)

TOC (5 to 9 days after completion of IV study therapy) and FU visit [14 days (+2) after completion of IV study therapy] must be completed for each subject.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any

unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose in IV study therapy is defined as administration of a total daily dose of IMI/REL in excess of 4 g (IMI) or 2 g (REL).

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 16 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 16. The investigator's assessment of causality is required for each adverse event. Refer to Table 16 for instructions in evaluating adverse events.

Table 16 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to the analyses made after the protocol has been finalized, but prior to the database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A non-randomized, non-controlled, open-label trial of IMI/REL in subjects with cIAI or cUTI.
Treatment Assignment	All enrolled subjects will receive IV study therapy of IMI/REL in an open-label manner.
Analysis Populations	Safety All Subjects as Treated (ASaT) population Efficacy Modified intention to treat (MITT) population and microbiologically-evaluable (ME) population; ME population will serve as the primary analysis population
Primary Endpoint(s)	Safety Safety parameters including adverse events (AEs), pre-defined limits of change (PDLCs), change from baseline in vital signs and laboratory tests Efficacy 1. Proportion of subjects with cIAI achieving favorable clinical response to IMI/REL at the EOT visit 2. Proportion of subjects with cUTI achieving favorable microbiological response to IMI/REL at the EOT visit
Secondary Endpoints	1. Proportion of subjects with cIAI achieving favorable clinical response to IMI/REL at the TOC visit 2. Proportion of subjects with cUTI achieving favorable microbiological response to IMI/REL at the TOC visit
Statistical Methods for Key Safety Analyses	AEs and PDLCs will be summarized by numbers and percentages of subjects. For broad clinical and laboratory AE category, 95% confidence intervals (CIs) based on the method of Agresti and Coull will be calculated for the proportion of subjects. Change from baseline in vital signs and laboratory tests will be calculated by visit.
Statistical Methods for Key Efficacy Analyses	A 95% CI based on the method of Agresti and Coull will be provided for the proportion of subjects with cIAI achieving favorable clinical response to IMI/REL at the EOT visit. The same analysis will be performed for the proportion of subjects with cUTI achieving favorable microbiological response to IMI/REL at the EOT visit. The same measures at the TOC visit will also be analyzed in the same manner.

Interim Analyses	No interim analysis is planned.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	A total of 80 subjects will be enrolled. For an AE or a specific safety event of interest, if the underlying incidence is 2%, then there is 80% chance that it is observed in at least one subject among the 80 subjects enrolled. In each of the cIAI and cUTI cohorts, if 40 subjects are enrolled, 28 subjects are included in the ME population and evaluable at the EOT visit, and 26 subjects achieve favorable response, then the estimated percentage and corresponding 95% CI of subjects achieving favorable response will be 92.9% (76.3%, 99.1%).

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. This trial is being conducted as a non-randomized, open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 Hypotheses/Estimation

The objectives of the study are stated in Section 3.

8.4 Analysis Endpoints

8.4.1 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.1. Safety endpoints will include AEs, PDLCs, and change from baseline in vital signs and laboratory tests. The baseline value is defined as the last available measurement prior to the start of the IV study therapy, which typically corresponds to the value obtained at Visit 2.

8.4.2 Efficacy Endpoints

A full description of the efficacy measures is provided in Section 4.2.3.2. The definition of favorable clinical and by-pathogen microbiological responses at each visit is summarized in Table 17. A favorable overall microbiological response for a subject at a particular visit requires favorable responses in all baseline pathogens at that visit.

Table 17 Definition of favorable clinical and microbiological responses by visit

Visit	Rating(s) considered a favorable response	
	Clinical	Microbiological[†] (by-pathogen)
EOT	"cure" or "improved"	"eradication" or "presumptive eradication"[‡]
TOC	"cure"	"sustained eradication" or "presumptive eradication"[‡]

[†] A favorable overall microbiological response for a subject at a particular visit requires favorable responses in all baseline pathogens at that visit.
[‡] cIAI only

8.5 Analysis Populations

8.5.1 Safety Analysis Population

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all enrolled subjects who receive at least one dose of IV study therapy.

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

8.5.2 Efficacy Analysis Population

Two populations, the MITT and the ME populations, will be used for the analysis of efficacy data in this study. The ME population will serve as the primary population for efficacy analyses in this study.

The MITT population is defined as all enrolled subjects who receive at least one dose of IV study therapy. In this study, this is identical with the ASaT population. The ME population is a subset of the MITT population that excludes subjects due to major deviations from the protocol that may substantially affect the results of the efficacy analyses. Potential deviations that may result in the exclusion of a subject from the ME population include the following:

1. The subject fails to meet the protocol definition of cIAI or cUTI
2. The subject had significant violations of inclusion/exclusion criteria that could impact the efficacy assessment (e.g., receipt of previous or concurrent systemic antibacterial therapy beyond those allowed per protocol)
3. The subject received less than 96 hours of IV study therapy (16 infusions)
4. (cIAI only) The subject's pre-study/post-operative culture from the site of infection fails to grow at least 1 gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI. (Note: Subjects who fail to grow a single gram-negative enteric and/or anaerobic pathogen from the site of infection are excluded from the ME population. That is, subjects with only gram-positive pathogens identified will be excluded, as well as those who do not grow any pathogens.)

   (cUTI only) The subject's pre-study urine culture fails to grow at least 1 gram-negative and/or anaerobic, pathogen at sufficient quantity specified in the inclusion criteria (See Section 5.1.2 for details)

The composition of the ME population at each time point of interest will be made prior to the database lock and will be documented in a separate memo.

Details on the approach to handling missing data are provided in Section 8.6.

8.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

8.6.1 Statistical Methods for Safety Analyses

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

The broad clinical and laboratory AE categories such as any AE, a drug-related AE, a serious AE, an AE which is both drug related and serious, who discontinued IV study therapy due to an AE, and who discontinued IV study therapy due to a drug-related AE, as well as specific AEs (system organ classes and preferred terms) and PDLCs will be summarized by numbers and percentages of subjects, along with 95% CIs based on the method of Agresti and Coull for the proportion of subjects (broad clinical and laboratory AE categories only).

Summary statistics for baseline, on-treatment, and change from baseline values will be provided for continuous measures such as vital signs and laboratory tests.

8.6.2 Statistical Methods for Efficacy Analyses

Missing values

In the analyses using the ME population, any subject with missing or indeterminate assessments for a specific endpoint (clinical or microbiological response) at any particular visit will be excluded from the assessment of that response at that time point. Exceptions follow:

1. (cIAI only) Subjects with a missing culture in the setting of a favorable clinical response: In such subjects, even in the setting of a missing culture at a particular time point, a favorable microbiological response will be presumed from the clinical response (i.e., "presumptive eradication").
2. Subjects discontinuing IV study therapy due to lack of efficacy (i.e., withdrawals with subsequent non-study antibiotic therapy, subjects requiring therapy beyond 14 days), including death due to index infection:
    - These subjects will be considered to be "failures" with respect to clinical response at the time of discontinuation and all subsequent time points post discontinuation, irrespective of whether the clinical response is listed as "indeterminate".
    - These subjects will be considered to have presumed persistence with respect to microbiological response at the time of discontinuation and all subsequent time points post discontinuation, irrespective of whether the microbiological response is listed as "indeterminate."

In the analyses using the MITT population, missing or indeterminate clinical or microbiological responses will be considered failure.

Proportions of subjects with favorable clinical/microbiological responses

A 95% CI based on the method of Agresti and Coull will be provided for the proportion of subjects with cIAI in the ME population achieving favorable clinical response at the EOT visit. The same analysis will be performed for the proportion of subjects with cUTI in the ME population achieving favorable microbiological response at the EOT visit. The same measures at the TOC visit will also be analyzed in the same manner. Supportive analysis using the MITT population will also be performed.

Table 18 summarizes key efficacy analyses.

Table 18 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. supportive approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary objectives				
Proportion of subjects with cIAI achieving favorable clinical response at the EOT visit	P	Agresti and Coull	ME	Data as observed[‡]
	S	Agresti and Coull	MITT	Missing = Failure
Proportion of subjects with cUTI achieving favorable microbiological response at the EOT visit	P	Agresti and Coull	ME	Data as observed[§]
	S	Agresti and Coull	MITT	Missing = Failure
Secondary objectives				
Proportion of subjects with cIAI achieving favorable clinical response at the TOC visit	P	Agresti and Coull	ME	Data as observed[‡]
	S	Agresti and Coull	MITT	Missing = Failure
Proportion of subjects with cUTI achieving favorable microbiological response at the TOC visit	P	Agresti and Coull	ME	Data as observed[§]
	S	Agresti and Coull	MITT	Missing = Failure

[†] P = primary, S = supportive
[‡] Subjects discontinuing IV study therapy due to lack of efficacy will be considered failures with respect to their clinical response. In subjects with missing culture in the setting of a favorable clinical response, a favorable microbiological response will be presumed from the clinical response.
[§] Subjects discontinuing IV study therapy due to lack of efficacy will be considered persistence with respect to their microbiological response.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for study/study therapy discontinuation will be displayed. Demographic variables (e.g., age, gender), primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables.

8.7 Interim Analyses

No interim analysis is planned.

8.8 Multiplicity

No multiplicity adjustment is planned.

8.9 Sample Size and Power Calculations

A total of 80 subjects will be enrolled.

For an AE or a specific safety event of interest, if the underlying incidence is 2%, then there is 80% chance that it is observed in at least one subject among the 80 subjects enrolled.

Based on the completed phase II studies (Protocols 003 and 004), it is expected that at least 70% of the enrolled subjects will be included in the ME population. In each of the cIAI and cUTI cohorts, if 40 subjects are enrolled, 28 subjects are included in the ME population and evaluable at the EOT visit, and the 26 subjects achieve favorable response, then the estimated percentage and corresponding 95% CI of subjects achieving favorable response will be 92.9% (76.3%, 99.1%). The estimated percentages and corresponding 95% CIs of subjects achieving favorable response under various assumptions are shown in Table 19.

Table 19 Estimate percentages (95% CIs) of subjects achieving favorable response under various assumptions

Number of subjects			Estimated percentage (95% CI)[†] of subjects achieving favorable response
Enrolled	Included in ME population and evaluable at EOT visit	Achieve favorable response	
30	21	19	90.5 (69.9, 98.6)
		20	95.2 (75.6, 100.0)
40	28	25	89.3 (72.0, 97.1)
		26	92.9 (76.3, 99.1)
		27	96.4 (80.8, 100.0)
50	35	32	91.4 (76.9, 97.8)
		33	94.3 (80.4, 99.4)
		34	97.1 (84.2, 100.0)

[†] Based on the method of Agresti and Coull

The maximum enrollment for each of the cIAI and cUTI cohorts will be limited to 50 subjects to ensure that a single disease cohort will not dominate the study population.

8.10 Subgroup Analyses

The proportion of subjects with cIAI achieving favorable clinical response at the EOT visit, as well as the proportion of subjects with cUTI achieving favorable microbiological response at the EOT visit, will be provided within each category of the classification variables listed below. The subgroup analyses will be performed for the ME population, separately by infection type.

- gender (female, male)
- age category (<65 years, ≥65 years)
- renal function (CLCr at baseline) [normal (≥90), mild insufficiency (60 to <90), moderate insufficiency (30 to <60), severe insufficiency (<30)]
- (cIAI only) APACHE II score at study entry (≤15, >15)
- (cIAI only) clinical diagnosis (liver abscess, appendicitis, cholecystitis, peritonitis, other)
- (cIAI only) poly vs. monomicrobial infections (poly infections, monomicrobial infections)

- (cUTI only) presence/absence of pyelonephritis with/without complication (complicated lower urinary tract infection, complicated pyelonephritis, uncomplicated pyelonephritis)

8.11 Compliance (Medication Adherence)

For each subject, treatment compliance will be calculated as follows.

$$\text{Compliance (\%)} = \frac{\text{Number of completed IV doses}}{\text{Number of expected IV doses}} \text{ x100}$$

Descriptive statistics of treatment compliance will be calculated for the ME and MITT populations.

8.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated for the ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 20.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 20 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-7655A, MK-7655 250 mg /Imipenem 500 mg / Cilastatin 500 mg	Powder for Constitution	Provided centrally by the Sponsor

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label, single-dose vials. No kitting is required.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator

when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives

and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.1

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.2

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit/Cycle/etc:	Screening	Treatment			Post-Treatment	
	Visit 1	Visit 2	Visit 3 (OTX)	Visit 4 (EOT)	Visit 5 (TOC)	Visit 6 (FU)
Blood Parameter	**Approximate Blood Volume (mL)**					
Hematology		2.0	2.0	2.0	2.0	2.0
Serum/Plasma Chemistry		9.0	9.0	9.0	9.0	9.0
Blood for Planned Genetic Analysis		8.5				
Plasma for PK	4.0	8.0	8.0			
Expected Total (mL) [a, b]	4.0	27.5	19.0	11.0	11.0	11.0

a. Additional blood samples may be collected in support for evaluation of an underlying etiology that may have caused an abnormal laboratory result (e.g., elevated liver transaminase level). The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder.
b. Blood cultures will be collected in all subjects prior to initiation of IV study therapy. Subjects with positive blood cultures at screening should have follow-up blood cultures until 2 sequential cultures demonstrate no growth. Depending on the results and frequency, additional blood volumes could range from approximately 40mL/patient (2 sets of blood cultures (10mL x 2 = 20mL)/aerobic culture; (10mL x 2 = 20mL)/anaerobic culture.) up to 560 mL. Blood cultures will be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard procedures. For Subjects who meet the criteria for sepsis, blood samples for culture are also required at EOT and, TOC visits (40 mL x 2/patients).

12.4 APACHE II Severity of Disease Classification System – APACHE II Score Form

A. Acute Physiology Score:

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

APACHE II Severity of Disease Classification System

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

12.5 List of Abbreviations

Abbreviation	Definition
AC	alveolar cells
AE	adverse event
ALT	alanine aminotransferase
APACHE	acute physiology and chronic health evaluation
ASaT	All subjects as treated
$AUC_{0-\infty}$	area under the concentration time curve
AST	Aspartate aminotransferase
β-hCG	β-Human Chorionic Gonadotropin
BLI	β-lactamase inhibitor
C-G	Cockcroft-Gault
cIAI	complicated intra-abdominal infection
CIL	cilastatin
CLCr	Creatinine clearance
CL_{plasma}	plasma clearance
CMS	colistimethate sodium
CR	carbapenem-resistant
cUTI	complicated urinary tract infection
DCIV	discontinuation of IV therapy
eCRF	electronic case report form
ELF	epithelial lung fluid
EOT	end of therapy
ESRD	end-stage renal disease
GFR	glomerular filtration rate
HABP	hospital-acquired bacterial pneumonia
IMI	imipenem/cilastatin
IV	intravenous (parental)
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	multi-drug resistant
ME	microbiologically-evaluable
MITT	modified intent-to-treat
MSCC	mid-stream clean catch
OTX	on-therapy visit
PD	pharmacodynamic
PGt	pharmacogenetic
PK	pharmacokinetic
REL	relebactam
$t_{1/2}$	terminal half-life
TOC	test of cure
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	