Official Protocol Title:	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection
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TITLE:

A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection

IND NUMBER: 108,754
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SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change	Rationale
8.1.1; 8.2.5.1; 8.2.8	Efficacy Analysis; Statistical Methods for Efficacy Analyses; Subgroup Analyses and Effect of Baseline Factors	Calculation of 90% confidence intervals for between-group differences has been added to the analysis plan for the primary efficacy endpoint and key secondary efficacy endpoints across the entire trial population and across specified subgroups, with stratification by infection type where appropriate.	This change allows for additional analysis of potential differences between treatment groups.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
5.5; 5.1.3.1; 5.1.3.2	Concomitant Medications/Vaccinations (allowed & prohibited); Exclusion Criteria, Treatment Groups 1 and 2; Exclusion Criteria, Open-Label, Treatment Group 3	Added additional allowed antibacterial medication for clarity.	Antibacterial trimethoprim/sulfamethoxazole (TMP/SMX) is commonly used in immunocompromised patients for prophylaxis of *Pneumocystis jiroveci* (fungal) infection. While TMP/SMX has some Gram-negative activity, prophylaxis regimens for *Pneumocystis* would not be expected to impact treatment of infections in the trial. A note was added to clarify this medication is allowed to continue in immunocompromised subjects.
8.1.1; 8.1.2; 8.2.4.1	Efficacy Analysis; Safety Analysis; Efficacy Analysis Populations	Added text to clarify that, in order to be included in the mMITT population, subjects with polymicrobial infections must have at least one baseline pathogen that meets the requirements of inclusion criterion #3, and all pathogens identified at the baseline time point must be susceptible to both IMI/REL and colistin.	This update was made to clarify the mMITT population criteria for subjects with polymicrobial infections.

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
8.2.8	Subgroup Analyses and Effect of Baseline Factors	Added "e.g." to the parenthetical list of race subgroups.	This update was made to clarify that race subgroups other than White, Black, and Asian will be evaluated as appropriate.
11	List of References	Added reference for Miettinen and Nurminen (1985) method for calculating confidence intervals for between-group differences.	This reference is now cited in the text.
Global		Minor editorial revisions.	Minor editorial revisions made for enhanced readability.

1.0 TRIAL SUMMARY

Abbreviated Title	IMI/REL (MK-7655A) vs. CMS + IMI in Subjects with Imipenem-Resistant Bacterial Infection
Trial Phase	III
Clinical Indication	Treatment of imipenem-resistant bacterial infection, including hospital-acquired/ventilator-associated pneumonia (HABP/VABP), complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI)
Trial Type	Interventional
Type of control	Active Control
Route of administration	Intravenous
Trial Blinding	Double-blind
Treatment Groups	Treatment Groups 1 and 2 will enroll subjects with bacterial infections (HABP/VABP, cIAI or cUTI) which are imipenem-resistant but susceptible to IMI/REL as well as colistin, while Treatment Group 3 will enroll subjects with bacterial infections which are imipenem-resistant and colistin-resistant but susceptible to IMI/REL: Treatment Group 1 (N=~36): Imipenem/cilastatin/relebactam (IMI/REL); Treatment Group 2 (N=~18): Colistin (in the form of colistimethate sodium, CMS) + Imipenem/Cilastatin (referred to as IMI throughout the protocol document). **NOTE**: Since subjects in Treatment Group 2 will receive 2 separate therapies (CMS and IMI), subjects in Treatment Group 1 will be provided placebo to CMS in addition to IMI/REL such that subjects in both treatment groups will receive 2 infusions in order to maintain study blind; Treatment Group 3: Subjects with documented imipenem-resistant and colistin-resistant bacterial infections may be eligible (reference Section 5.1.2.2 for eligibility criteria) for participation in the study to receive open-label treatment with IMI/REL.
Number of trial subjects	Approximately 54 subjects will be enrolled into Treatment Groups 1 and 2. Additional eligible subjects may be enrolled into Treatment Group 3 to receive open-label therapy.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 21 months (~84 weeks) of enrollment + up to 21 days (3 weeks) of IV study therapy + at least 14 days (2 weeks) of safety follow-up = 89 weeks from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 4 to 5 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact, depending on the duration of IV study therapy. After a screening visit, each subject will receive assigned IV study therapy for approximately 5 (cIAI or cUTI) or 7 (HABP/VABP) to up to 21 days. After the end of IV study therapy, each subject will be followed for at least 14 days. All subjects must also have a study visit 28 days following randomization. The total duration for each subject in the study will be up to 35 days.

Randomization Ratio	2:1 for Treatment Group 1 (IMI/REL): Treatment Group 2 (CMS + IMI)

A list of abbreviations used in this document can be found in Section 12.7.

2.0 TRIAL DESIGN

2.1 Trial Design

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

This is a randomized, double-blind (with in-house blinding), active-controlled, parallel-group, multi-site trial of IMI/REL compared with colistin (in the form of colistimethate sodium [CMS]) + IMI in subjects with imipenem-resistant bacterial infection. This study will be conducted in conformance with Good Clinical Practices.

Approximately 54 subjects with imipenem-resistant bacterial infection (with colistin and IMI/REL susceptibility) will be randomized in a 2:1 ratio to the 2 blinded, randomized arms of the study, with ~36 subjects in Treatment Group 1 (IMI/REL) and ~18 subjects in Treatment Group 2 (CMS + IMI) in order to obtain a minimum of 45 subjects (15 per infection type) who meet the criteria for inclusion in the microbiological modified intent-to-treat (mMITT) population. Subjects with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), complicated intra-abdominal infection (cIAI), or complicated urinary tract infection (cUTI) as a primary infection site will be eligible for enrollment. Subjects with bloodstream infections (bacteremia) secondary to HABP/VABP, cIAI, or cUTI are eligible for enrollment. Randomization into Treatment Group 1 and Treatment Group 2 will be stratified by infection type and approximately18 subjects will be enrolled per infection type (See Section 5.4 for details). At the discretion of the Sponsor, enrollment may be stopped prior to reaching 54 total subjects if a sufficient number of mMITT subjects have been obtained. Enrollment may also be extended beyond 54 subjects at the discretion of the Sponsor for the following reasons: 1) if additional subjects beyond 54 are required to obtain the target number of mMITT subjects; or 2) if enrollment in any individual stratum has not been completed, while other strata remain open (even after a sufficient number of mMITT subjects have been obtained in those strata), until all 3 strata have reached full capacity (i.e., 15 mMITT evaluable subjects each).

For subjects in Treatment Group 1, IMI and REL will be provided together in a single vial (and therefore a single infusion) as a fixed-dose combination product in this study (IMI/REL, also known as MK-7655A). Since subjects in Treatment Group 2 will receive 2 separate therapies (CMS and IMI), subjects in Treatment Group 1 will be provided a placebo which matches CMS in addition to IMI/REL so that subjects in both treatment groups receive 2 infusions. This will maintain the study blind (see Figure 2).

In addition to the ~54 randomized subjects, subjects with documented imipenem- and colistin-resistant but IMI/REL-susceptible bacterial infection will be enrolled into a third non-randomized, unblinded/open-label treatment group (Treatment Group 3) to receive IMI/REL. Subjects enrolled in Treatment Group 3 will follow the same study procedures as randomized subjects in Treatment Groups 1 and 2. Although enrollment into the open-label arm will not be limited, the Sponsor estimates approximately 5 to 10 subjects will be enrolled, as resistance to colistin remains relatively uncommon. Since the number of subjects could vary depending on resistance rates within each enrolling institution, it is

difficult to estimate the actual number that will be obtained. Enrollment in Treatment Group 3 will be ongoing until enrollment in Treatment Groups 1 and 2 is complete.

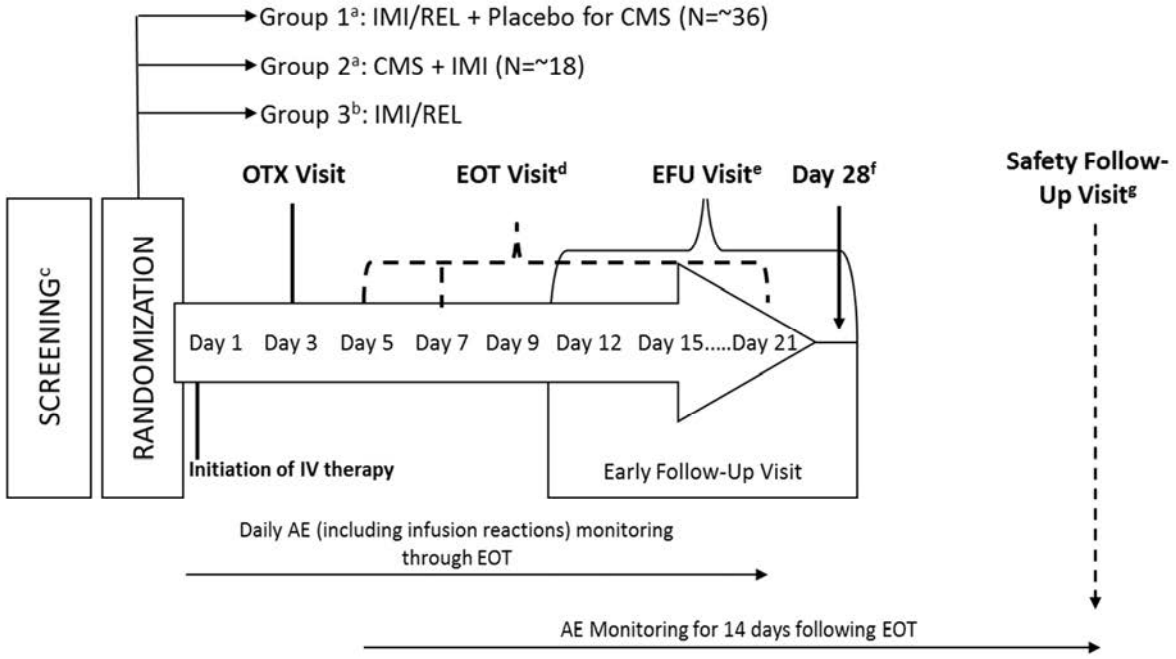
After a maximum 24-hour screening period, subjects will receive a minimum of either 5 (cIAI and cUTI strata) or 7 (HABP/VABP stratum) days up to a maximum of 21 days of intravenous (IV) study therapy. Duration of study therapy longer than 21 days must be approved by the Sponsor. While on study therapy, study visits will be performed on Day 1 (randomization), Day 3 (on therapy visit, OTX), 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 the early follow-up, EFU visit). In addition, a Day 28 post-randomization visit will be performed in all subjects (which may be performed on the same day as EFU, depending on the duration of IV study therapy). Depending on duration of IV study therapy, a safety follow-up visit may also be required in order to collect information on adverse experiences that occur during the 14 days following completion of IV study therapy. All subjects will remain in the study for a total of up to 35 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 in Figure 1.



OTX= on therapy, EOT= end of therapy; EFU = early follow-up (days 5 to 9 post EOT); Day 28 = Day 28 post-randomization; AE= adverse experience.
[a] Subjects in Treatment Groups 1 and 2 will enroll patients with bacterial infections which are imipenem-R but susceptible to IMI/REL as well as colistin.
[b] In addition to the 54 randomized subjects, eligible subjects with documented imipenem- and colistin-resistant bacterial infection (with IMI/REL susceptibility) will be enrolled into a third non-randomized treatment group (Treatment Group 3) to receive IMI/REL.
[c] The screening visit must occur ≤24 hours prior to randomization. Screening and randomization may be on the same day.
[d] The EOT visit must occur ≤24 hours after the last dose of IV study therapy. Minimum duration of IV therapy is 5 full days for cIAI and cUTI and 7 full days for HABP/VABP. Maximum duration must not exceed 21 days.
[e] 5 to 9 days (up to an additional 2 days) following EOT. The EFU and Day 28 visits may be combined as long as compliance with the visit windows is maintained for both visits. In this case, all procedures required for each visit must be completed for the combined visit.
[f] 28 days (up to an additional 3 days) following randomization.
[g] If the Day 28 post-randomization visit occurs prior to 14 days following EOT, a safety follow-up visit must be performed to collect adverse experience information, including hematology and chemistry tests for safety.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) Objective: To estimate the proportion of subjects with favorable overall response to IMI/REL (Treatment Group 1 only) and to CMS + IMI (Treatment Group 2).

The overall response will be estimated based on the following: (a) survival (based upon all-cause mortality) through Day 28 post-randomization in subjects with HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI and (c) the composite clinical and microbiological response at the early follow-up visit, EFU (Day 5 to 9 following completion of therapy) for subjects with cUTI.

(2) Objective: To evaluate the safety and tolerability profile of IMI/REL (Treatment Group 1 only).

No hypothesis testing will be performed.

3.2 Secondary Objective(s) & Hypothesis(es)

3.2.1 Key Secondary Objectives

(1) Objective: To estimate the proportion of subjects with a favorable clinical response to IMI/REL (Treatment Group 1 only) and CMS + IMI (Treatment Group 2) at Day 28 post-randomization.

(2) Objective: To estimate the incidence of all-cause mortality through Day 28 post-randomization in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI).

(3) Objective: To estimate the proportion of subjects who experience treatment-emergent nephrotoxicity in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI).

3.2.2 Other Secondary Objectives

(1) Objective: To estimate the proportion of subjects with a favorable clinical response to IMI/REL (Treatment Group 1 only) and CMS + IMI (Treatment Group 2) at the Day 3 on-therapy visit (OTX), at the end of therapy (EOT) visit and at the early follow-up visit (EFU, Day 5 to 9 post EOT).

(2) Objective: For subjects with cUTI, to estimate the proportion of subjects with a favorable microbiological response to IMI/REL (Treatment Group 1 only) and to CMS + IMI (Treatment Group 2) at the following visits: OTX, EOT, and EFU.

3.3 Exploratory Objectives

(1) Objective: To summarize the proportion of subjects with a favorable clinical response by infection type in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI) at EOT.

(2) Objective: To summarize the proportion of subjects with favorable clinical response (for all subjects) and favorable microbiological response (for cUTI) by baseline pathogen(s) in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI) at EOT.

(3) Objective: To summarize the pharmacokinetics (PK) and to evaluate the pharmacokinetic-pharmacodynamic (PK/PD) association of REL, imipenem, and cilastatin (CIL; PK only).

(4) Objective: To describe the emergence of resistance to IMI/REL, to imipenem and to colistin by pathogen in all randomized subjects.

(5) Objective: For subjects enrolled in Treatment Group 3, to evaluate the safety, tolerability and efficacy of IMI/REL.

Efficacy will be summarized based on the proportion of subjects with a favorable clinical response for all subjects and microbiological response for subjects with cUTI to IMI/REL at OTX, EOT, EFU and Day 28 post-randomization (clinical response only).

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

MK-7655 (relebactam) 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 of imipenem/cilastatin/relebactam (MK-7655A) 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 these 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.

Relebactam (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. This BLI is highly potent for 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).

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 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 patients

with varying degrees of renal insufficiency have been studied, including patients with end stage renal disease (ESRD) on hemodialysis.

Unblinded safety data from the Phase 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 co-administered 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 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 $AUC_{0-\infty}$ ≥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. 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. Enrollment in PN004 was completed on 8-Jul-2014 and last patient last visit was achieved on 12-Aug-2014. 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 ≥ 5 X ULN and 2) ALT or AST ≥ 3 X ULN and total bilirubin ≥ 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. Enrollment in PN003 was completed on 05-Jun-2015 and last patient last visit was achieved on 28-Jul-2015. 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.

4.1.2 Ongoing Clinical Trials

A Phase III clinical trial of IMI/REL in HABP/VABP (PN014) was recently initiated. PN014 is a randomized, double-blind, active comparator-controlled clinical trial to study the safety, tolerability, and efficacy of IMI/REL (MK-7655A) versus piperacillin/tazobactam in subjects with HABP/VABP. Approximately 536 subjects will be randomized in 1:1 ratio to one of the two treatment groups (1) IMI/REL (500mg/250mg) administered intravenously (IV) as a fixed-dose combination, (2) piperacillin/tazobactam (PIP/TAZ: 4000mg/500mg) administered IV as a fixed-dose combination.

4.1.3 Information on Other Trial-Related Therapy

Subjects in the comparator arm of this trial will receive colistin (in the form of CMS) and IMI as combination therapy.

Colistin is a polymyxin antimicrobial agent active against a variety of Gram-negative bacteria. Originally used clinically in the late 1950s, colistin was abandoned shortly thereafter due to reports of potential nephrotoxicity and neurotoxicity [1, 2]. The incidence of neurotoxicity reported in the literature was generally less than 10%; however reports of nephrotoxicity were frequent and some reports suggested rates as high as 100% [3-9]. More recently, with the increasing emergence of significant carbapenem-resistant (CR) pathogens worldwide, the lack of approved antibiotics targeting these infections as well as the limited number of anti-infective agents in pharmaceutical development, colistin has been resurrected as a last-resort therapeutic agent for treatment of CR infections. Although early experience with colistin resulted in a high incidence of nephrotoxicity, more recent data suggest that the incidence of nephrotoxicity may be significantly lower compared with this early experience [10-14]. While it is difficult to quantify the actual degree of expected toxicity in recent reports due to conflicting data associated with various definitions of renal toxicity, as well as

inconsistent dosages of colistin administered, the majority of studies have shown a trend toward lower rates (0 to 30%) than seen historically [10-14]. These data also show that most cases of nephrotoxicity were mild and reversible. Recent data consistently show that neurotoxicity is rare [14-17]. Nephrotoxicity, regardless of the true incidence, appears to be more common than neurotoxicity and is the potential adverse experience of most concern to prescribing clinicians [1].

Colistin is available for intravenous administration as CMS, an inactive prodrug. After parenteral administration, CMS is metabolized to colistin. Colistin acts by binding phospholipids in the outer membrane of Gram-negative bacteria, causing cell wall destabilization and cell death. Colistin is active against many resistant Gram-negative bacteria, including *P. aeruginosa*, *Acinetobacter baumannii*, *K. pneumoniae*, and *Escherichia coli* [18]. Activity against other bacterial isolates, such as *Haemophilus influenzae, Salmonella* species (spp.), *Shigella* spp., *Legionella pneumophila, Aeromonas* spp., *Citrobacter* spp. and *Bordetella pertussis*, has also been reported [18]. Colistin is not active against *Proteus* spp., *Providencia* spp., *Burkholderia cepacia, Brucella* spp., *Edwardsiella* spp. or *Serratia* spp. [18, 19]. Gram-negative and Gram-positive aerobic cocci, Gram-positive aerobic bacilli, and all anaerobes are resistant to colistin [19]. Colistin is currently used in clinical situations such as in critically ill patients with CR Gram-negative infections. Successful treatment outcomes have been documented for various infections, including UTI, IAI, and bronchial and lower respiratory tract infections, including both HABP and VABP [11-13, 20-28].

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 (CIL) sodium is an inhibitor of this enzyme and effectively prevents renal metabolism of imipenem so that, when given together, full adequate antibacterial levels of imipenem are achieved. According to the approved package circular, IMI 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.

The rationale for using colistin (CMS) + IMI as the comparator in this study is provided in Section 4.2.2.6.

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.

The current epidemic of multi-drug resistant (MDR) bacterial infections is a critical challenge in healthcare today. The organisms known as "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, A. baumannii, P. aeruginosa*, and

Enterobacter species) predominate in the resistance epidemic and have become a significant problem in hospital-acquired infections [29]. 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 [30-39]. Over the last decade, the emergence of several highly resistant Gram-negative pathogens, including CR *P. aeruginosa* and CR Enterobacteriaceae (predominantly KPC), had posed a particularly troubling, and escalating, global health issue [31, 40]. 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% [12, 13, 20-26]. 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 [12, 13, 20-26]. These are also of the most common sites of healthcare-associated infections. This study will enroll patients with certain CR, Gram-negative infections (CR *P. aeruginosa* and KPC) at several prevalent infection sites, including HABP/VABP, cIAI, and cUTI. The study will be restricted to individuals meeting the appropriate diagnostic criteria for these infections (see Appendix 12.5) as a primary infection site. Subjects with bloodstream infections (bacteremia) secondary to HABP/VABP, cIAI, or cUTI are eligible for enrollment.

Although relatively infrequent, resistance to colistin is becoming more common [18]. Without colistin, very few treatment options remain for subjects with CR bacterial infection. For this reason, a third, open-label treatment arm (Treatment Group 3) has been included in this study for subjects with imipenem- and colistin-resistant but IMI/REL-susceptible infections.

The safety and efficacy of IMI + REL has been evaluated in 2 Phase II studies (PN003 in patients with cUTI, and PN004 in patients with cIAI) in order to establish clinical proof-of-concept and to identify the optimal dose for REL for subsequent studies. Infections caused by imipenem-resistant isolates in the Phase II studies represent a small proportion of all the infections, so this separate study (Protocol 013) is being conducted specifically in subjects with imipenem-resistant infections in order to evaluate the clinical safety and efficacy of IMI/REL in the treatment of subjects with infections caused by imipenem-resistant bacteria.

Subjects ≥18 years of age will be eligible for participation in this study. Phase I data for subjects administered REL either alone or with IMI support use in both young and elderly males and females. Although the product circular for CMS does not contain sufficient data in subjects ≥65 years of age to determine whether they respond differently to the drug, there has been extensive experience with colistin in critically ill patients, including elderly patients up to 98 years of age, reported in recent literature [20, 22, 23, 25, 26, 41]. Given the growing incidence of CR infections and the lack of effective antibiotic treatments, colistin is often the only antibiotic active against such Gram-negative bacteria and is frequently used in clinical practice without regard to advanced age.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Imipenem/Relebactam (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). In order to inform the choice of dose for the current proposed study, results of an interim analysis of combined safety data from PN003 and PN004 were reviewed by a standing internal Data Management Committee (siDMC). The interim analysis included an evaluation of the safety and tolerability of the 250 mg dose of REL given in combination with IMI in comparison to the control regimen (IMI + placebo to REL) and in comparison to the 125 mg dose of IMI + REL. The analysis was performed after 50% of planned subjects across PN003 and PN004 (N=331) were followed through the early follow-up visit (5 to 9 days following completion of study therapy). The data from the interim analysis supported the use of a 250 mg dose of REL with IMI. The safety profile of the 250 mg dose is further supported by unblinded data from both Phase II studies (PN003 and PN004) which showed that the safety and tolerability profile of the 250 mg dose was similar to the 125 mg dose of REL as well as to IMI alone (See Section 4.1.1 for further details). 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.

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. The IMI package circular also includes reduced daily doses for patients with lower body weight. The total daily dose for IMI-containing therapy (IMI/REL and IMI) for subjects in this study will not be adjusted for weight. This approach is consistent with general clinical practice and other recent clinical trials using IMI as a comparator. For example, clinical trials for HABP/VABP published since 2006 have administered IMI at standard dosages without an adjustment for weight. Efficacy rates in these trials have ranged from ~60 to 80% without significant toxicity [42 – 45]. The few published clinical trials in which IMI dosage was adjusted for weight describe similar efficacy and safety [46, 47]. Furthermore, weight is already a component of calculated creatinine clearance, used for determination of

renal function and need for dose adjustment, thus raising the theoretical concern of under-dosing in subjects with low body weight. Population PK-based simulations were conducted to evaluate the impact of removal of weight-based adjustments for IMI. Results of these simulations indicate that in individuals of lower weight, exposures of IMI/REL are significantly lower than those in higher weight ranges when doses are adjusted based on weight, and are supportive of dose adjustments based solely on renal function, as has been described above in clinical practice. Specifically, simulation results indicate that in 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 11).

4.2.2.2 Colistin as Colistimethate Sodium (CMS)

Colistin dosing recommendations are complicated by the use of several non-interchangeable units including International Units (IU), milligram (mg) of CMS and mg of colistin base activity (CBA). As shown in Table 1, it has been established that there are approximately 12,500 IU and approximately 0.4 mg CBA per 1 mg of CMS [14, 48]. The dosage of intravenous CMS recommended by the US manufacturer (X-Gen Pharmaceuticals, Inc.) in the package circular is 2.5 to 5 mg/kg per day of CMS divided into 2 to 4 equal doses with a maximum daily dose equal to no more than 300 mg CBA (approximately 9 million IU or 720 mg CMS) [49]. Dose adjustment for renal insufficiency is recommended. Although it is important to note the recommendations available in the manufacturer's package circular, an evaluation of more recent data support modifications to these recommendations [50, 51].

Table 1 Approximate Dosing Units for Colistin

Colistimethate sodium (IU)	Colistimethate sodium (mg)	Colistin-base activity (CBA) (mg)[a]
12 500	1	0.4
150 000	12	5
1 000 000	80	34
2 300 000	180	75
3 400 000	270	115
4 500 000	360	150
9 000 000	720	300

[a] Based on a nominal potency of the drug substance of 12,5000 IU/mg CMS or 0.424 mg CBA/mg CMS: both IU and mg CBA are expressions of potency and have only approximate relation to the mass of drug substance [48].

Colistin is available for intravenous administration as the inactive prodrug, CMS. CMS has never been subjected to contemporary drug development procedures. As a result, there are very limited PK data available to guide appropriate CMS dose selection, especially in critically ill patients. Early studies, including those used for current product labeling, utilized nonspecific microbiological assays. Since CMS is not bactericidal itself, determination of the appropriate PK target and associated dosing scheme must include an accurate measurement of its active moiety, colistin. CMS is relatively unstable and is readily

converted to colistin at low concentrations in plasma and urine, and differentiation of colistin present in biological samples at the time of collection from that formed from CMS *in vitro* during the incubation phase of microbiological assays is essential [51]. Early assays were not able to differentiate between colistin and CMS converted *in vitro* [14]. Therefore, current dosing guidelines are not based on complete PK/PD data and, as a result, have led to treatment failure, as well as emergence of resistance to colistin [14, 52, 53].

Understanding the PK/PD relationship of colistin has been an area of considerable research in recent years [1, 50 – 57]. In fact, a recent clinical PK study in 105 critically ill patients developed the first evidence-based guidelines for dosing CMS to achieve a desired target steady state plasma concentration of formed colistin in patients with varying degrees of renal function [50]. In this large PK study, a population PK model was developed that indicated that creatinine clearance and body weight are significant covariates on the PK of CMS and colistin. Population PK based simulations were used to derive suggested loading and maintenance dosing regimens for patients of varying weight and renal function, including those on hemodialysis and continuous renal replacement, in order to obtain average target concentrations at steady state of 2.5 mg/L. This model serves as the basis of dosing instructions in this study (see Table 12, Section 5.2.1.1), with minor adjustments made to the proposed schema including a constant (rather than weight-based) loading dose given to patients of varying weights and creatinine clearance. Specifically, simulations of a constant loading dose of 300 mg of CBA (~9 million IU or 720 mg CMS) for patients of varying weights and renal function indicate that the PK target is achieved more quickly and there is less variation among individuals in colistin PK. These simulations also indicate that as renal function increases, steady state is achieved more slowly following a loading dose. If maintenance dosing is initiated after 12 hours, rather than 24 hours, steady state is essentially achieved immediately following the loading dose. Based on these results, the published dosing scheme [50] has been modified to incorporate these changes (see Table 12, Section 5.2.1.1). As both recommended in the published model-based recommendations [50] and the package circular, regardless of renal function, with the exception of the first 24 hours of therapy, subjects will not be administered more than the maximum total daily dose of 300 mg CBA (~ 9 million IU or 720 mg CMS). It is recognized that concerns for potential nephrotoxicity by colistin may limit the total daily amount of CMS that can be administered. However, data suggest that kidney damage is associated with total cumulative dose and the duration of CMS therapy [58]. Given that initial therapy is likely critical to rapid clearance of the infection and thus potentially shorter duration of therapy, an initial 24-hour period of exposure to doses exceeding the package circular recommendations will be beneficial to the success of therapy, and hence the efficacy of the treatment.

4.2.2.3 Imipenem/Cilastatin

IMI will be provided as combination therapy with CMS, as a separate infusion. For treatment in severe, life-threatening infections caused by moderately susceptible organisms, a 3- to 4-gram daily dose is recommended for IMI monotherapy. While the infections in this study are anticipated to be serious, imipenem-resistant organisms are the target pathogens for this study and there is no recommended dosing regimen for resistant organisms, since IMI would not be used as monotherapy for imipenem-resistant organisms. IMI is not being used as the primary treatment modality in this study and has been added as part of a combination regimen with CMS (*Note*: additional discussion regarding rationale for combination therapy

of CMS + IMI is included in Section 4.2.2.6). Furthermore, prior to study entry, *in vitro* susceptibility results must show confirmed susceptibility of the pathogens to colistin. For these reasons, as well as in an effort to support blinding feasibility as well as a straightforward safety and efficacy evaluations, the chosen dose for IMI in this study is 500 mg, administered IV once every 6 hours (i.e., 2 gram total daily dose).

The dosage of IMI will be adjusted in patients 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 may be adjusted. As previously discussed (See Section 4.2.2.1), adjustments for body weight will not be made. Specific dosing guidelines for IMI are included in Section 5.2.1.1, Table 11.

4.2.2.4 Placebo

In this study, all study subjects will receive active antimicrobial therapy (IMI/REL vs. CMS + IMI). IMI/REL will be provided together in a single vial as a fixed-dose combination product; therefore, subjects in Treatment Group 1 will be assigned to receive a single infusion of active product at one time compared with subjects in Treatment Group 2 who could receive as many as 2 active-product infusions at a time. Placebo to CMS will be utilized in Treatment Group 1 so that all subjects will receive the same number of infusions in order to maintain the study blind (see Figure 2, Section 5.2.2). Based on the dosing scheme for CMS, subjects in Treatment Group 1 will receive a placebo-matching infusion. Due to a slight difference in the appearance of CMS solution for infusion and the placebo infusion, the infusion bags will be covered in an opaque sleeve by an Unblinded Study Pharmacist (or qualified designee) to ensure that other study personnel and all subjects remain blinded to clinical material assignment. The intravenous line (through which the infusion is administered) does not require opaque covering as the differences between the clinical materials are not visually distinguishable within the tubing. Study supplies will be provided in an open-label fashion to the sites; hence, an Unblinded Study Pharmacist (or qualified designee) at the study site will be responsible for preparing the IV study therapy for this study; this individual(s) will not be involved in any safety or efficacy evaluations of the study participants.

Additional details for preparation and administration of all study drugs, including appropriate diluents for reconstitution of all study therapies are provided in a separate Pharmacy Manual.

4.2.2.5 Duration of Therapy

IV study therapy will be administered for a minimum of either 5 (cIAI and cUTI) or 7 (HABP/VABP) days up to a maximum of 21 days. Duration of study therapy longer than 21 days must be approved by the Sponsor. MDR, including CR, infections are treated for a wide range of treatment durations. The recommended duration of treatment for CR infections is customarily based on the site of infection and physician assessment of the patient's clinical condition. Based on a review of several retrospective studies, treatment duration of colistin for CR infections ranged from 3 to 46 days with an approximate average of 2 weeks [20, 21, 23-25]. The current data for REL support up to 1 month of administration; REL was studied for toxicity in monkeys and in rats for up to 3 months with acceptable results. Current clinical practice guidelines suggest limiting treatment of infection types included in this study to less than 3 weeks; guidelines published by the Infectious

Diseases Society of America (IDSA) recommend limiting treatment of catheter-associated UTI to less than 2 weeks, limiting treatment of cIAI to less than 1 week for most infections, and limiting treatment of HABP/VABP to as little as 1 week [59 – 62]. Although most treatment guidelines suggest shorter courses of therapy, based on preclinical data supporting longer treatment durations and the clinical complexity of subjects in the study, the present study permits up to 21 days of study therapy for subjects who may require extended durations of treatment (e.g., those with suppressed immunity) and permits durations of treatment longer than 21 days with approval from the Sponsor.

Refer to the Investigator's Brochure (IB) for more detailed information on preclinical toxicity studies MK-7655A.

4.2.2.6 Rationale for Choice of Comparator

In this study, approximately 54 subjects will be randomized in a 2:1 ratio to receive IMI/REL (Treatment Group 1) or CMS + IMI (Treatment Group 2), with ~36 subjects in Treatment Group 1 and ~18 subjects to Treatment Group 2. The sample size of Protocol 013 is small in order to minimize the duration of enrollment in this challenging study, thereby making the data on the use of IMI/REL in subjects with unmet medical need available more quickly. Given the small sample size, the number of subjects receiving a controlled comparator regimen within Protocol 013 has been limited by utilizing a disproportionate randomization scheme. Enrolling the majority of subjects to receive treatment with IMI/REL will maximize experience with IMI/REL.

Severe hospital-acquired infections due to CR Gram-negative bacteria are associated with high morbidity and mortality. The increasing incidence of CR infections and the lack of effective antibiotics have resulted in the use of colistin as a "salvage" antibiotic, essentially making colistin one of a few treatment options in critically ill patients infected with CR Gram-negative bacteria. Given its common use and relative treatment success in the target population for this current study, colistin (as CMS) is an appropriate comparator for evaluation of IMI/REL.

Although subjects infected with imipenem-resistant bacteria are the target population for this study, the combination of CMS with IMI was chosen as the comparator regimen for several reasons:

- Although colistin is commonly used in clinical practice today, the original development of colistin occurred prior to institution of the current standardized rigorous drug development procedures. As a result, there is a relative lack of pharmacological information to maximize antibacterial activity and minimize development of resistance and toxicity. Recent data suggest that the recommended dosage of colistin likely leads to suboptimal efficacy, particularly in certain patient subgroups [14, 53, 54]. Results of a recent large PK study demonstrated that, even at the maximum daily dose recommended in the package circular, it is not possible to reach adequate plasma concentrations of formed colistin, especially in patients with healthy renal function [50]. Given these results, it has been suggested that colistin might best be used as part of a highly active combination.

- In recent years, there have been worldwide reports of emergence of resistant bacteria during colistin monotherapy [63, 53, 30, 64, 65]. Combination therapy may reduce the potential outgrowth of hetero-resistant subpopulations of bacteria.
- Colistin causes an incompletely understood 'detergent' effect on the cell wall, resulting in increased cell permeability and potentially allowing for increased ability of other drugs to reach their antibacterial target [19]. *In vitro* studies have demonstrated a synergistic effect of colistin in combination with other antibacterial therapies, including carbapenems [66 – 68].
- Although robust controlled clinical studies are still needed to evaluate the effect of combination therapy, multiple recent studies have demonstrated improved efficacy due to combination therapy in the treatment of CR infections [12, 20, 22, 69, 70, 71].

In summary, combination therapy of colistin plus a carbapenem (such as IMI) will likely provide improved clinical success due to an expected increased bactericidal effect, and will likely limit potential toxicity by ensuring administration of maximum daily maintenance doses within the limits specified by manufacturer.

The carbapenem IMI is among the drugs of choice for treatment of severe nosocomial infections in critically ill patients [72]. Additionally, IMI is active against a wide range of Gram-positive and Gram-negative organisms, including both anaerobes and aerobes, thus providing broad-spectrum coverage. Consequently, carbapenems are often administered in clinical practice as part of a combination regimen with CMS in patients with CR infection [12, 20, 22]. Furthermore, the use of IMI in this study as the active co-comparator will allow for a straightforward evaluation of the efficacy and safety of REL as compared to colistin, as all patients in the study will receive the same β-lactam as background therapy.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

For evaluation of the primary and secondary analyses, response to IMI/REL and to CMS+IMI will be based only on randomized subjects (i.e., those enrolled into Treatment Group 1 and Treatment Group 2).

The primary efficacy endpoint of the study is overall response. As the efficacy in clinical studies is typically measured differently for different infection types, overall response will be estimated based on the following: (a) all-cause mortality through Day 28 post-randomization in subjects with HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI and (c) the composite clinical and microbiological response at EFU (Day 5 to 9 following completion of therapy) for subjects with cUTI. Evaluation of the overall response will allow for a summary of REL efficacy utilizing a combination of responses that are relevant for each infection type. In addition, each of these chosen endpoints for these 3 infection types are supported in United States FDA Guidance for Industry.

There are two key secondary measurements for efficacy in this study:

- Clinical response at 28 days following initiation of IV study therapy (through Day 28 post-randomization): Evaluation of clinical response at a fixed timepoint for all subjects, regardless of infection type, will allow for comparison at a consistent timepoint across the entire study population. In addition, since the maximum duration of IV study therapy is 21 days, unless a longer duration is approved by the Sponsor, subjects will be evaluated after completion of IV study therapy, thereby allowing an assessment of clinical response at least one week following cessation of therapy in a majority of subjects.
- All-cause mortality within 28 days after initiation of study therapy (through Day 28 post-randomization): Given the severity of illness in hospitalized patients who acquire CR bacterial infections, have failed prior antibiotic treatments, and routinely require in-hospital treatment with IV antibiotics, evaluation of mortality is appropriate. A one-month mortality endpoint has commonly been used for evaluation of efficacy of antibacterial therapy against CR infections [12, 21, 23, 26].

Several additional secondary efficacy endpoints will be evaluated:

- Clinical response will be estimated at various other timepoints during the trial, including at OTX, EOT and EFU. Evaluation of clinical response at these timepoints will provide valuable data to fully characterize the response profile of the test product relative to the comparator.
- Microbiological response in subjects with cUTI will be evaluated at OTX, EOT and at EFU. Microbiological response will be measured in subjects with cUTI only since appropriate specimens (i.e., urine) can be feasibly and consistently collected at each of the endpoint visits throughout the study. Collection of lung and/or intra-abdominal specimens at all study visits may not be medically appropriate for all subjects, thus making it difficult to measure an overall microbiological response in subjects with these infections.

In addition, since there will likely be differences in clinical outcome of the various infection types being studied, as well as the potential for significant differences in duration of IV study therapy for each of these infection types, clinical response by infection type will be evaluated at EOT as an exploratory endpoint in randomized subjects. Other exploratory endpoints in this study include clinical and microbiological response by pathogen in randomized subjects, PK/PD evaluation for all subjects, and an assessment of the emergence of resistance to IMI/REL and to colistin during study therapy in randomized subjects.

Clinical response at all endpoint visits and microbiological response (cUTI) at OTX, EOT and EFU in Treatment Group 3 subjects will also be summarized as exploratory efficacy endpoints.

4.2.3.1.1 Definition of Efficacy Endpoints

4.2.3.1.1.1 Overall Response

The overall response will be estimated based on the following: (a) survival (based upon all-cause mortality) through Day 28 post-randomization in subjects with HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI and (c) the composite clinical and microbiological response at EFU for subjects with cUTI. Overall response will be determined by summarizing the proportion of subjects who survive through Day 28 post-randomization (HABP/VABP), or have a "favorable" clinical (cIAI) or "favorable" composite microbiological and clinical (cUTI) response.

A favorable response is defined differently for each infection type, and these definitions will be combined to provide an estimate of favorable overall response (See Table 2 for a description of the components of the overall response). The definitions for the relevant response types that contribute to overall response are included in each of the referenced sections describing survival/all-cause mortality assessment (Section 4.2.3.1.1.1.1), clinical response (Section 4.2.3.1.1.1.2) and microbiological response (Section 4.2.3.1.1.1.3). Details regarding determination of microbiological and clinical response ("favorable" or "unfavorable") in support of evaluation of overall response at Day 28 post-randomization are provided in Section 8.2.

Table 2 Description of Individual Infection Site Responses Supporting Determination of Favorable Overall Response (Primary Endpoint)

Infection Site	Type of Response (Timing)	Favorable Response	Reference (Section/Table #) for Definition of Response
HABP/VABP	Survival/All-Cause Mortality (Day 28)	Survival at Day 28	Section 4.2.3.1.1.1.1
cIAI	Clinical Response (Day 28)	• Sustained cure • Cure	Section 4.2.3.1.1.1.2 Table 5
cUTI	Composite Clinical (EFU) and Microbiological Response (EFU)	Clinical Response: • Sustained cure • Cure Microbiological Response: • Sustained eradication	Clinical Response: Section 4.2.3.1.1.1.2 Table 5 Microbiological Response: Section 4.2.3.1.1.1.3 Table 8

4.2.3.1.1.1.1 Survival/All-Cause Mortality

Survival status (i.e., whether the subject is alive or dead) at Day 28 will be evaluated for all subjects. In support of the primary objective of overall response, survival will be specifically determined in subjects with HABP/VABP. In addition, the key secondary efficacy endpoint will be based on an all-cause mortality evaluation in all subjects, regardless of primary infection site, at Day 28 following randomization.

4.2.3.1.1.1.2 Clinical Response

In support of evaluation of both the primary endpoint (i.e., overall response), as well as secondary and exploratory endpoints for the study, efficacy assessments will include evaluation of clinical response. Clinical response will be assessed for all subjects based on evaluation by the investigator at the OTX, EOT, EFU and Day 28 post-randomization 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 3 (for OTX visit), Table 4 (for EOT visit) and Table 5 (for EFU and Day 28 visits).

In support of evaluation of efficacy endpoints that include clinical response (i.e., overall response and 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 8.2.

Table 3 Definitions of the Clinical Response Rating at the OTX Visit (Day 3)

Clinical Response[a]	Response Definition
Improved	All or most pretherapy signs and symptoms[b] of the index infection(s) have improved or resolved (or returned to "preinfection status") **AND**, for cIAI subjects, no unplanned surgical procedures or percutaneous drainage procedures have been performed.
Persistence	Little apparent response to IV study therapy in prestudy signs and symptoms[b] of the index infection(s): persistence of most or all pretherapy signs and symptoms.
Progression	No apparent response to IV study therapy in prestudy signs and symptoms[b] of the index infection(s): progression/worsening of most or all pretherapy signs and symptoms.
Indeterminate	Study data are not available for evaluation of clinical response for any reasons at the OTX visit, 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 for any reason; **OR** c) Extenuating circumstances preclude classification as "improved," "persistence," or "progression;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

[a] A favorable clinical response at OTX requires an assessment of "improved".
[b] Refer to Table 13 for a description of disease-specific clinical signs and symptoms.

Table 4 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 withdrawn 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 13 for a description of disease-specific clinical signs and symptoms.

Table 5 Definitions of the Clinical Response Rating at the EFU and Day 28 Post-Randomization Visit

Clinical Response[a]	Response Definition
Sustained Cure	All pretherapy signs and symptoms[b] of the index infection(s) have resolved (or returned to "preinfection status") with no evidence of resurgence **AND** no additional antibiotic therapy (beyond IV study therapy) was required, **AND**, for cIAI subjects, no unplanned surgical procedures or percutaneous drainage procedures have been performed.
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[c]
Relapse	Subjects with a favorable clinical response (cure or improved) at the EOT visit have worsening signs and symptoms[b] of the index infection(s) by the EFU or Day 28 post-therapy visit.
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 "sustained cure," "failure," or "relapse;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

[a] A favorable clinical response at EFU or Day 28 post-randomization requires an assessment of "cure" or "sustained cure". To be considered "sustained cure", the clinical response for the prior visit must have been considered "cure". A clinical response of "cure" is only relevant at EFU for subjects with a response of "improved" at EOT.
[b] Refer to Table 13 for a description of disease-specific clinical signs and symptoms.

4.2.3.1.1.1.3 Microbiological Response

In addition to clinical response assessments, subjects with cUTI will be evaluated for microbiological response. Microbiological response will be evaluated separately for each qualifying baseline uropathogen. For randomized subjects, a qualifying pathogen is defined as any Gram-negative baseline pathogens that are imipenem-resistant, IMI/REL-susceptible, and colistin-susceptible. For subjects enrolled in Treatment Group 3, a qualifying pathogen is defined as any Gram-negative baseline pathogens that are imipenem-resistant and colistin-resistant, but IMI/REL-susceptible. The by-pathogen response rating will be determined by the Sponsor. The by-pathogen microbiological response rating will be determined at the OTX, EOT, and EFU visits based on local laboratory results (per eCRF data provided by the investigator) from urine cultures collected at each of these visits relative to the pathogen(s) isolated at baseline/admission, as described in Table 6 (for the OTX visit), Table 7 (for the EOT visit) and Table 8 (for the EFU visit). Of note, microbiological samples are not collected at the Day 28 post-randomization visit.

Antibiotic susceptibility results as well as microbiological response will be summarized by qualifying pathogen. In support of evaluation of efficacy endpoints that include microbiological response (i.e., microbiological response and overall 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 qualifying uropathogens present in the baseline culture) as "favorable" or "unfavorable." For subjects from whom only one qualifying 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 qualifying baseline pathogen is isolated, the overall microbiological response outcome will be based on microbiological culture results for all qualifying 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 8.2.

Table 6 Definitions of the By-Pathogen Microbiological Response Rating at the OTX Visit (Day 3)

Microbiological Response[a,b,c]	**Response Definition**
Eradication	A urine culture taken at the OTX visit shows eradication of the uropathogen (e.g., $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry.
Persistence[d]	A urine culture taken at the OTX visit grows a uropathogen (at $\geq 10^4$ CFU/mL) found at study entry.
Superinfection	A urine culture at the OTX visit 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 OTX 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 qualifying pathogen isolated at baseline.
[b] If a new/emergent pathogen is identified after initiation of IV therapy which was not identified at baseline, regardless of susceptibility profile, the microbiological response rating for the new pathogen will be considered "superinfection".
[c] A favorable overall microbiological response at OTX requires "eradication" of all baseline pathogens.
[d] 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 7 Definitions of the By-Pathogen Microbiological Response Rating at the EOT Visit

Microbiological Response[a,b,c]	**Response Definition**
Sustained eradication[d]	A urine culture taken at the EOT visit[c] still shows eradication of the uropathogen (e.g., $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry.
Eradication[e]	A urine culture taken at the EOT visit[c] shows eradication of the uropathogen (e.g., $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry.
Persistence[f]	A urine culture taken at the EOT visit[g] grows a uropathogen (at $\geq 10^4$ CFU/mL) found at study entry.
Superinfection	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[c] 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 qualifying pathogen isolated at baseline.
[b] If a new/emergent pathogen is identified after initiation of IV therapy which was not identified at baseline, regardless of susceptibility profile, the microbiological response rating for the new pathogen will be considered "superinfection".
[c] A favorable overall microbiological response at EOT requires "eradication" or "sustained eradication" of all baseline pathogens.
[d] A microbiological response of "sustained eradication" at EOT is used when the microbiological response assessment at OTX visit was also "eradication".
[e] A microbiological response of "eradication" at EOT is used when this is the first time that microbiological response assessment is "eradication (i.e., OTX visit microbiological response assessment was not "eradication").
[f] 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.
[g] 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 8 Definitions of the By-Pathogen Microbiological Response at the EFU Visit

Microbiological Response[a,b,c]	Response Definition
Sustained eradication[d]	A urine culture taken at the EFU 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 EFU 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 qualifying pathogen isolated at baseline.
[b] If a new/emergent pathogen is identified after EOT which was not identified at baseline, regardless of susceptibility profile, the microbiological response rating for the new pathogen will be considered "new infection".
[c.] A favorable overall microbiological response at EFU visit requires "sustained eradication" of all baseline pathogens.
[d] A microbiological response of "sustained eradication" at EFU is used when the microbiological response assessment at EOT visit is also "eradication".

4.2.3.2 Safety Endpoints

In support of the primary objective to evaluate the safety and tolerability profile of IMI/REL, the safety and tolerability of IMI/REL (as well as the safety of the comparator, CMS + IMI) 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.

In addition, due to concern for potential renal toxicity of colistin, the relative rates of nephrotoxicity of IMI/REL and CMS + IMI will be evaluated as a secondary endpoint in this study. Evaluation of potential nephrotoxicity will be performed based on laboratory test results from blood samples.

As discussed in Section 4.1.3, the reported incidence of nephrotoxicity associated with colistin administration is variable. In addition to the lack of a standard dosing algorithm for colistin, a major difficulty in determining the true incidence of nephrotoxicity associated with intravenous colistin therapy is the absence of a standardized and consistently applied definition of nephrotoxicity. In this study, the definition of nephrotoxicity will be based on alterations in baseline serum creatinine and renal function as described in Table 9. Serum creatinine level as well as creatinine clearance are commonly used in clinical practice to measure renal function. In addition, there is evidence that changes in serum creatinine are associated with an increase in short-term morbidity and even mortality, thus making serum creatinine an appropriate marker for measuring acute kidney injury [73]. Changes in

creatinine and renal function have frequently been used in the literature to describe colistin-associated nephrotoxicity [13, 17, 21-23, 26, 74, 75, 76].

Table 9 Criteria for Defining Nephrotoxicity

Baseline Renal Function Category	Baseline Serum Creatinine Level	Definition of Nephrotoxicity
Normal	<1.2 mg/dL	Doubling of serum creatinine (to >1.2 mg/dL), **OR** Reduction in the calculated creatinine clearance[a] (CL_{Cr}) of ≥50%.
Pre-Existing Renal Dysfunction	≥1.2 mg/dL	Increase in serum creatinine by ≥1 mg/dL, **OR** Reduction from baseline in calculated CL_{Cr}[a] of ≥20%, **OR** Need for RRT.

RRT= Renal replacement therapy
[a] Calculated from serum creatinine using the equation provided in Section 5.2.1.1.

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 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA (blood) specimens collected during this clinical trial. Importantly, a subject may participate in the main trial without participating in Future Biomedical Research portion of this study.

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 specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. 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. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects enrolled in this trial are generally hospitalized patients with multi-drug resistant infections requiring treatment with IV therapy. As discussed in Section 4.2, available treatment options for patients infected with resistant pathogens are limited. If randomized to receive IMI/REL, subjects can potentially benefit from treatment with this investigational agent specifically targeted for treatment of Gram-negative imipenem-resistant infections. Subjects randomized to the comparator arm will also receive a treatment regimen expected to be efficacious against these infections (see Section 4.2.2.6). Regardless of treatment assignment, the study has been designed to support prompt receipt of appropriate therapy for all eligible subjects. Typical treatment of hospitalized patients with any bacterial infection is decided based on *in vitro* susceptibility of pathogens isolated from an infection-site specimen. In order to support timely initiation of effective study therapy and thus reduce risk of treatment failure, in vitro susceptibility results confirming susceptibility for both the investigational and comparator agents in this trial is required prior to randomization. The Sponsor will provide susceptibility panels to all investigator sites to support this testing.

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 patient population. Additional burden may be incurred due to visits following release from the hospital. However, the procedures performed at these visits are generally not likely to lead to significant harm (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 patients 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 and female subjects who are at least 18 years of age and have an imipenem-resistant Gram-negative bacterial infection involving one of 3 primary infection types (HABP/VABP, cIAI, or cUTI) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

5.1.2.1 Treatment Groups 1 and 2

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 at the randomization visit.

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

2. require hospitalization and treatment with IV antibiotic therapy for a new, persistent (defined as inadequate response to current therapy or failure to improve as expected) or progressing (defined as clinically worsening despite treatment) bacterial infection with at least one of the following primary infection types:

   - Hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP)
   - Complicated intra-abdominal infection (cIAI)
   - Complicated urinary tract infection (cUTI)

     NOTE: Diagnostic criteria, including relevant radiographic, clinical and microbiological evidence, for each infection type are in Appendix 12.5.

3. has positive culture data obtained from the primary infection-site specimen collected within 1 week of study entry and at least one of the suspected causative pathogen(s) from that specimen meets all of the following criteria:

   a. has been identified as a Gram-negative bacterium, AND

   b. has culture-confirmed imipenem resistance (MIC of isolate is above the imipenem-susceptible breakpoint) based on panels provided by the Sponsor, AND

   c. has culture-confirmed susceptibility to colistin (MIC of isolate is at or below the colistin-susceptible breakpoint) and to IMI/REL (MIC of isolate is at or below the imipenem-susceptible breakpoint) based on panels provided by the Sponsor.

4. 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.
5. 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.
6. 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 (cannot be used in conjunction with cervical cap/spermicide)
      - cervical cap with spermicide (nulliparous women only)
      - 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), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle

and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.1.2.2 Open-Label, Treatment Group 3

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 at the randomization visit.

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

2. require hospitalization and treatment with IV antibiotic therapy for a new, persistent (defined as inadequate response to current therapy or failure to improve as expected) or progressing (defined as clinically worsening despite treatment) bacterial infection with at least one of the following primary infection types:

   - Hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP)
   - Complicated intra-abdominal infection (cIAI)
   - Complicated urinary tract infection (cUTI)

     NOTE: Diagnostic criteria, including relevant radiographic, clinical and microbiological evidence, for each infection type are in Appendix 12.5.

3. have positive culture data obtained from the primary infection-site specimen collected within 1 week of study entry and at least one of the suspected causative pathogen(s) from that specimen meets all of the following criteria:

   a. has been identified as a Gram-negative bacterium, AND

   b. has culture-confirmed imipenem resistance (MIC of isolate is above the imipenem-susceptible breakpoint) and colistin resistance (MIC of isolate is above the colistin-susceptible breakpoint) based on panels provided by the Sponsor, AND

   c. has culture-confirmed susceptibility to IMI/REL (MIC of isolate is at or below the imipenem-susceptible breakpoint) based on panels provided by the Sponsor.

4. agree to allow any bacterial isolates obtained from protocol-required specimens related to the current infection be provided to the Central Microbiology Reference Laboratory for study-related microbiological testing, long-term storage, and other future testing.

5. 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.

6. 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 (cannot be used in conjunction with cervical cap/spermicide)
      - cervical cap with spermicide (nulliparous women only)
      - 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), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.1.3 Subject Exclusion Criteria

5.1.3.1 Treatment Groups 1 and 2

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

1. has an APACHE II score >30 at screening
2. has an infection in which any of the causative pathogens are any of the following:
   - Imipenem-resistant *Acinetobacter* spp.
   - suspected Class B metallo-beta-lactamase-producing bacteria (including NDM-1, IMP or VIM-containing strains)
3. has a concurrent infection that would interfere with evaluation of response to the study antibiotics (IMI/REL or CMS + IMI), including any of the following:
   - endocarditis
   - osteomyelitis
   - meningitis
   - prosthetic joint infection
   - active pulmonary tuberculosis
   - a disseminated fungal infection
4. has received treatment with any form of systemic colistin for > 24 hours within the 72 hours immediately prior to initiation of study therapy.
5. has HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.
6. 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-ureteral 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.

7. has a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to <u>any</u> of the following:

   - any carbapenem, cephalosporin, penicillin, or other β-lactam agent
   - colistimethate sodium (colistin) or to polymyxin B
   - other β-lactamase inhibitors (e.g., tazobactam, sulbactam, clavulanic acid, avibactam)

   <u>NOTE</u>: Subjects with a history of mild rash to penicillins or other β-lactams may be enrolled and closely monitored.

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 <u>any</u> of the following medical conditions at screening:

   - history of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years)
   - myasthenia gravis
   - porphyria
   - cystic fibrosis
   - granulomatous disease

10. is anticipated to be treated with <u>any</u> of the following medications during the course of study therapy:

    - valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening)
    - concomitant IV, oral, or inhaled antimicrobial agents with known coverage of Gram-negative bacteria of interest (i.e., Enterobacteriaceae, *Pseudomonas* spp. and Gram-negative anaerobic bacilli), in addition to those designated in the study treatment groups.

      <u>NOTE</u>: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected methicillin-resistant *S. aureus* (MRSA) infection, use of IV linezolid or IV daptomycin to treat confirmed or suspected vancomycin-resistant *Enterococcus* spp. (VRE) infection, or use of trimethoprim-sulfamethoxazole (TMP/SMX) or other standard-of-care agent for prophylaxis of opportunistic infection (e.g., *Pneumocystis jiroveci* infection) in immunocompromised subjects is allowed. Daptomycin is not indicated for the treatment of HABP/VABP (Refer to Section 5.5).

11. 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 Cockcroft-Gault (C-G) equation:

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

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

12. is currently undergoing hemodialysis or peritoneal dialysis.
13. 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.
14. 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.
15. is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.
16. has previously participated in this study at any time.

5.1.3.2 Open-Label, Treatment Group 3

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

1. has an infection in which any of the causative pathogens are any of the following:
   - Imipenem-resistant *Acinetobacter* spp.
   - suspected Class B metallo-beta-lactamase-producing bacteria (including NDM-1, IMP or VIM-containing strains)
2. 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
   - a disseminated fungal infection
   - active pulmonary tuberculosis

3. has HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.
4. 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.
5. 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)

     NOTE: Subjects with a history of mild rash to penicillins or other β-lactams may be enrolled and closely monitored.
6. 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.
7. 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)
8. is anticipated to be treated with any of the following medications during the course of study therapy:
   - valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening)
   - concomitant IV, oral, or inhaled antimicrobial treatments with known coverage of Gram-negative bacteria of interest (i.e., Enterobacteriaceae, *Pseudomonas* spp. and Gram-negative anaerobic bacilli) in addition to those designated in the study treatment groups (prior use of antimicrobial agents is permitted).

     NOTE: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected methicillin-resistant *S. aureus* (MRSA) infection, use of IV linezolid or IV daptomycin to treat confirmed or suspected vancomycin-resistant *Enterococcus* spp. (VRE) infection, or use of TMP/SMX or other standard-of-care agent for prophylaxis of opportunistic infection (e.g., *P. jiroveci* infection) in immunocompromised subjects is allowed. Daptomycin is not indicated for the treatment of HABP/VABP (Refer to Section 5.5).

9. 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:

   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

10. is currently undergoing hemodialysis or peritoneal dialysis.
11. 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.
12. 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.
13. is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.
14. has previously participated in this study at any time

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 10.

Table 10 Trial Treatments

Drug	Dose/Potency[b]	Dose Frequency	Route of Administration	Regimen/Treatment Period[c]	Use
Treatment Group 1 (N = 36) or Treatment Group 3					
Imipenem/ cilastatin/relebactam (IMI/REL)[a]	Imipenem: 500 mg Relebactam: 250 mg	Every 6 hours	IV	5 or 7 to 21 days	Experimental
Placebo for CMS (diluent for CMS as directed in the Pharmacy Manual)	N/A	Loading dose followed after 12 hours by maintenance dose every 12 hours	IV	5 or 7 to 21 days	Placebo-control
Treatment Group 2 (N = 18)					
Colistin as colistimethate sodium (CMS)	Total maximum daily maintenance dose: 300 mg CBA[d]	Loading dose followed after 12 hours by maintenance dose every 12 hours	IV	5 or 7 to 21 days	Active-comparator
Imipenem/cilastatin (IMI)	Imipenem: 500 mg	Every 6 hours	IV	5 or 7 to 21 days	Active-comparator

CBA: Colistin base activity (300 mg CBA corresponds to approximately 720 mg CMS or ~9 million IU)

[a] IMI/REL will be provided combined in a single vial.

[b] Adjustments to dosage of IMI/REL, IMI and CMS may be required. Dose adjustment for IMI/REL and IMI are required for subjects with renal insufficiency (Reference Table 11 in Section 5.2.1.1). Dose adjustment for CMS dose in subjects with renal insufficiency is also required (Reference Table 12 in Section 5.2.1.1).

[c] IV study therapy should be administered for a minimum of 120 hours (5 full days) for subjects with cIAI or cUTI or 168 hours (7 full days) for subjects with HABP/VABP. The corresponding number of doses required is described in Section 7.1.5.2. The total duration of IV study therapy should not exceed 21 days. Duration of study therapy longer than 21 days must be approved the Sponsor.

[d] Subjects who require a loading dose of CMS (Reference Table 12 in Section 5.2.1.1) will receive >300 mg CBA during the first 24 hours of study therapy.

Trial therapy should begin on the same day as IVRS assignment of therapy for all subjects (i.e., randomization for Treatment Groups 1 and 2 or allocation assignment for Treatment Group 3). The first dose of prescribed study therapy should be administered at the Day 1 visit. The Unblinded Study Pharmacist (or qualified designee) will contact the interactive voice response system/integrated web response system (IVRS/IWRS) for assignment of the study therapy to be administered. Sites should not call IVRS/IWRS for drug administration until the subject has met all entry criteria for the study and ready to be randomized. All subjects in each treatment group will receive a minimum of either 5 days (cIAI, cUTI) or 7 days (HABP/VABP) up to a maximum of 21 days of intravenous (IV) study therapy. Duration of study therapy longer than 21 days must be approved the Sponsor.

Detailed dosing guidelines, including dose selection and timing of dose administration, are outlined in Section 5.2.1.1 and Section 5.2.2, respectively.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

For subjects with renal insufficiency, the dose of IMI/REL (in Treatment Group 1 or Treatment Group 3) and IMI (in Treatment Group 2) must be adjusted based upon the degree of renal function impairment, as determined by the estimated or actual creatinine clearance. It is important to note that if a change in the subject's creatinine clearance during IV study therapy could result in dosage adjustments at any time during IV therapy. Dose adjustments according to creatinine clearance are included in Table 11.

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

Subjects in Treatment Group 2 will also receive colistin as CMS. Upon randomization and initiation of IV study therapy, the dosage of the first dose of CMS for Treatment Group 2 subjects will depend on the subject's previous history of receipt of colistin within the 72 hours prior to entry in the study. Specifically, if a loading dose >200mg CBA (corresponding to ~ 470 mg CMS or 5.9 million IU) was administered prior to entry, the subject should begin maintenance doses described in Table 12 upon initiation of IV study therapy. It should be noted that a loading dose is defined based on the dosage of any individual dose(s) administered rather than the total dosage over a series of doses in a subject who has received >1 dose prior to entry. If the subject has not received a loading dose (i.e., an individual dose ≥ 200 mg CBA) prior to study entry, the protocol-specified loading dose of CMS of 300 mg CBA (corresponding to ~ 720 mg CMS or ~9 million IU) should be provided as shown in Table 12, regardless of the dosage previously administered.

Twelve (12) hours after the initial loading dose, maintenance dosing will begin and then continue every 12 hours (q12h) thereafter. The maintenance dose of CMS will be based on creatinine clearance according to Table 12. Creatinine clearance may be calculated from serum creatinine concentration by the equation previously provided. It is important to note that a change in the subject's creatinine clearance during IV study therapy could result in dosage adjustments at any time during IV therapy.

Subjects assigned to Treatment Group 1 will receive a matching placebo for CMS on the same schedule as subjects in Treatment Group 2 (first dose upon initiation of therapy followed by q12h maintenance doses beginning 12 hours later). Since Treatment Group 3 is open-label, no placebo will be administered to subjects enrolled into this Treatment Group.

Table 11 Administration Dosage of IMI/REL and IMI According to Renal Function

Creatinine Clearance (mL/min)	IMI/REL[a]	IMI
≥ 90	500/250 mg q6h	500 mg q6h
< 90 to ≥ 60	400/200 mg q6h	400 mg q6h
< 60 to ≥ 30	300/150 mg q6h	300 mg q6h
< 30 to ≥ 15	200/100 mg q6h	200 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 Treatment Group 1 subject who has a creatinine clearance of 50 mL/min should receive a 150 mg q6h dose of REL according to the table. Since the dose is reduced by 50% during preparation, the total mg of IMI would also be reduced by 50%, thus resulting in a 300 mg q6h dose of IMI.

Table 12 Administration Dosage of Loading and Daily Maintenance Doses of CMS According to Renal Function

Creatinine Clearance (mL/min)	Loading Dose[a]	Maintenance Dose[b]
≥ 90	300 mg CBA (~720 mg CMS or ~9 million IU)	150 mg CBA (~360 mg CMS or ~4.5 million IU)
< 90 to ≥ 60		150 mg CBA (~360 mg CMS or ~4.5 million IU)
< 60 to ≥ 30		115 mg CBA (~270 mg CMS or ~3.4 million IU)
< 30 to ≥ 15		75 mg CBA (~180 mg CMS or ~2.3 million IU)

CMS = colistimethate sodium; CBA = colistin base activity.

[a] If a loading dose ≥ 200 mg CBA (~470 mg CMS or ~5.9 million IU) was administered prior to study entry, the subject should begin maintenance doses upon initiation of IV study therapy. If the subject has not previously received a loading dose, a loading dose should be provided as described, regardless of the dosage previously administered.

[b] With the exceptions noted in footnote a, the maintenance dose will be administered 12 hours following administration of the loading dose and will be administered every 12 hours thereafter.

5.2.2 Timing of Dose Administration

The dosage of the IV study drugs may be adjusted based on the subject's renal function as shown in Table 11 and Table 12. The frequency of IMI/REL and of IMI administration will be every 6 hours (q6h). Each infusion should be administered within 60 minutes of the scheduled dose.

The frequency of CMS administration (or placebo for CMS) will be every 12 hours (q12h). A loading dose (300 mg CBA [corresponding to ~720 mg CMS or ~9 million IU]) will be administered upon initiation of study therapy, except in certain subjects who have been administered colistin prior to study entry (see Section 5.2.1.1). Twelve (12) hours following the loading dose, the maintenance dose will be initiated and then continued q12h thereafter.

Since IMI-containing therapy will be administered q6h and CMS (or placebo to CMS) will be administered q12h, CMS (or placebo to CMS) will be administered at the same hour of the day as the IMI-containing study therapy (IMI or IMI/REL) at each 12-hour interval. An illustration of the dosing scheme for each treatment group is provided in Figure 2.

IMI/REL (Treatment Group 1 or Treatment Group 3), IMI (Treatment Group 2) and CMS (Treatment Group 2) should be administered over 30 ± 5 minutes. The study therapy must NOT be administered simultaneously through the same infusion line/lumen with any other drugs (including other IV study or 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. In instances when IMI/REL or IMI require administration at the same hour of the day as the CMS (or placebo to CMS), the 2 infusions should be administered either 1) sequentially with the IMI-containing infusion first followed by an appropriate volume of saline flush prior to administration of the CMS/placebo OR, 2) via a separate infusion line at the same time as the CMS/placebo.

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

Hour	Treatment Group 1 /3[a] IMI/REL[b] (q6h) + Placebo for CMS (q12h)		Treatment Group 2 CMS[c] (q12h) + IMI[b] (q6h)	
0	IMI/REL	Placebo to CMS	CMS	IMI
2				
4				
6	IMI/REL			IMI
8				
10				
12	IMI/REL	Placebo to CMS	CMS	IMI
14				
16				
18	IMI/REL			IMI
20				
22				
24	IMI/REL	Placebo to CMS	CMS	IMI
26				
28				
30	IMI/REL			IMI
32				
34				
36	IMI/REL	Placebo to CMS	CMS	IMI
38				
40				
42	IMI/REL			IMI
44				
46				
48	IMI/REL	Placebo to CMS	CMS	IMI

IMI/REL = impenem/cilastatin/relebactam; IMI = Imipenem/cilastatin; CMS = colistimethate sodium

[a] Subjects in Treatment Group 3 will receive IMI/REL only (no placebo) since therapy will be provided open-label.

[b] The dosage of IMI/REL or IMI may be adjusted based on renal sufficiency according to Table 11.

[c] The dosage of CMS may be adjusted based on renal sufficiency according to Table 12.

Figure 2 Dosing Scheme for Study Therapies

5.2.3 Trial Blinding/Masking

Treatment Groups 1 and 2

A double-blind/masking technique will be used for randomized subjects (Treatment Group 1 and Treatment Group 2). IMI/REL, IMI, CMS, and placebo to CMS will be dispensed in a blinded fashion to these subjects. All study therapy supplies will be provided in an open-label fashion to the sites. Since randomized subjects (Treatment Group 1 and Treatment Group 2) will be provided study therapy in a blinded fashion, an Unblinded Study Pharmacist (or qualified designee) at the study site will be responsible for preparing all of the IV study therapy for this study; this individual(s) will not be involved in any safety or efficacy evaluations of the study participants. Due to a slight difference in the appearance of CMS solution for infusion and the placebo infusion, the infusion bags will be covered in an opaque sleeve by an Unblinded Study Pharmacist (or qualified designee) to ensure that other study personnel and all subjects remain blinded to clinical material assignment. The intravenous

line (through which the infusion is administered) does not require opaque covering as the differences between the clinical materials are not visually distinguishable within the tubing.

Once each infusion is properly prepared and masked with an opaque sleeve, the study therapy will be administered by qualified trial site personnel. The personnel involved in the administration of the study infusion treatment should be unaware of the treatment group assignments. Similarly, the subject, the investigator, and Sponsor personnel or delegate(s) who are involved in the clinical evaluation of the subject should also remain unaware of the treatment group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

Treatment Group 3

Subjects who are enrolled to receive IMI/REL in Treatment Group 3 will do so in an open-label fashion.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 randomized treatment arms. Subjects will be assigned randomly in a 2:1 ratio to IMI/REL + placebo to CMS (Treatment Group 1; N=~36) or CMS + IMI (Treatment Group 2; N=~18), respectively. Subjects enrolled into the open-label arm (Treatment Group 3) will be provided with IMI/REL through IVRS/IWRS as well.

5.4 Stratification

Randomization will be stratified according to the following infection types:

1. HABP/VABP
2. cIAI
3. cUTI

Subjects diagnosed with more than one of the infection types listed above can be enrolled into the study as long one of the infections listed above is identified as the primary site. Both the primary site of infection as well as any secondary infection sites will be documented on the relevant eCRF(s). Stratification will be determined based on a hierarchy of the 3 specified infection types. Specifically, subjects with multiple sites of infection, regardless of the primary site, will be stratified in order of priority (based on the presence of any of the 3 infection types) into the HABP/VABP stratum first, followed by the cIAI stratum, and finally the cUTI stratum.

Given the potential differences in severity of the various infection types, enrollment of an excess number of subjects in a stratum with less severe disease could have significant impact on the ability to evaluate the efficacy endpoints. For this reason, randomization will be stratified by infection type. Approximately 18 subjects will be enrolled into each of the 3 strata. Once 18 subjects have been enrolled into an individual stratum, this stratum may be considered fully enrolled but enrollment into that stratum may remain open at the discretion of the Sponsor until the other strata have reached full capacity. Hierarchical stratification of

subjects with multiple infection sites will continue regardless of status of enrollment in each stratum.

A total of 15 mMITT subjects are required per infection site (45 total across the 3 strata). At the discretion of the Sponsor, enrollment may be stopped prior to reaching 54 total subjects if a sufficient number of mMITT subjects have been obtained. Enrollment may also be extended beyond 54 subjects at the discretion of the Sponsor for the following reasons: 1) if additional subjects beyond 54 are required to obtain the target number of mMITT subjects; or 2) if enrollment in any individual stratum has not been completed, while other strata remain open (even after a sufficient number of mMITT subjects have been obtained in those strata), until all 3 strata have reached full capacity (i.e., 15 mMITT evaluable subjects each).

The primary site of infection as well as any secondary infection sites will be documented on the relevant eCRF(s) for subjects enrolled into Treatment Group 3 as well. Since Treatment Group 3 will not be randomized, stratification variables will not be used for this group and no limits will be placed on the number of subjects per infection site. Enrollment in Treatment Group 3 will be ongoing until enrollment is completed in the randomized cohort.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Listed below are some specific restrictions for concomitant therapy or vaccination during the course of the trial. If there is a clinical indication for one of these or other medications or vaccinations 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.

NOTE: With the exception of >24 hours of colistin for subjects in Treatment Groups 1 and 2 (see Section 5.1.3.1, Criterion #4) there are no restrictions to prior antimicrobial therapy.

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

1. Valproic acid/divalproex sodium

2. Non-study IV, oral, or inhaled antibacterial treatments with known coverage of Gram-negative bacteria of interest (i.e., Enterobacteriaceae, *Pseudomonas* spp. and Gram-negative anaerobic bacilli).

   Importantly, the following antibacterial medications are permitted:

   a. IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected MRSA infection. If added, IV vancomycin, daptomycin, or linezolid should be used according to the investigator's usual practice. Daptomycin is not indicated for the treatment of HABP/VABP.

b. IV linezolid or IV daptomycin to treat confirmed or suspected VRE infection. If added, linezolid or daptomycin should be used according to the investigator's usual practice. Daptomycin should not be used to treat HABP/VABP.

c. TMP/SMX or other standard-of-care agent for prophylaxis of opportunistic infection (e.g., *P. jiroveci* infection) in immunocompromised subjects.

3. Use of systemic antifungal therapy for disseminated fungal infection, fungemia, or for pulmonary infection in HABP/VABP subjects.

   Antifungal medications are permitted in the following clinical situations:

   a. Antifungal medications for treatment of mucocutaneous infection (e.g., vaginal candidiasis, onychomycosis).

   b. Antifungal medications for prophylaxis of invasive fungal infections, such as in immunocompromised patients.

   c. Antifungal medications for treatment of fungal pathogens isolated in polymicrobial cIAI, if treatment of isolated fungal pathogens is required.

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

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from IV study therapy but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Discontinuation from IV study therapy is permanent. Once a subject has discontinued IV study therapy, even though he/she continues to be monitored in the trial, he/she shall not be allowed to begin IV study therapy again.

A subject must be discontinued from the trial for any of the following reasons:

1. The subject or legal representative (such as a parent or legal guardian) withdraws consent.

2. The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

A subject must be discontinued from IV study therapy (but should continue to be monitored in the trial) for any of the following reasons:

1. 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 body temperature ≥38.0°C [≥100.4°F]), 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 [with at least 50% increase from transaminase values collected at randomization (Day 1)] that is not anticipated from their underlying medical condition.
   - ALT or AST ≥3 X ULN and new onset of clinical signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (defined as body temperature ≥38.0°C [≥100.4°F]), 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 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.

2. A post-baseline decline in estimated or actual creatinine clearance to a value of less than 15 mL/min.
3. The subject requires initiation of hemodialysis or peritoneal dialysis.
4. The subject has a confirmed positive serum or urine (sensitivity of < 25 million IU/L is required if using urine test) pregnancy test.
5. 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.
6. A new imipenem-resistant Gram-negative bacterium is isolated from an infection site during study therapy and is not susceptible to IMI/REL and colistin.

   NOTE: Since subjects enrolled into Treatment Group 3 are required to have a colistin-resistant infection at randomization, development of a new colistin-resistant infection would not require discontinuation.

5.9 Subject Replacement Strategy

A subject who discontinues from the 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, discontinues 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 Title:	**Visit 1 Screening**	**Visit 2 Randomization /Initiation of Therapy**	**Visit 3 On Therapy (OTX)**	**Visit 4 End of Therapy (EOT)**	**Visit 5 Early Follow-Up (EFU)**	**Visit 6 Day 28[a]**	**Visit 7 Safety Follow-Up Visit (Optional[b])**
Scheduled Day	≤24 hours pre-randomization	Day 1	Day 3	Day 5/7 to Day 21[c]	5 to 9 days following EOT	Day 28 post-randomization	14 days following EOT
Scheduling Window	≤24 hours pre-randomization	N/A	N/A	≤24 hours after last dose of study therapy	+ 2 days	+3 days	+ 2 days
Administrative Procedures							
Informed Consent	X						
Informed Consent for Future Biomedical Research (optional)	X						
Inclusion/Exclusion Criteria	X						
Subject Identification Card	X						
Medical History, including full assessment of details of infection site diagnoses[d]	X						
Prior or Concomitant Medication Review	X	X	X	X	X	X	X
Treatment Allocation/Randomization & Stratification		X					
IVRS Contact[e]	X	← Daily →		X	X	X	X
Administration of IV Study Therapy		← Daily →					
Clinical Procedures/Assessments							
APACHE II Score	X						
Full Physical Examination		X					
Directed Physical Examination			X	X	X	X	X
Vital Signs (heart rate, blood pressure, respiratory rate, oral/tympanic temperature)[f]		← Daily during IV therapy →		X	X	X	X
Height		X					
Weight[g]		X	X				
Adverse Events Monitoring[h]	X	← Daily during IV therapy →		X	X	X	X
Local infusion tolerability monitoring[h]		← Daily during IV therapy →		X			
Review of clinical signs and symptoms of infection (including both primary and secondary infections)[i]		← Daily during IV therapy →		X	X	X	
Chest x-ray (HABP/VABP only)		X[j]		X			
PaO_2/FiO_2 Ratio and O_2 Saturation (HABP/VABP only)[k]		← Daily during IV therapy →		X	X	X	

Trial Period:	Screening	IV Study Therapy			Post-Therapy		
Visit Title:	Visit 1 Screening	Visit 2 Randomization /Initiation of Therapy	Visit 3 On Therapy (OTX)	Visit 4 End of Therapy (EOT)	Visit 5 Early Follow-Up (EFU)	Visit 6 Day 28[a]	Visit 7 Safety Follow-Up Visit (Optional[b])
Scheduled Day	≤24 hours pre-randomization	Day 1	Day 3	Day 5/7 to Day 21[c]	5 to 9 days following EOT	Day 28 post-randomization	14 days following EOT
Scheduling Window	≤24 hours pre-randomization	N/A	N/A	≤24 hours after last dose of study therapy	+ 2 days	+3 days	+ 2 days
Infection source control review[l]		X	X	X			
Laboratory Procedures/Assessments							
Blood for hematology[m]		X	X	X	X	X	X
Blood for chemistry[m]		X	X	X	X	X	X
Urine for urinalysis[m, n]		X		X			
β-Human Chorionic Gonadotropin (β-hCG), in women of reproductive potential only[o]	X					X	
Blood for Future Biomedical Research (optional)[p]		X					
IMI, IMI/REL and colistin susceptibility[q]	X						
Infection Site Specimen for Culture and Susceptibility							
HABP/VABP, cIAI[r]		X[s]	X[s]	X[s]	X[s]		
cUTI[t]		X[u]	X	X	X		
Blood Specimen for Culture and Susceptibility[v]		X	As clinically indicated or, if prestudy blood culture was positive, repeat daily until negative on 2 consecutive cultures				
Population Pharmacokinetics Analysis							
Whole blood to collect plasma for REL, IMI, and CIL assay[w]	X	X					
Efficacy Evaluation							
Clinical Response Assessment[x]			X	X	X	X	
Microbiological Response Rating[y]			X	X	X		
Survival Assessment						X	

PaO_2 = partial pressure of oxygen in arterial blood; FiO_2 = Fraction of inspired oxygen

[a] The Day 28 post-randomization visit may be combined with the EFU visit as long as compliance with the visit windows is maintained for both visits. Specifically, if a subject receives 17– 21 days of IV study therapy, the EFU visit may potentially be combined with the Day 28 visit. For example, if 17 days of IV therapy are provided, the EFU visit could be scheduled 11 days (9+2) following completion of therapy which would be 28 days (17 days of IV therapy +11 days of follow-up) following randomization. It is required that for any case, the allowable visit window ranges are maintained and all procedures required for each visit must be completed for the combined visit.

[b] This visit is required if the Day 28 (+3 day-window) post-randomization visit occurs prior to 14 days following EOT (i.e., to obtain a full 14 days of safety follow-up following EOT, subjects who receive ≥18 days of therapy would require this safety follow-up visit since 18 + 14 would be outside of the window for the Day 28 visit).

[c] IV study therapy should be administered for a minimum of 5 full days for subjects with cIAI and cUTI or 7 full days with HABP/VABP. The total duration of IV study therapy should not exceed 21 days, unless a longer duration is approved by the Sponsor. See Section 7.1.2.1 for further details

[d] The details of any primary or secondary infection-site diagnoses (HABP/VABP, cIAI and/or cUTI) will be documented separately on the appropriate eCRF(s). Details should include the diagnosis and an additional diagnostic details associated with the infection site (e.g., characterization of the complicated nature of the cIAI and/or cUTI).

[e] For the purpose of monitoring renal function during IV treatment, the most recently collected creatinine clearance should also be reported to IVRS daily to support dosage determination. (refer to Table 11 and Table 12 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.

[f] Vital signs should be performed and documented on the appropriate electronic case report forms (eCRFs) at the randomization visit (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.

[g] Enter weight if a clinically significant weight change occurred and resulted in a change in CrCl category.

[h] 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 possibly, probably or definitely 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.

[i] Clinical signs and symptoms, radiographic (daily reporting not required for radiographic findings) and laboratory characteristics associated with the primary bacterial infection and any secondary bacterial infection sites (see Table 13) will be reviewed and documented on the appropriate electronic case report forms (eCRFs) daily during IV study therapy and at the additional visits specified.

[j] A chest x-ray should only be performed in subjects with an infection site of HABP/VABP if a prior chest x-ray or chest CT has not been performed in association with the current infection within 3 days of randomization. Relevant radiographic findings should be recorded on the appropriate eCRF(s).

[k] For subjects with an infection site of HABP/VABP, FiO_2, PaO_2 (measured via ABG in ventilated subjects who have existing arterial access or planned arterial blood collection) and O_2 saturation via pulse oximetry, must be collected on Day 1 prior to initiation of IV study therapy. For the treatment period between Day 2 and EOT, daily collection of all 3 measurements is preferred; however, if PaO_2 is not available (for example, because arterial blood gas is not clinically indicated) then FiO_2 and O_2 saturation should be documented. These tests should also be performed at EOT, EFU, and Day 28 post-randomization visit. All measured values should be documented on the appropriate electronic case report forms (eCRF).

[l] 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. VABP: information regarding extubation or replacement of the endotracheal tube. 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.

[m] Blood for laboratory safety tests (hematology and chemistry) should be collected for submission to the central safety laboratory at the randomization visit (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 EFU, Day 28 as well as the Safety Follow-up visit (if this visit required). Urine for urinalysis should be collected for submission to the central safety laboratory at the randomization visit (Day 1) prior to administration of the first dose of study therapy and at EOT.

[n] The urinalysis should be performed on mid-stream clean catch urine or catheter urine specimen, if possible.

[o] 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 the Day 28 visit should be a serum β-HCG.

[p] Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on enrolled subjects only, or at a later date as soon as the informed consent is obtained.

[q] Susceptibility to IMI, IMI/REL and to colistin of the previously-isolated (from primary infection site sample collected within 1 week [see Section 4.1.2.1 and 4.1.2.2, inclusion criteria #3 and #4] prior to entry) suspected causative bacterial pathogen(s) must be determined prior to randomization by the local laboratory using susceptibility

panels provided by the Sponsor.

[r] Obtain sample for culture and susceptibility testing from infection site prior to initiation of IV study therapy for all subjects with HABP/VABP and/or cIAI. Collection of a baseline sample from the infection site is strongly preferred; 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 at the time of study entry is not required. In these cases, an isolate of the suspected causative bacterial pathogen must have been collected within 1 week (see Section 5.1.2.1 and 5.1.2.2, inclusion criteria #3 and #4) of study entry and must be available for submission to the Central Microbiology Reference Laboratory; relevant data for the prior culture must be collected as well. 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, colony count and susceptibility results must be collected on the appropriate eCRF.

[s] Culture from the infection site (HABP/VABP, cIAI), including susceptibility testing of any identified pathogens on culture, should also be performed and collected on the appropriate eCRF at any time that there is clinical or laboratory evidence of persistence or progression of the infectious process (including persistent fever, elevated white blood cell count, or significant changes in the subject's clinical condition) and at the time of any surgical or drainage procedure (if required). Bacterial isolates will be stored for future research.

[t] 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.

[u] Urine samples must be collected prior to initiation of IV study therapy.

[v] 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 daily until 2 consecutive cultures demonstrate 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.

[w] 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 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. 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.

[x] 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 13.

[y] A by-pathogen and overall microbiological response will be determined by the Sponsor based on culture data reported on the appropriate eCRFs in subjects with cUTI only.

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 must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research.

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/ERC 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 after the subject provides written informed consent.

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 resistant 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 any primary and secondary infection-site diagnoses (HABP/VABP, cIAI and/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 and record all 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 randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Randomization Number

All subjects eligible for enrollment into the randomized treatment arms (Treatment Groups 1 and 2) will be randomly allocated and will receive a randomization number. Randomization will be stratified by infection site (see Section 5.4 for details). The randomization number identifies the subject for all procedures occurring after randomization.

All subjects eligible for enrollment into the non-randomized, open-label arm (Treatment Group 3) will be allocated, by non-random assignment, and will receive an allocation number. The allocation number identifies the subject for all procedures occurring after treatment allocation.

Once a 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 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 from Day 6 to end of therapy require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be performed by the blinded investigator and/or blinded trial staff.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Study Drug Administration

All study drugs will be reconstituted and administered in separate infusion bags according to a separate Pharmacy Manual. Dosing regimens for IMI/REL (Treatment Group 1 or Treatment Group 3), IMI (Treatment Group 2), CMS (Treatment Group 2) and placebo for CMS (Treatment Group 2) are described in Section 5.2.1.1 and Section 5.2.2. The dosing scheme is illustrated in Section 5.2.2, Figure 2 and the specific dosage for administration for each study therapy is provided in Section 5.2.1.1, Table 11 and Table 12.

An Unblinded Study Pharmacist (or qualified designee) at the study site will be responsible to prepare the IV study therapy for this study; this individual(s) will not be involved in any of the safety and efficacy evaluations of the study participants. Due to this slight difference in appearance between CMS and placebo for CMS, the infusion bags will be covered in an opaque sleeve by the Unblinded Pharmacist (or qualified designee) to ensure that other study personnel and all patients remain blinded to clinical material assignment.

All infusions should be administered over 30 ± 5 minutes. The study therapy must NOT be administered simultaneously through the same infusion line/lumen with any other drugs (including other IV study or 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. In instances when IMI/REL or IMI require administration at the same hour of the day as the CMS (or placebo to CMS), the 2 infusions should be administered either 1) sequentially with the IMI-containing infusion first followed by an

appropriate volume of saline flush prior to administration of the CMS/placebo OR, 2) via a separate infusion line at the same time as the CMS/placebo.

Further details on the preparation, storage and administration of all intravenous study antibiotics and matching placebo by the Unblinded Study Pharmacist (or qualified designee) are provided in a separate Pharmacy Binder.

IV study therapy should be administered for a minimum of 5 full days for subjects with cIAI or cUTI or 7 full days for subjects with HABP/VABP. This translates to either 20 (cIAI, cUTI) or 28 (HABP/VABP) dose of IMI-containing therapy based on the q6h dosing regimen. This also translates to either 10 (cIAI, cUTI) or 14 (HABP/VABP) doses of CMS/placebo to CMS (including a loading dose). The total duration of IV study therapy should not exceed 21 days. Duration of study therapy longer than 21 days must be approved by the Sponsor.

7.1.2.2 APACHE II Score

Severity of illness in this study will be determined by APACHE II score [77]. See Appendix 12.6 for details regarding the calculation of this score. Results of APACHE II score calculations must be entered on the appropriate eCRF(s).

7.1.2.3 Full and Directed Physical Examinations

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

A complete 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 directed 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).

7.1.2.4 Vital Signs

Vital signs should include heart rate (HR), blood pressure (BP), respiratory rate (RR), and oral temperature. For those subjects who are intubated and cannot sit up, HR, BP, and RR will be taken in a supine or semi-recumbent position. Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary methods are acceptable.

Subjects should be resting in a seated or semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained.

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

7.1.2.5 Height and Weight

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

7.1.2.6 Adverse Event Monitoring

Clinical adverse events will be collected from the time of initiation of the first dose of IV study therapy through 14 days following completion of all IV study therapy. 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 adverse events should be documented on the appropriate eCRF.

Laboratory adverse experiences will be based on safety laboratory tests (both central and local results), including hematology and chemistry tests from blood and urinalysis from urine. Please refer to Section 7.1.3 and 6.0 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.

7.1.2.7 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 and any secondary 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 13) 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 13 Infection-Site Specific Clinical Signs and Symptoms

Infection Site	Clinical Signs and Symptoms[a]
HABP/VABP	New onset or worsening of cough, dyspnea, tachypnea (e.g., respiratory rate greater than 25 breaths per minute), expectorated sputum production, requirement for mechanical ventilation, hypoxemia, need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (via ABG or PaO_2/FiO_2 assessment), needed changes in the amount of positive end-expiratory pressure, new onset of suctioned respiratory secretions, chills/rigors, chest pain and body temperature changes (fever or hypothermia)
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 Appendix 12.5 for relevant abnormalities for each infection site).

7.1.2.7.1 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 VABP, information regarding extubation or replacement of the endotracheal tube 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.

7.1.2.7.2 Chest X-Ray (HABP/VABP only)

A chest x-ray should only be performed in subjects with an infection site of HABP/VABP. For randomization, a chest x-ray is not required if a prior chest x-ray or chest CT has been performed in association with the current infection within 3 days of randomization. All subjects must have a chest x-ray at the end of study therapy.

Chest x-ray results (or prior chest CT results, if relevant) including a description, location, and extent of infiltrates or consolidation must be documented on the appropriate eCRF(s). The presence of a pleural effusion and other abnormalities should also be noted.

7.1.2.7.3 PaO_2/FiO_2 Ratio and O_2 (HABP/VABP only)

PaO_2, FiO_2 and O_2 saturation will only be collected for subjects with an infection site of HABP/VABP. PaO_2, (measured by arterial blood gas in ventilated subjects who have an existing arterial access or planned arterial blood collection), FiO_2, and O_2 saturation (measured by pulse oximetry) must be collected on Day 1 prior to initiation of IV study therapy. For the treatment period between Day 2 and EOT, daily collection of all 3 measurements is preferred; however, if PaO_2 is not available (for example, because arterial blood gas is not clinically indicated) then at minimum FiO_2 and O_2 saturation should be documented. These tests should also be performed at the additional visits specified in Section 6.0 (Trial Flow Chart).

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 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 14.

Table 14 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)	Microscopic exam, if abnormal results are noted	
	Bicarbonate		
	Calcium		
	Chloride		
	Creatinine		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		

Hematology	Chemistry	Urinalysis	Other
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

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.

7.1.3.2 Culture and Susceptibility Testing

Culture (aerobic for all infection-site specimens and anaerobic for cIAI specimens) and *in vitro* susceptibility testing of infection site specimens collected within 1 week prior to study entry as well as specimens collected at the study-specified time points (see Section 6.0, Trial Flow Chart) will be performed. The local laboratory for each site will be provided with panels to determine *in vitro* susceptibility for IMI, IMI/REL and colistin according to procedures specified by the Sponsor in a separate laboratory manual. Other susceptibility testing for medical management should be performed by the site's local laboratory per each laboratory's standard procedures. In addition to local laboratory testing, all Gram-negative pathogens obtained from infection-site specimens collected from randomized subjects will be retained by the local clinical microbiology laboratory and sent to the central microbiology reference laboratory. 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

In order to be considered eligible for participation in PN013, identification and *in vitro* susceptibility of infection-site pathogens from samples collected within 1 week prior to study entry must be determined. Specifically, for randomized as well as open-label, nonrandomized subjects, the culture-associated criteria (Inclusion Criterion #3) described in Section 5.1.2.1 and 5.1.2.2, respectively, must be confirmed. In order to avoid potential delay in receipt of effective therapy for study subjects, the local laboratory for each site will be provided with panels to determine *in vitro* susceptibility (to IMI, IMI/REL and colistin) of Gram-negative bacterial isolates obtained from specimen types of interest as part of routine standard-of-care testing at the institution. Local laboratories will include the Sponsor-provided susceptibility panels in parallel with routine, first-line susceptibility testing of specified Gram-negative bacterial isolates scheduled for *in vitro* susceptibility testing per routine standard-of-care by the site's local laboratory (a separate microbiology laboratory manual will be provided for the Sponsor panels). Since subjects cannot be randomized until supportive culture and *in-vitro* susceptibility data are confirmed, information obtained from this routine testing will allow for rapid eligibility evaluation. In this way, subjects can be randomized without delay incurred due to specimen collection and subsequent culture and susceptibility testing. This will also allow for enrollment of subjects who may not otherwise be eligible as a consequence of inability to collect baseline cultures (e.g., cIAI in whom prior sample was obtained perioperatively).

Once a subject is randomized into the study and consent is obtained, all Gram-negative pathogen(s) isolated from the specimen obtained for pre-screening must be submitted to the central microbiology laboratory. Culture and susceptibility data associated with pre-screening will also be recorded on the appropriate eCRFs. Bacterial isolates and related data will not be provided to the Sponsor unless consent is obtained from the study subject at the time of entry.

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

7.1.3.2.2 On-Study Infection-Site Specimens

Infection-site specimens for culture and *in vitro* susceptibility testing should be obtained according to Section 6.0 (Trial Flow Chart). 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. Further blood cultures are required in the event of a positive result.

For subjects with HABP/VABP or cIAI, collection of a baseline sample from the infection site is strongly preferred; however, for subjects in which infection site specimen collection is not medically acceptable, as discussed in Section 7.1.3.2.1, collection at the time of study entry is not required. Additional unscheduled cultures from the infection site (HABP/VABP or cIAI), including susceptibility testing of any identified pathogens on culture, should also be performed using the panels provided by the Sponsor at any time that there is clinical or laboratory evidence of persistence or progression of the infectious process (including persistent fever, elevated white blood cell count, or significant changes in the subject's clinical condition) and at the time of any surgical or drainage procedure (if required). All

Gram-negative isolates collected from any unscheduled samples should also be provided to the central microbiology laboratory for testing.

For subjects with cUTI, infection-site specimens for culture and *in vitro* susceptibility testing using the panels provided by the Sponsor is required for all visits specified in Section 6.0 (Trial Flow Chart). Relevant culture and susceptibility data from these samples should also be recorded on the appropriate eCRFs.

A depiction of the process flow for collection and testing of study-related microbiology samples (including both samples collected prior and during the study) is shown in Figure 3.

As described in Section 7.1.3.2, the local laboratory for each site will perform *in vitro* susceptibility testing on all protocol-specified infection-site and blood specimens using panels provided by the Sponsor. Results from testing, including microscopy, identification and *in vitro* susceptibility (from Sponsor-provided susceptibility panels only), should be recorded on the appropriate eCRFs for all scheduled and any unscheduled visits. Pure isolates of all Gram-negative pathogens obtained from protocol-specified infection-site specimens must also be sent to the central microbiology laboratory. Any additional local susceptibility testing required for medical management of the subject may be performed at the investigator's discretion per the laboratory's standard procedures.

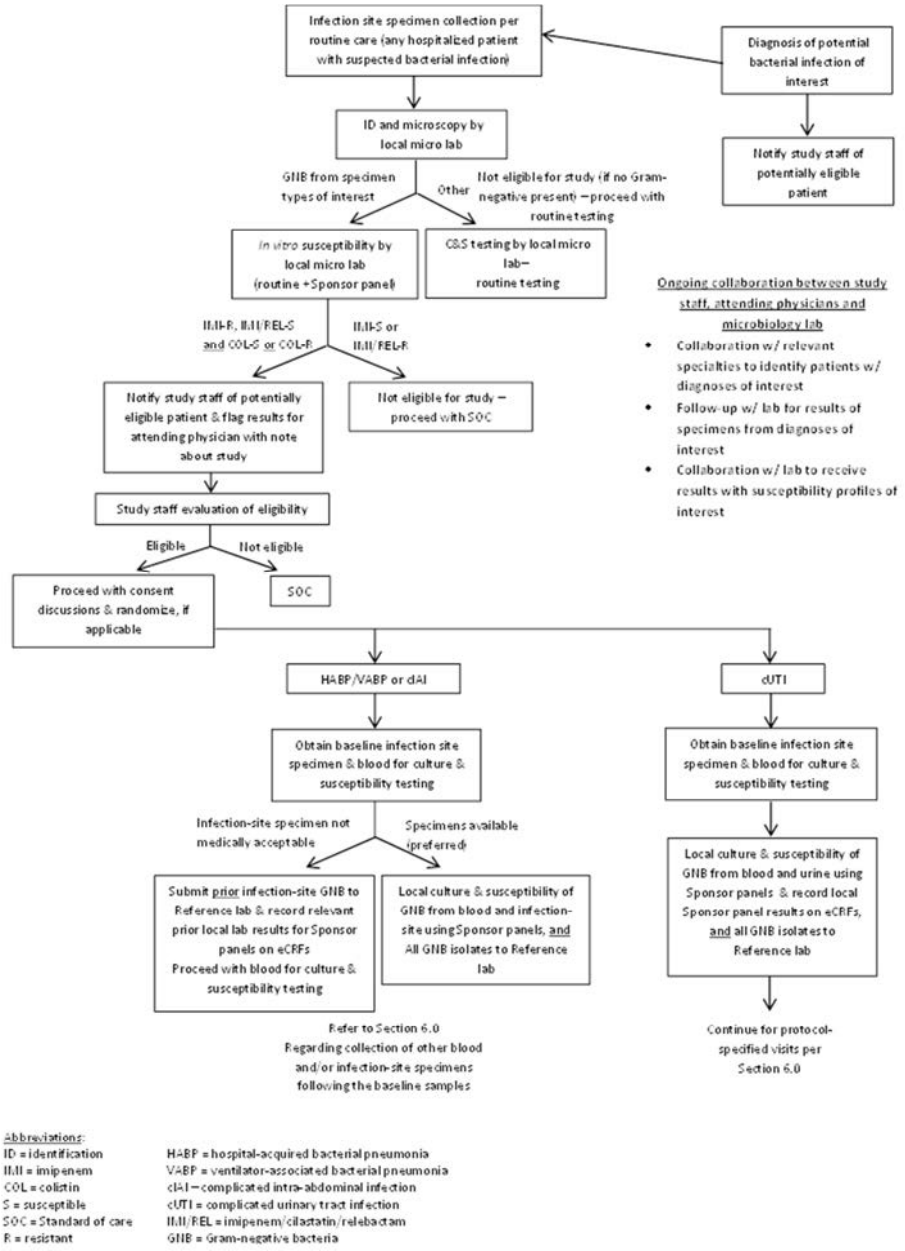


Figure 3 Process Flow for Collection and Testing of Study-Related Microbiology Samples

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

Whole blood to obtain plasma samples will be collected for population PK analysis of REL, imipenem, and CIL concentrations. Please refer to Section 6.0 (Trial Flow Chart) for protocol-specified time points for whole blood sample collection for population PK analyses.

Actual whole blood collection date and time for this sample must be recorded in the eCRFs.

7.1.3.3.1 Blood Collection for Plasma for MK-7655

Sample collection, storage and shipment instructions for PK samples will be provided in a separate laboratory manual.

7.1.3.4 Future Biomedical Research

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

- Blood for genomics use

7.1.3.5 Efficacy Evaluation

7.1.3.5.1 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 4.2.3.1.1.1.2 (Table 3, Table 4, and Table 5). In subjects with multiple infection types, a single clinical response rating will be determined and therefore pre-therapy signs and symptoms of all infections present at baseline must be considered in determining the response. A detailed list of disease-specific signs and symptoms in support of evaluation of the clinical response rating are included in Section 7.1.2.7, Table 13 and Appendix 12.5.

7.1.3.5.2 By-Pathogen Microbiological Response

Microbiological response will be evaluated separately for each baseline pathogen meeting the culture criteria in Section 5.1.2.1 and 5.1.2.2 Inclusion #3 (i.e., by-pathogen) in subjects with cUTI at OTX, EOT and EFU relative to the pathogen(s) isolated at baseline/admission. The by-pathogen microbiological response rating will be determined by the Sponsor 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 as described in Section 4.2.3.1.1.1.3 (Table 6, Table 7, and Table 8). For a bacterial organism to be considered a pathogen at admission, it must be a typical uropathogen (i.e., not a normal colonizer or contaminant).

7.1.3.5.3 Survival Assessment

For each subject, survival status (i.e., whether the subject is alive or dead) at Day 28 post-randomization will be collected. Results of the assessment, including date and cause of death if relevant, will be recorded on the appropriate eCRF.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from IV study therapy prior to completion of the IV study therapy regimen should continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and

Recording Adverse Events. Please refer to Section 5.8 for trial-specific subject discontinuation criteria.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. 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 PPD, and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call-center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

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

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

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 for subjects with cIAI or cUTI or 7 full days for subjects with HABP/VABP. This translates to either 20 (cIAI, cUTI) or 28 (HABP/VABP) dose of IMI-containing therapy based on the q6h dosing regimen. This also translates to either 10 (cIAI, cUTI) or 14 (HABP/VABP) doses of CMS/placebo to CMS. The total duration of IV study therapy should not exceed 21 days. Duration of study therapy longer than 21 days must be approved by the Sponsor.

7.1.5.3 Post-Therapy

An EFU (Day 5 to 9 post-therapy) and a Day 28 post-randomization visit must be completed for each subject. Depending on the total duration of IV study therapy, the EFU and Day 28 post-randomization visit may be combined into a single visit. These visits may only be combined as long as compliance with the protocol-specified visit windows is maintained for both visits. Specifically, if a subject receives 17 to 21 days of IV study therapy, the EFU visit may potentially be combined with the Day 28 visit. For example, if 17 days of IV therapy are provided, the EFU visit could be scheduled 11 days (9+2) following completion of therapy which would be 28 days (17 days of IV therapy +11 days of follow-up) following randomization. It is required that for any case, the allowable visit window ranges are maintained and all procedures required for each visit must be completed for the combined visit. For durations of study therapy longer than 21 days, combining visits should be discussed with the Sponsor.

A Safety Follow-Up Visit (Day 14 post-therapy) is required if the Day 28 (+3 day-window) post-randomization visit occurs prior to 14 days following EOT. In order to obtain a full 14 days of safety follow-up following EOT, subjects who receive ≥18 days of therapy would require this Safety Follow-Up Visit since 18 + 14 would be outside of the window for the Day 28 visit.

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 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 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 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 study therapy is defined as administration of a total daily dose of IMI/REL in excess of 4 g (IMI) + 2 g (REL) OR a total daily dose of IMI in excess of 4 g per day OR a total daily dose of CMS in excess of the protocol-specified doses in Section 5.2.1.1, Table 12.

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 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 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 15 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until 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 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 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 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. post baseline laboratory test values that meet the following criteria: 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.

3. a confirmed (i.e., verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5 × 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 15. The investigator's assessment of causality is required for each adverse event. Refer to Table 15 for instructions in evaluating adverse events.

Table 15 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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 U.S. 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.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analysis

This study will randomize approximately 54 subjects in a 2:1 ratio into 2 treatment groups (Group 1: IMI/REL and Group 2: CMS + IMI) in order to obtain a minimum of 45 subjects (15 per infection type) who meet the criteria for inclusion in the microbiological modified intent-to-treat (mMITT) population.

The mMITT population is defined as all randomized subjects who receive at least one dose of each study drug within a given IV study therapy regimen, and who have a baseline bacterial pathogen meeting inclusion criterion #3; in the case of a polymicrobial infection, at least one pathogen must satisfy the requirements of inclusion criterion #3, and all pathogens identified at the baseline time point must be susceptible to both IMI/REL and colistin. An additional 5 to 10 subjects with imipenem-resistant and colistin-resistant bacterial infection will be enrolled into a third non-randomized, open-label treatment group (Group 3: IMI/REL). The analysis and summarization of the efficacy data will be limited to point estimates and summary statistics such as 95% confidence intervals. No inferential testing between the treatment groups will be performed.

The primary objective of the study is to estimate the proportion of subjects with a favorable overall response within each of the randomized treatment groups (Group 1: IMI/REL and

Group 2: CMS + IMI). This primary estimation will incorporate data from three different subgroups of subjects defined by infection site (HABP/VABP, cIAI, and cUTI). Within each infection type, favorable overall response is defined differently and this information will be pooled to provide an estimate of favorable overall response. In addition, an estimate of favorable response within each of Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) will be provided for each infection type. Favorable overall response will be estimated based on the following: (a) survival status (based upon all-cause mortality) through Day 28 post-randomization in subjects with HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI and (c) the composite clinical and microbiological response at the early follow-up visit, EFU (Day 5 to 9 following completion of therapy) for subjects with cUTI. In addition, the difference between Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) will be estimated along with a 90% confidence interval. The within-group 95% confidence intervals will be calculated using the Agresti & Coull method. The between-group 90% confidence interval will be calculated using the Miettinen and Nurminen method [78].

Key secondary efficacy objectives of the study are to estimate: 1) the proportion of subjects with a favorable clinical response within each of Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) at Day 28 post-randomization, and 2) the incidence of all-cause mortality through Day 28 post-randomization in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI). In addition, the difference between Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) will be estimated along with the 90% confidence interval for these key secondary endpoints.

IV study therapy will be administered for a minimum of either 5 (cIAI and cUTI) or 7 (HABP/VABP) days up to a maximum of 21 days, unless a longer duration is approved by the Sponsor (see Section 7.1.2.1). The duration of therapy will be summarized by treatment group for the overall population as well as by infection site. In addition, the impact of any difference in duration of therapy on the treatment group comparisons will be assessed.

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 16. The mMITT population will serve as the primary population for efficacy analyses in this study.

8.1.2 Safety Analysis

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses. The ASaT population consists of all subjects who received at least one dose of IV study therapy. The ASaT includes non-randomized subjects in Treatment Group 3 (IMI/REL), as well as randomized subjects in Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI).

Any safety analysis that involves a comparison of IMI/REL to CMS + IMI will be based on Treatment Group 1 and Treatment Group 2 (the randomized treatment groups). Safety for Treatment Group 3(the non-randomized treatment group) will be summarized separately using descriptive statistics.

A stated key secondary safety objective of the study is to estimate the proportion of subjects who experience treatment-emergent nephrotoxicity in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI). The incidence of treatment-emergent nephrotoxicity will be compared between Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI).

Table 16 Summary of Analysis Strategy for Primary and Key Secondary Endpoints

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Proportion of subjects with an favorable overall response	95% confidence interval (Agresti & Coull) for single group proportion	mMITT[a]	Missing = Failure
Key Secondary:			
Proportion of subjects with favorable clinical response at Day 28 post randomization	95% confidence interval (Agresti & Coull) for single group proportion	mMITT[a]	Missing = Failure
Proportion of subjects with all-cause mortality at Day 28 post randomization	95% confidence interval (Agresti & Coull) for single group proportion	mMITT[a]	Missing = Failure
Proportion of subjects who experience treatment-emergent nephrotoxicity	95% confidence interval (Agresti & Coull) for single group proportion and Fisher Exact Test	ASaT[a]	Data as Observed

[a] The mMITT population is defined as all randomized subjects who receive at least one dose of each study drug within a given IV study therapy regimen, and who have a baseline bacterial pathogen meeting inclusion criterion #3; in the case of a polymicrobial infection, at least one pathogen must satisfy the requirements of inclusion criterion #3, and all pathogens identified at the baseline time point must be susceptible to both IMI/REL and colistin. The ASaT population consists of all subjects who received at least one dose of IV study therapy.

8.1.3 Power and Sample Size

This study will randomize approximately 54 subjects in a 2:1 ratio into 2 treatment groups (Group 1: IMI/REL and Group 2: CMS + IMI) in order to obtain a minimum of 45 subjects (15 per infection type) who meet the criteria for inclusion in the microbiological modified intent-to-treat (mMITT) population. An additional 5 to 10 subjects with imipenem-resistant and colistin-resistant bacterial infection will be enrolled into a third non-randomized, open-label treatment group (Group 3: IMI/REL). This is an estimation study; no formal statistical testing will be performed for the efficacy endpoints. The sample sizes planned for the study arise from logistic feasibility and are not driven by statistical considerations.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. Certain specific analyses such as PK and the evaluation of PK/PD association will be the responsibility of the appropriate departments of the Sponsor.

Separate functional unblinding for bioanalysis will be conducted in support of PK evaluations. A small team as specified in a separate Modeling and Simulation (M&S) Modeling Analysis Plan, and who are separate from the study team, will be unblinded for the

purpose of preparing the PK analyses. No interim data or results will be shared with the study team before the primary analyses have been completed, and the unblinded group will not be members of the study team. No decisions are made based on this functional unblinding that will influence the conduct of the trial.

This study will be conducted as a double-blind study under in-house blinding procedures (except for Treatment group 3). The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

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

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.2.3.1 Efficacy Endpoints

A full description of the efficacy measures is provided in Section 4.2.3.1. The primary efficacy endpoint is the proportion of subjects with a favorable overall response as assessed for each of the three infection types. Key secondary endpoints are: 1) the proportion of subjects with a favorable clinical response at 28 days following initiation of IV study therapy and 2) the incidence of all-cause mortality within 28 days after initiation of study therapy.

Other secondary endpoints include: 1) the proportion of subjects with a favorable clinical response at the OTX, EOT and EFU timepoints, 2) the proportion of subjects with a favorable microbiological response at the OTX, EOT and EFU timepoints, and 3) the proportion of subjects with favorable overall response for each infection type.

The duration of IV study therapy will be summarized by treatment group for each of the infection types. The proportion of subjects with favorable clinical and microbiological response will be assessed separately for each pathogen identified at baseline as exploratory endpoints.

The proportion of subjects with a favorable clinical response at all endpoint visits and a favorable microbiological response (cUTI) at OTX, EOT and EFU will be summarized for Treatment Group 3 subjects as exploratory efficacy endpoints.

8.2.3.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.2.

The proportion of subjects who experience treatment-emergent nephrotoxicity will be summarized by treatment group. In addition, Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) will be compared with respect to the incidence of treatment-emergent nephrotoxicity.

The rest of the safety analysis will follow a tiered approach and will use only data from the randomized treatment groups: Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters (requires that at least 4 subjects in at least one treatment group exhibit the event) will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

For this protocol, the following are pre-specified events of interest (Tier 1 events).

1. Treatment-emergent nephrotoxicity as defined in Table 9.
2. An elevated AST or ALT laboratory value that is greater than or equal to 3 X ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 X ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 X ULN, as a result of within-protocol-specific testing or unscheduled testing.
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.

The broad clinical and laboratory adverse experience (AE) categories, consisting of the percentage of subjects with any AE, a drug-related AE, a serious AE, an AE which is both drug related and serious, who discontinued IV study therapy due to an AE, and who discontinued IV study therapy due to a drug-related AE, will be considered Tier 2 endpoints. Please refer to Section 8.2.5.2 for further details regarding these safety endpoints and their analyses.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The microbiological modified Intention to Treat (mMITT) population will serve as the primary population for efficacy analyses in this study. The mMITT population is defined as all randomized subjects who receive at least one dose of each study drug within a given IV study therapy regimen, and who have a baseline bacterial pathogen meeting inclusion criterion #3. In the case of a polymicrobial infection, at least one pathogen must satisfy the requirements of inclusion criterion #3, and all pathogens identified at the baseline time point must be susceptible to both IMI/REL and colistin. Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using the mMITT population.

The per-protocol (PP) population will serve as the secondary population for the primary efficacy endpoint (proportion of subjects with a favorable overall response as assessed for each of the three infection types). The PP population is a subset of the mMITT population who also meet the following criteria:

1. Meet important diagnostic criteria for entry into the study,

2. Have no significant deviation from the protocol that could impact the assessment of efficacy, and
3. Receive the minimum duration of IV study therapy as detailed in Section 5.2

The final exclusion criteria and list of patients who will be excluded from the PP population will be documented prior to unblinding.

Details on the approach to handling missing data are provided in Section 8.2.5 (Statistical Methods).

8.2.4.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of IV study therapy. The ASaT includes non-randomized subjects in Treatment Group 3 (IMI/REL), as well as randomized subjects in Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI). Subjects will be included in the therapy group corresponding to the study therapy they actually received for the analysis of safety data using the ASaT population. Subjects who are administered incorrect study therapy for the entire treatment period will be included in the therapy group corresponding to the study therapy actually received.

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.

Since the assessment of treatment-emergent nephrotoxicity requires serum creatinine measurements at baseline and after at least on dose of IV study therapy, subjects who have missing data at either of these time points will be excluded from the summaries/analyses of this endpoint.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 (Statistical Methods).

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

This is an estimation study; no formal statistical testing will be performed for the efficacy endpoints. All of the efficacy endpoints in this study are binary. Within-group 95% confidence intervals for these endpoints will be calculated using the Agresti & Coull method. In addition, between-group 90% confidence intervals for the primary and key secondary endpoints will be calculated using the stratified Miettinen and Nurminen method [78], an unconditional, asymptotic method. The between-group estimates will be stratified by infection type where appropriate.

Missing Values

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

- Subjects discontinuing IV study therapy due to lack of efficacy (e.g., withdrawals with subsequent non-study antibiotic therapy) will be considered as "failures" with respect to clinical response at the time of discontinuation and all subsequent time points.
- Subjects discontinuing IV study therapy due to lack of efficacy will be presumed to have persistence for the microbiological response at the time of discontinuation and all subsequent time points.

8.2.5.2 Statistical Methods for Safety Analyses

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

Any analysis of safety data that involves a comparison of IMI/REL to CMS + IMI will be restricted to Treatment Group 1 and Treatment Group 2 (the randomized treatment groups). Data from Treatment Group 3 will be summarized separately using descriptive statistics.

Due to concern for potential renal toxicity of colistin, Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) will be compared with respect to the proportion of subjects who experience treatment-emergent nephrotoxicity using the two-sided p-value from the Fisher Exact Test.

Other safety parameters will follow a tiered approach (Table 17). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. All other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the (unstratified) Miettinen and Nurminen method [78], an unconditional, asymptotic method (with the exception of treatment-emergent nephrotoxicity as described above).

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

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

Continuous measures such as changes from baseline in laboratory parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. Laboratory values from the Central Laboratory will be used for these analyses when available.

Table 17 Analysis Strategy for Safety Parameters

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

† Adverse Experience references refer to both Clinical and Laboratory AEs.

‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for study/IV 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 treatment using descriptive statistics for continuous or categorical variables, as appropriate.

Population PK Analyses

Based on PK data and PD data obtained within this study, population PK and the relationship between PK and PD will be assessed. The results of these exploratory analyses will be included in a separate report performed by the Sponsor.

8.2.6 Multiplicity

No multiplicity adjustment is necessary as there are no statistical hypothesis tests for this protocol.

8.2.7 Sample Size and Power Calculations

This study will randomize approximately 54 subjects in a 2:1 ratio into 2 treatment groups (Group 1: IMI/REL and Group 2: CMS + IMI) in order to obtain a minimum of 45 subjects (15 per infection type) who meet the criteria for inclusion in the microbiological modified intent-to-treat (mMITT) population. An additional 5 to 10 subjects with imipenem-resistant and colistin-resistant bacterial infection will be enrolled into a third non-randomized, open-label treatment group (Group 3: IMI/REL). This is an estimation study; no formal statistical testing will be performed for the efficacy endpoints. The sample sizes planned for the study arise from logistic feasibility and are not driven by statistical considerations.

Table 18 displays two-sided 95% confidence intervals for the proportion of subjects with a favorable overall response under varying assumptions for the number of successes in Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI). Estimates are provided for:

- N=5 (number of Treatment Group 2 subjects in each infection type),
- N=10 (number of Treatment Group 1 subjects in each infection type),
- N=15 (number of Treatment Group 2 subjects combined over all infection types),
- N=30 (number of Treatment Group 1 subjects combined over all infection types).

NOTE: These intervals are not symmetric around the point estimate.

Table 18 Two-Sided 95% Confidence Intervals for Favorable Overall Response

Number of subjects in population	Observed Number with Favorable overall response	(%)	Two-Sided 95% Confidence Interval[a]
5	2	40.0%	(11.6, 77.1)
	3	60.0%	(22.9, 88.4)
	4	80.0%	(36.0, 98.0)
10	4	40.0%	(16.7, 66.8)
	5	50.0%	(23.7, 76.3)
	6	60.0%	(31.2, 83.3)
	7	70.0%	(39.2, 89.7)
	8	80.0%	(47.9, 95.4)
15	6	40%	(19.8, 64.3)
	9	60%	(35.7, 80.2)
	12	80%	(54.0, 93.7)
30	12	40.0%	(24.6, 57.7)
	15	50.0%	(33.2, 66.8)
	18	60.0%	(42.3, 75.4)
	21	70.0%	(52.0, 83.5)
	24	80.0%	(62.3, 90.9)

[a] 95% confidence intervals calculated with the Agresti & Coull method.

Table 19 displays several possible study outcomes for the comparison of Treatment Group 1 (IMI/REL) to Treatment Group 2 (CMS + IMI) with regard to the difference in the proportion of subjects who experience treatment-emergent nephrotoxicity. This table shows that a difference between the groups of about 3 events favoring Treatment Group 1 (IMI/REL) would be associated with a two-sided p-value that is less than 0.05.

Table 19 Fisher Exact two-sided p-values Comparing Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) – Possible Study Outcomes

		# with Nephrotoxicity in CMS+IMI group (N=15)						
		0	1(6.7%)	2 (13.3%)	3 (20%)	4 (26.7%)	5 (33.3%)	6 (40%)
# with Nephrotoxicity in IMI/REL group (N=30)	0	>0.5	0.333	0.106	0.032	0.009	0.002	<0.001
	1 (3.3%)	>0.5	>0.5	>0.5	0.101	0.036	0.012	0.003
	2 (6.7%)	>0.5	>0.5	>0.5	0.315	0.085	0.032	0.011
	3 (10%)	>0.5	>0.5	>0.5	>0.5	0.199	0.095	0.042

8.2.8 Subgroup Analyses and Effect of Baseline Factors

To assess the consistency of the treatment effect across various subgroups, the proportion of subjects with a favorable overall response (with a nominal 95% confidence interval) within each of the randomized treatment groups (primary endpoint) will be estimated within each category of the following classification variables:

- Infection type (HABP/VABP, cIAI, cUTI)
- Gender (female, male)
- Race (e.g., White, Black, Asian)
- Ethnicity (Hispanic/Latino, non-Hispanic/non-Latino)
- Age (<65 years, ≥65 years)
- Weight (<70 kg, ≥70 kg) at study entry
- APACHE II score at study entry (≤15, >15)

In addition, the difference between Treatment Group 1 (IMI/REL) and Treatment Group 2 (CMS + IMI) will be estimated along with 90% confidence interval when the subgroups are sufficiently large (≥4 subjects in each group).

8.2.9 Interim Analyses

No formal interim analyses are planned for this study.

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.

Table 20 Product Descriptions

Product Name & Potency	Dosage Form
MK-7655A, MK-7655 250 mg (Anhydrous Equivalent), IMIPENEM 500 mg (Anhydrous Equivalent) and CILASTATIN EQUIVALENT 500 mg	Powder for Constitution
IMIPENEM 500 mg (Anhydrous Equivalent) and CILASTATIN EQUIVALENT 500 mg (PRIMAXIN I.V.)	Powder for Reconstitution
Colistimethate Sodium for Injection (Equivalent to 150 mg Colistin)	Lyophilized Powder for I.V. Injection

All other supplies not indicated in Table 20 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

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 blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. IV study therapy identity (name, strength or potency) is included in the label text.

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign IV study therapy to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

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:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 member 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 or through a secure password-protected electronic portal 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/ERC 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 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 discarding 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 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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 by the Sponsor.

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

i. 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.

ii. 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.

iii. 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

15. 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.

16. 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.

17. 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.

18. 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

- **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.

- **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.

- **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 DNA specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

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 Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

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, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first 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 first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. 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 the specific analysis is performed will be

returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox PPD and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction can not 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These

data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results

obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

13. Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
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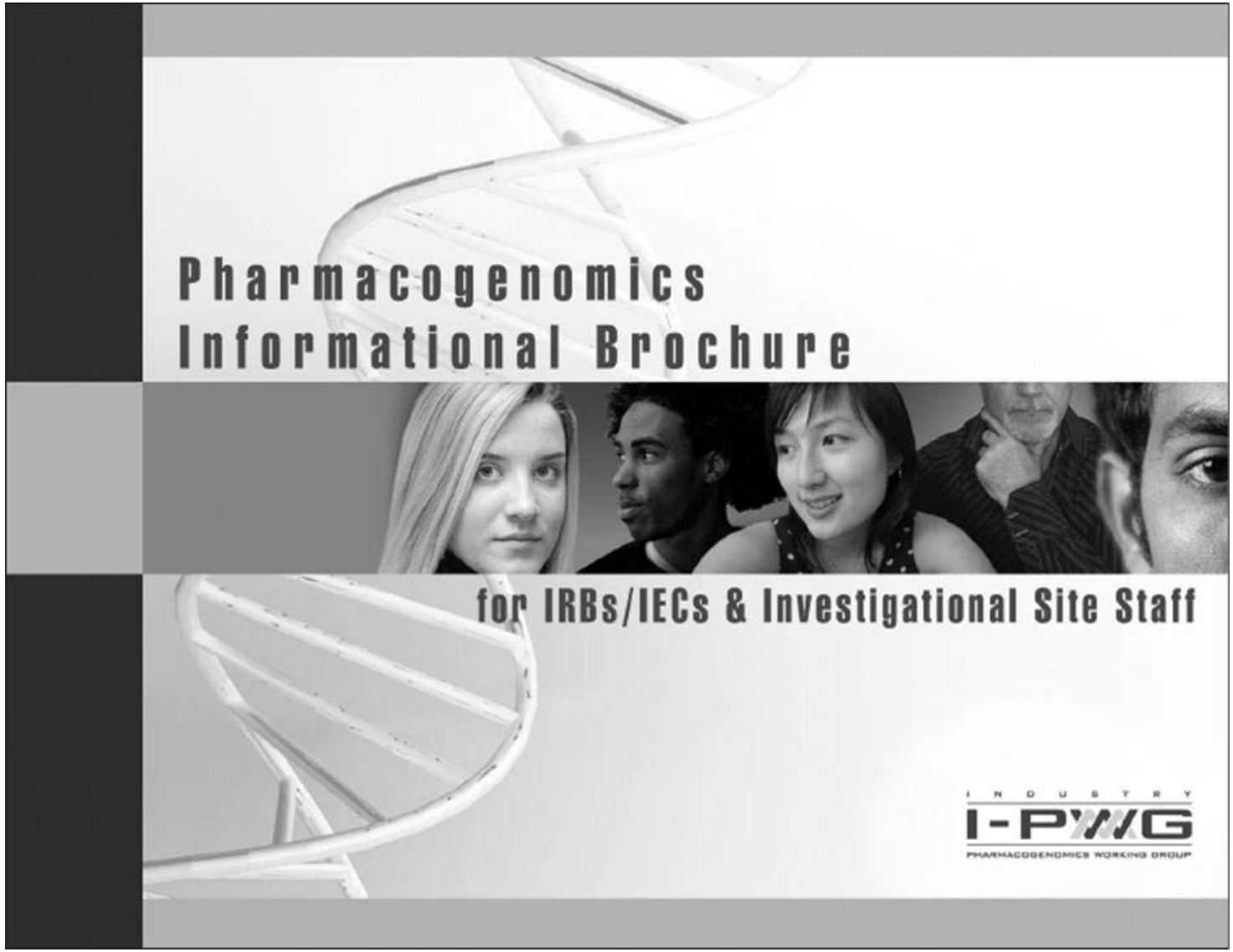
12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



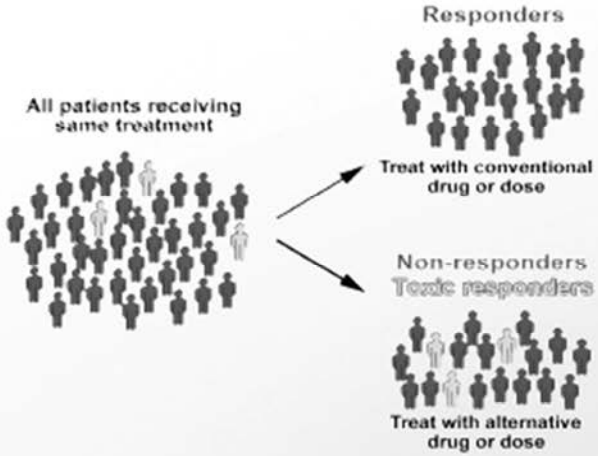
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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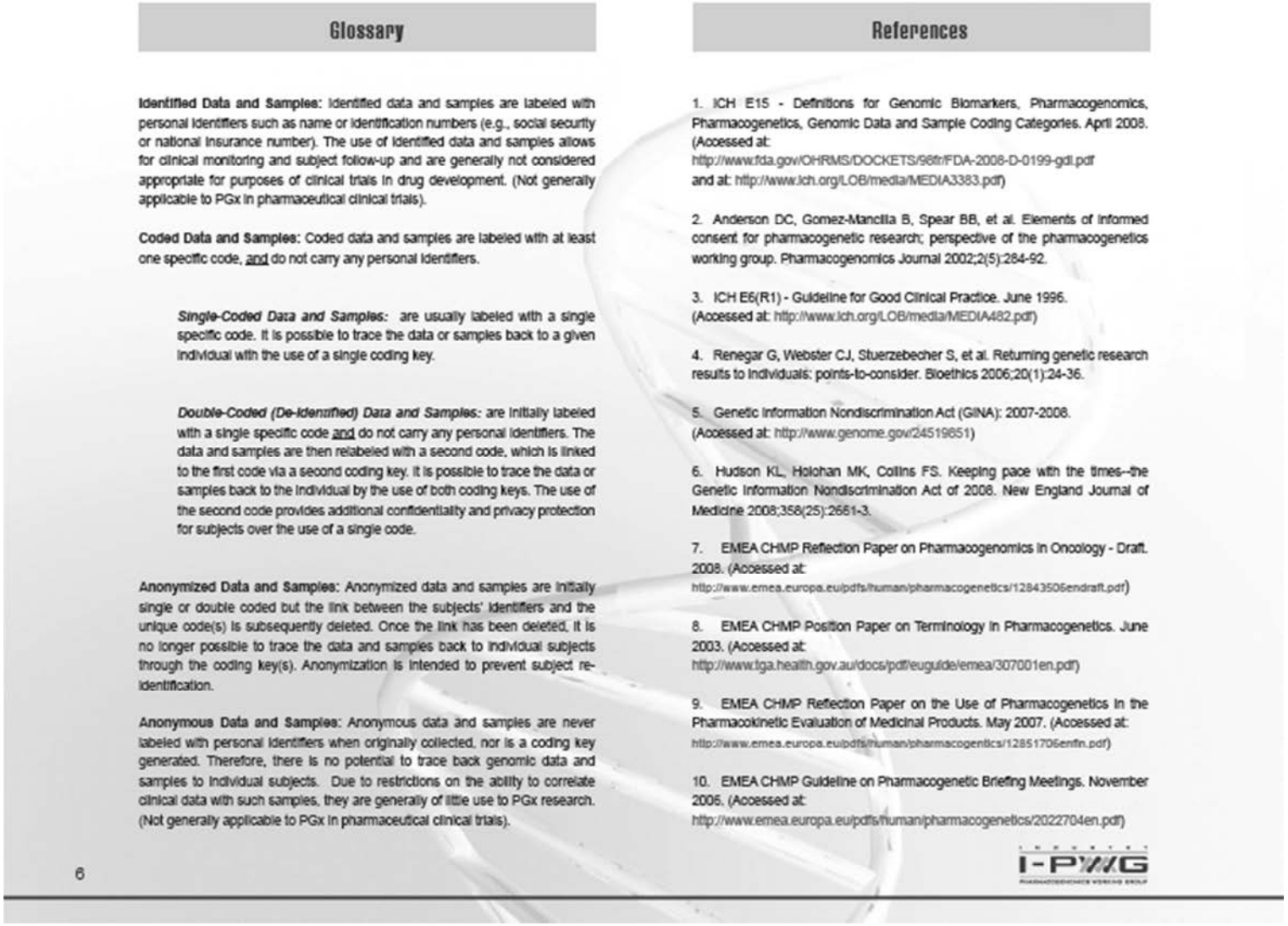

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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References

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6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. New England Journal of Medicine 2008;358(25):2661-3.

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8. EMEA CHMP Position Paper on Terminology in Pharmacogenetics. June 2003. (Accessed at: http://www.tga.health.gov.au/docs/pdf/euguide/emea/307001en.pdf)

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10. EMEA CHMP Guideline on Pharmacogenetic Briefing Meetings. November 2006. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/2022704en.pdf)

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11. EMEA CHMP Reflection Paper on Pharmacogenomic Samples, Testing, and Data Handling. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

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17. FDA Guidance - Pharmacogenomic Data Submissions. March 2005. (Accessed at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf)

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http://www.i-pwg.org

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

Trial Visit	Screening	Treatment			Post-Treatment		
	Screening	Randomization	OTX	EOT	EFU	Day 28	Day 14
Blood Parameter	**Approximate Blood Volume (mL)**						
Hematology		2.0	2.0	2.0	2.0	2.0	2.0
Serum/Plasma Chemistry		5.0	5.0	5.0	5.0	5.0	5.0
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]	5.5					5.5	
Blood for Future Biomedical Research		8.5					
Serum/plasma for PK/PD evaluation	4.0	8.0					
Expected Total (mL)[b,c]	13.0	23.5	7.0	7.0	7.0	5.5	7.0

a. For female subjects of child bearing potential only

b. Additional blood samples may be collected 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. Depending on the results of initial testing, additional blood volumes could range from approximately 8.5 mL up to approximately 92.0 mL and could include HIV and/or hepatitis testing.

c. Blood cultures will be collected in all subjects prior to initiation of IV study therapy. Subjects with positive blood cultures at screening should have follow-up blood cultures collected daily until 2 consecutive blood cultures demonstrate no growth. Depending on the results, 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.

12.5 Disease Definition and Diagnostic Guidelines for Infection Types Targeted for Enrollment in Protocol 013

Diagnostic criteria, including clinical, radiologic (if relevant), and microbiological characteristics, for each infection type of interest for Protocol 013 are outlined within this Appendix. To be considered eligible, a subject must meet the diagnostic criteria within these guidelines for the relevant primary infection site.

In addition to those listed in Table 13, clinical signs and symptoms described for each of the infection types within this document will be monitored by the Primary Investigator (or designee) at baseline and throughout the study to determine resolution, persistence, or progression at each relevant time point described in the protocol.

Contents

I. HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA (HABP/VABP)

A. Definitions

1. Hospital-Acquired Bacterial Pneumonia (HABP)

   HABP is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms accompanied by presence of new or progressive infiltrate on chest radiograph occurring in a subject after being hospitalized for more than 48 hours or within 7 days after discharge from hospital. Of note, such subjects may or may not require mechanical ventilation (ventilated HABP and non-ventilated HABP).

2. Ventilator-Associated Bacterial Pneumonia (VABP)

   VABP is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms accompanied by presence of new or progressive infiltrate on chest radiograph occurring in a subject already receiving mechanical ventilation via an endotracheal tube for a minimum of 48 hours.

B. Diagnostic Guidelines

For a diagnosis of HABP/VABP, supportive radiographic, clinical, and microbiological findings should be present, with onset of criteria occurring after more than 48 hours of hospitalization or within 7 days after discharge from a hospital (for HABP) or at least 48 hours after mechanical ventilation (for VABP):

1. Radiographic

   The chest radiograph should show the presence of a new or progressive infiltrate(s) characteristic of bacterial pneumonia.

2. Clinical

   Subjects should have at least one of the following clinical findings that support a diagnosis of HABP/VABP:

   - New onset or worsening pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (e.g., respiratory rate greater than 25 breaths per minute), expectorated sputum production, or requirement for mechanical ventilation
   - Hypoxemia (e.g., a partial pressure of oxygen less than 60 millimeters of mercury while the patient is breathing room air, as determined by arterial blood gas (ABG) or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2))
   - Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO2/FiO2) or needed changes in the amount of positive end-expiratory pressure
   - New onset of suctioned respiratory secretions

   AND,

   Subjects should have at least one of the following clinical findings:

   - Fever, defined as body temperature greater than or equal to 38.0°C (100.4°F);
   - Hypothermia, defined as core body temperature less than or equal to 35°C (95.2°F);
   - Total peripheral white blood cell (WBC) count greater than or equal to 10,000 cells/cubic millimeter (mm3)
   - Leukopenia with total WBC less than or equal to 4,500 cells/mm3;
   - Greater than 15 percent immature neutrophils (bands) noted on peripheral blood smear

3. Microbiological

   Subjects must have a recognized bacterial pathogen isolated from an appropriate lower respiratory tract specimen.

Microscopic examination of Gram stained smears must have been performed prior to randomization to ensure the adequacy/quality of the specimen. The low-power microscopic view of the Gram stain can be used to ascertain the quality of the respiratory specimen, which helps to ensure that the respiratory specimen sent for culture does not represent oropharyngeal contamination (e.g., fewer than 10 squamous epithelial cells and greater than 25 neutrophils is an example of an adequate expectorated sputum specimen).

II. 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

The subject must have had an operative procedure during which an infection-site culture was obtained within 1 week. Procedures include open laparotomy, laparoscopy, and percutaneous drainage of intra-abdominal abscess.

For a diagnosis of cIAI, supportive clinical and microbiological findings should be present.

1. Clinical

A diagnosis of cIAI should include at least one of the following as evidence of intraperitoneal infection:

- 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
- 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 body temperature greater than or equal to 38.0°C (100.4°F);
- Hypothermia, defined as core body temperature less than or equal to 35°C (95.2°F);
- 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

- White blood cell count elevated beyond the upper limit of the normal laboratory range or the proportion of band forms of the white blood cell differential count beyond the upper limit of the normal laboratory range

2. Microbiological

The subject has recognized pathogens cultured from purulent material from intra-abdominal space obtained during a surgical operation or percutaneous drainage.

III. 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 <u>at least two</u> of the following local or systemic signs and symptoms:

- Local signs and symptoms: Dysuria, urinary frequency, suprapubic or pelvic pain, or urinary urgency
- Systemic signs and symptoms: Fever (defined as body temperature greater than or equal to 38.0°C (100.4°F), chills or rigors (accompanied by fever), nausea or vomiting, flank pain or costovertebral angle (CVA) tenderness on physical examination

<u>AND</u>

- 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/mm3 in unspun urine.

<u>NOTE</u>: 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 must be present:

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

OR,

Subject has pyelonephritis and normal urinary tract anatomy.

3. Microbiological

Subject has a positive urine culture 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, OR
- $\geq 10^2$ CFU/mL of uropathogen from a straight catheter specimen

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.

12.6 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) 4 - spontaneously 3 - to verbal command 2 - to painful stimul 1 - no response	Motor response (M) 6 - to verbal command 5 - localizes to pain 4 - withdraws to pain 3 - decorticate 2 - decerebrate 1 - no response	Verbal - Response (V) 5-oriented and controversed 4-confused and disoriented 3-inappropriate words 2-incomprehensible sounds 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=_____		

12.7 List of Abbreviations

Abbreviation	Definition
AC	alveolar cells
AE	adverse event
ALT	alanine aminotransferase
APACHE	acute physiology and chronic health evaluation
ASaT	All-Subjects-asreated
$AUC_{0-\infty}$	area under the concentration time curve
AST	Aspartate aminotransferase
β-hCG	β-Human Chorionic Gonadotropin
BLI	β-lactamase inhibitor
CBA	colistin base activity
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
EFU	early follow-up
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
IU	international units
IV	intravenous (parental)
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	multi-drug resistant
ME	microbiologically-evaluable
mg	milligram
mMITT	microbiological modified intent-to-treat
MSCC	mid-stream clean catch
OTX	on-therapy visit
PD	pharmacodynamic
PGt	pharmacogenetic
PK	pharmacokinetic
REL	relebactam
SMX	sulfamethoxazole
$t_{1/2}$	terminal half-life
TMP	trimethoprim
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

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 – 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	SIGNATURE	DATE
_____	_____	_____