Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	**An Open-label Pharmacokinetic Study of Imipenem-Cilastatin-Relebactam in Critically-Ill Patients with Augmented Renal Clearance**
Request Date:	**Original Submission: February 7, 2019** **Amendment 1 Version: May 14, 2020** **Amendment 2 Version: July 31, 2020** **Amendment 3 Version: December 22, 2020**
Institution Name	**Hartford Hospital**
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	1.0 Amendment 1 – Dated May 14, 2020 1. Imipenem-relebactam changed to imipenem-cilastatin-relebactam throughout the protocol to document inclusion of cilastatin. This maintains consistency with the package insert for the drug and also clarifies the dosage. 2. The dosage has been changed to 1.25 grams throughout the protocol. This total dose is consistent with the package insert and contains 500mg of imipenem, 500mg of cilastatin, and 250mg of relebactam. Note, the total amount of imipenem and relebactam administered to the patient is not different from the original protocol. 3. Section 2.1: correct misspelling 4. Section 2.2: Background updated to indicate approval of imipenem-cilastatin-relebactam for complicated urinary tract and intra-abdominal infections. 5. Section 2.5 modified to indicate collection of blood in K2EDTA lavender tubes instead of sodium heparin tubes. The assay to be used requires K2EDTA tubes for collection. As a result, the maximum blood volume per sample has been reduced from 7 mL to 4 mL, since the latter is the maximum volume of a lavender top tube. Additional details provided on processing of plasma with MES stabilizer. 6. Section 2.5 modified to add free drug assessments of imipenem and relebactam. 7. Section 2.7 modified to provide details of analytical service by Q2 Solutions, Ithaca NY. 8. Section 2.7 modified to incorporate fraction unbound estimates into Monte Carlo simulations. 1.1 Amendment 2 – Dated July 31, 2020 1. Section 2.5 modified to indicate collection of additional pre-dose blood sample within 30 minutes of infusion start time. 1.2 Amendment 3 – Dated December 22, 2020 1. Section 2.5 inclusion criteria #3 modified to lower creatinine clearance (CrCL) from 150 mL/min to 130 mL/min. This has been changed throughout protocol accordingly. This will increase the target population while still limiting patients to those with augmented renal clearance. 2. Section 2.5 inclusion criteria #4 modified to include only antibiotic use as a method for determining whether or not a patient has a documented or presumed infection, and removing other criteria related to infection (temperature, elevated WBC). 3. Section 2.5 inclusion criteria #10 modified to reduce minimum APACHE II score from >12 to ≥10. The threshold of 12 was arbitrary, while the intent is to include relatively sick patients in the study, which will still be the case. 4. Section 2.5 exclusion criteria #9 modified to remove valproic acid. 5. Section 2.5 addition of criteria #10 excluding patients currently receiving or anticipated to receive valproic acid. The change in criteria 9 and 10 will allow for patients to receive imipenem-cilastatin-relebactam despite a prior recent history of valproic acid use.

	2.1 Objectives 1. Determine the single-dose pharmacokinetics of intravenous imipenem (when administered as imipenem-cilastatin-relebactam 1.25 grams as a 30 minute infusion) in adult critically ill patients with known or suspected sepsis and ARC 2. Determine the single-dose pharmacokinetics of intravenous relebactam (when administered as imipenem-cilastatin-relebactam 1.25 grams as a 30 minute infusion) in adult critically ill patients with known or suspected sepsis and ARC 3. Determine a dose of imipenem-cilastatin-relebactam that achieves greater than 90% probability of pharmacodynamic target attainment using the imipenem *P. aeruginosa* susceptibility breakpoint of 2 µg/mL and the MIC distribution of a contemporary *P. aeruginosa* and KPC producing *K. pneumoniae* population 4. Assess the safety and tolerability of single-dose imipenem-cilastatin-relebactam in adult critically ill patients with known or suspected sepsis and ARC 2.1.1 Null Hypotheses The pharmacokinetics of imipenem and relebactam will not be affected by the presence of augmented renal clearance in adult critically ill patients.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	The continuous rise of bacterial resistance to antibiotics is among the most challenging concerns in contemporary clinical medicine. Imipenem-relebactam (Merck&Co, Inc., Kenilworth, NJ) is an investigational broad-spectrum antibiotic that combines the known carbapenem, imipenem, with the novel beta-lactamase inhibitor, relebactam (1). The addition of relebactam provides imipenem protection against serine based carbapenemases, including the *Klebsiella pneumoniae* carbapenemase (KPC), as well as improved activity against imipenem non-susceptible *Pseudomonas aeruginosa* (2). Imipenem-cilastatin-relebactam is approved in the United States for complicated urinary tract infections and complicated intra-abdominal infections; it is under investigation for hospital-acquired and ventilator-associated pneumonia, and specifically for multidrug resistant Gram-negative infections when it retains activity (1). Given its potent activity against KPC producing Enterobacteriaceae and imipenem non-susceptible *P. aeruginosa*, it is reasonable to consider that imipenem-cilastatin-relebactam will be used in patients who are critically ill in the intensive care unit (ICU). Critically ill patients may have varied kidney dysfunction as a result of acute infection. Most clinicians are familiar with acute and chronic kidney impairment, which results in decreased elimination of drugs that are cleared by glomerular filtration. Both imipenem and relebactam are predominantly excreted via the kidneys (3); therefore, dosage adjustments will be required based on calculated creatinine clearance. Sepsis in ICU patients, however, may also produce a syndrome called Augmented Renal Clearance (ARC), whereby increased blood flow to the kidneys results in enhanced renal elimination and solute clearance (4). This enhanced clearance is typically defined by an 8 hour urine creatinine clearance ≥ 130 ml/min/1.73 m^2 and has been observed in as many as 65% of ICU patients on at least one day during their ICU admission (4,5). ARC has been directly linked to sub-therapeutic concentrations of β-lactam antibiotics, including imipenem (6,7,8,9). Furthermore, simulation of another carbapenem, meropenem, based on pharmacokinetics observed in patients with ARC resulted in regrowth of a susceptible *Pseudomonas aeruginosa* in hollow-fiber experiments (10).

	To our knowledge, the pharmacokinetics of relebactam, with or without imipenem, have not been studied in critically ill patients with ARC. If ARC affects relebactam clearance to a similar degree as imipenem and other renally eliminated β-lactams, larger doses or prolonged infusion may be required to maintain optimized pharmacodynamic exposure. Importantly, the effect of ARC on beta-lactam exposure is highly dependent on the MIC of the causative organism. Therefore, it is also possible that the lower MICs observed with imipenem when combined with relebactam may mean that ARC has little effect on achievable time above the MIC exposure.
2.3 Study Design	This will be a single center, observational, pharmacokinetic study. Eligible patients will be evaluated for inclusion/exclusion criteria. Following consent by the patient, legal authorized representative (LAR), or next of kin, participants will receive a single dose of imipenem-cilastatin-relebactam 1.25 grams administered as a 30 minute infusion. Blood samples will be collected over the following 6 hours (consistent with proposed dosing interval) for characterization of imipenem and relebactam concentrations. Pharmacokinetic analyses will be conducted to describe parameter estimates in patients with ARC. We aim to enroll up to 12 patients so that complete data for 8 patients with ARC can be collected.
2.4 Study Flowchart	N/A
2.5 Study Procedures	Study Locations The Center for Anti-Infective Research and Development (CAIRD), Hartford Hospital, CT will coordinate the study. The study will conducted in the medical, surgical, and neurosurgical ICUs at Hartford Hospital, an 890 bed tertiary care hospital in Hartford, CT. Institutional Review Board approval will be required based on local regulations. If LAR or next of kin are consented, local regulations will be followed to collect written informed consent from the patient once able to provide consent. Study Population *Inclusion Criteria* Patients eligible to participate in the study must meet all of the following criteria prior to any study-related procedure: 1. Male or female aged 18-54 years; 2. APACHE II score ≥ 10 and ≤ 35; 3. Creatinine clearance (CrCL) ≥130 mL/min (as calculated by the Cockcroft-Gault equation using ideal or adjusted body weight) within 24 hours of dosing (*Note:* using a higher CrCL threshold for Cockcroft-Gault CrCL will increase likelihood that enrolled participants have a urine CrCL ≥ 130 ml/min/1.73 m^2 and thus qualify as ARC); 4. Documented infection or presumed infection by receiving another antibiotic. *Exclusion Criteria* Patients will be considered ineligible if they meet any of the following criteria: 1. If female, currently pregnant or breast feeding; 2. History of any moderate or severe hypersensitivity or allergic reaction to any β-lactam antibiotic (*Note:* mild rash or erythema to penicillin or cephalosporin antibiotics would not disqualify a patient if they have received a carbapenem without problem); 3. History of chronic kidney disease, hemodialysis, or peritoneal dialysis; or history of acute renal replacement therapy (e.g., hemodialysis,

hemofiltration, hemodiafiltration) or extracorporeal membrane oxygenation (ECMO) associated with current illness;
4. Suspected rhabdomyolysis or creatine kinase > 10,000 U/L;
5. Any serum creatinine (SCr) before dosing that is increased ≥ 0.3 mg/dL from the baseline SCr used qualifying for enrollment;
6. Urinary output <20 ml/hour for at least 2 hours (oliguria) within 24 hours before enrollment;
7. Sustained (at least 1 hour) hypotension (systolic pressure < 90 mmHG or mean arterial pressure < 55 mmHg) refractory to vasopressors or IV fluid resuscitation for at least 24 hours before enrollment;
8. Significant anemia defined as a hemoglobin < 8 g/dL at baseline;
9. Use of probenecid or imipenem within 3 days before study drug infusion;
10. Current use of valproic acid or anticipated use during study enrollment.
11. Acute liver injury, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal, or AST or ALT > 3 times the upper limit of normal with an associated total bilirubin > 2 times upper limit of normal;
12. Any rapidly-progressing disease or immediately life-threatening illness (defined as imminent death within 48 hours in the opinion of the investigator);
13. Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the patient or the quality of study data;
14. Planned or prior participation in any other interventional drug study within 30 days.

Study Procedures

Screening/Baseline

Screening/Baseline assessments and procedures must be completed within 24 hours before the start of the study drug infusion. Potential subjects who do not meet enrollment criteria may, as appropriate, repeat the screening assessments once at a later time for possible enrollment into the study. Local laboratory results will be used to determine subject eligibility for study enrollment. Any protocol-required eligibility laboratory evaluations already done as part of the patient's regular medical care within 24 hours before the start of the study drug infusion on Study Day 1 do not have to be repeated for purposes of determining eligibility for this study.

- Obtain informed consent in writing from patient, legal authorized representative, or next of kin, according to local regulations.

- Clinical Assessments:
  - Obtain a complete medical and surgical history, including: a) all active conditions and all conditions diagnosed within the previous 1 year
  - Perform a complete physical examination (general/appearance; head, eyes, ears, nose, and throat [HEENT]; neurological; pulmonary; cardiovascular; gastrointestinal; musculoskeletal; and skin)
  - Record height and weight
  - Record resting pulse, blood pressure, and respiratory rate; oxygen saturation (by pulse oximeter), including rate of supplemental oxygen (i.e., FiO2); ventilator support; and highest (or lowest if hypothermia) daily temperature (oral, rectal, tympanic, or core) measured
  - Record total fluid balance including total fluid intake and total fluid output for the period encompassing the signing of the ICF to the start of the study drug infusion
  - Record each component of the Acute Physiology and Chronic Health Evaluation II (APACHE II) assessment at Screening/Baseline

- Record all prior medications taken or received within 3 days before study drug infusion
- Identify, assess, and record any new adverse events or Serious Adverse Events (SAE) after signing of informed consent

- Laboratory Assessments:
  - Collect the following labs within 24 hours of study dose administration: serum creatinine, blood urea nitrogen, glucose, sodium, potassium, chloride, bicarbonate, albumin, total protein, complete blood count (CBC) with differential, total bilirubin, direct bilirubin, alkaline phosphate, alanine aminotransferase, aspartame aminotransferase, and urine analysis with microscopy. A serum hCG test will be collected for females of child-bearing potential.

  - Calculation of CrCL using Cockcroft-Gault based on screening/baseline serum creatinine:

$$\text{Calculated CrCL} = \frac{(140 - \text{age in years}) \times \text{ideal body weight (kg)}^{a,b,c}}{72 \times \text{SCr (mg/dL)}}$$

Multiply by 0.85 for female patients

[a] Ideal body weight (IBW, kg): Males = 50 + [2.3 × (Height (in) - 60)]; Females = 45.5 + [2.3 × (Height (in) - 60)]

[b] For patients with total body weight (TBW) that is greater than 20% over IBW, use adjusted body weight (ABW, kg): IBW + 0.4*(TBW-IBW)

[c] If TBW is less than IBW, use TBW in equation

Study Medication Administration

All participants will receive a single dose of imipenem-cilastatin-relebactam 1.25 grams as a 30 minute (+/- 5 minutes) infusion. Imipenem-cilastatin-relebactam vials will be supplied by the study sponsor. The dose will be prepared according to manufacturer recommendations in precisely 100 ml of 0.9% sodium chloride. Imipenem-cilastatin-relebactam must be administered through a peripheral intravenous catheter, peripherally inserted central catheter (PICC), central line, or port-a-catheter, whichever is determined to be most appropriate by the local investigator and care provider for each participant. Participants will also receive standard intravenous antibiotic therapy (excluding generic or branded intravenous imipenem) to treat their suspected infection, as determined by the responsible provider. No other intravenous medications will be co-administered with imipenem-cilastatin-relebactam.

Study Day 1

- Within 8 hours of beginning study medication infusion, a pre-dose SCr will be collected to confirm calculated CrCL remains ≥130 mL/min and that no change in SCr was observed to be ≥ 0.3 mg/dL from the baseline SCr used qualifying for enrollment.
- An 8 hour (± 1 hour) urine creatinine collection will be initiated within 4 hours prior to study medication infusion. The results of the measured urine CrCL will be used to confirm ARC in the patient over the time period that blood samples for imipenem-cilastatin-relebactam are collected.

Measured CrCL (ml/min) = $\frac{\text{UCr (mg/dL) x urine volume (mL)}}{\text{Predose-SCr x time}^{a}}$

Abbreviations: CrCl = creatinine clearance; SCr = serum creatinine; UCr = urine creatinine.

[a] Time = The 8-hour urine collection has a ± 1 hour window (i.e., 480 min ± 60 min); use the exact number of minutes of the urine collection in the equation

- Vital signs (temperature, heart rate, blood pressure, respiratory rate) will be recorded within 15 minutes prior to starting the study drug infusion.
- Participants will receive the single dose of imipenem-relebactam as described above. Exact start and stop times will be recorded in military time.
- Identify, assess, and record any new adverse events or Serious Adverse Events (SAE)
- Concomitant medications will be recorded.
- Blood Sample Collection: Seven blood samples (4 ml per sample) will be collected in K2EDTA vacutainers at the following time points to determine the concentrations of imipenem and relebactam in plasma: 0 hour (within 30 minutes prior to the start of infusion), 0.5 hours (end of infusion), 0.75, 1, 2, 4, and 6 hours after the start of the infusion. The timing of all blood samples should be +/- 5 minutes of protocol defined time, except for the 0.5 hour (peak concentration), which can be + 5 minutes and should be collected as close to the end of the infusion as possible. All blood samples will be collected via a peripheral intravenous catheter inserted into the contralateral arm to drug administration for collection of blood samples. Alternatively, venipuncture may be used to collect the seven blood samples.
- Blood samples will be immediately stored on ice and centrifuged within 30 minutes of collection at 1000-1300 x g (rcf) for 10 minutes at 4°C to separate the plasma.
- Immediately after centrifugation of whole blood, use a 1.0 mL pipette to transfer exactly 1.0 mL of plasma to labeled, cryovials containing 1.0 mL of plasma stabilizer (2-(N-morpholino) ethanesulfonic acid (MES)). Add a second 1.0 mL of plasma to a second cryovial to serve as a back-up sample.
- Cap the cryovials and mix the plasma with the preservative stabilizer by inverting at least six times. Freeze and store at -80 °C. No more than 60 minutes should elapse between the blood draw and freezing of plasma sample.
- An additional 8ml blood sample will be collected for imipenem and relebactam protein binding determination at 0.5 hours (end of infusion). Plasma will be separated by centrifugation as previously explained. Approximately 0.9 mL of plasma will be loaded in an ultrafiltration device (Centrifree®, Merck Millipore Ltd., Ireland) and centrifuged for 45 minutes at 10º C at 2,000 x g to obtain an ultrafiltrate containing only free-drug concentrations. Protein binding will be conducted in triplicate. The protein-free ultrafiltrate volume will be measured, transferred to a cryovial and then, an equal volume of the stabilizer will be added (confirmation of processing instructions for protein-free imipenem and relebactam will be provided by Q2 Solutions, Ithaca, NY). The cryovials will be stored at -80º C until concentration determination. The final protein percentage will be calculated by dividing the free concentration by the total plasma concentration and subtracting from 100 (%).

Study Day 2

- Clinical Assessments:
  - Perform a complete physical examination

	• Record resting pulse, blood pressure, and respiratory rate; oxygen saturation (by pulse oximeter), including rate of supplemental oxygen (i.e., FiO2); ventilator support; and highest (or lowest if hypothermia) daily temperature (oral, rectal, tympanic, or core) measured • Identify, assess, and record any new adverse events or Serious Adverse Events (SAE) • Laboratory Assessments: • Collect the following labs within 24 hours after completion of last blood sample collection: serum creatinine, blood urea nitrogen, glucose, sodium, potassium, chloride, bicarbonate, albumin, total protein, complete blood count (CBC) with differential, total bilirubin, direct bilirubin, alkaline phosphate, alanine aminotransferase, aspartame aminotransferase, and urine analysis with microscopy.
2.6 Study Duration	Final Protocol 2 months IRB Approval 2 months Enrollment and Sampling 10 months Imipenem-relebactam Analytical (by Sponsor) TBD Pharmacokinetic Analyses 1 months Final Report 1 months
2.7 Statistical Analysis and Sample Size Justification	<u>Data Analyses</u> *Data Collection* Patient demographics, medical/surgical history, concomitant medications, and adverse event data will be collected throughout the study on a provided case report form. Protected Health Information (PHI) will be maintained at CAIRD. *Analysis Populations* All patients enrolled will be included in the safety population. However, only the 8 patients who meet the definition of ARC will served as the primary pharmacokinetic population. Any additional patients enrolled who do not meet the definition of ARC will have imipenem and relebactam concentrations determined for informational purposes. These patients will not be included in the summary pharmacokinetic analyses. *Analytical* Cryovials containing plasma and protein free filtrate will be overnight shipped on dry ice to Q2 Solutions (Ithaca, NY) for imipenem and relebactam concentration determination. The back-up vial will be shipped separately. Imipenem and relebactam concentrations will be determined by a liquid chromatography mass spectrometry assay. *Pharmacokinetic Analyses* *Non-compartmental* Non-compartmental modeling will be conducted using WinNonlin (Pharsight Corporation, Cary, NC) using the latest version licensed for the laboratory. All concentration time curves will be plotted for visual inspection. The following pharmacokinetic parameters will be estimated for imipenem and relebactam in each of the 8 participants. The maximum concentration (C_{max}) will be the highest concentration observed for the concentration time profile of each participant. The time to maximum concentration (T_{max}) will be the observed sampling time of the C_{max}. The minimum concentration (C_{min}) will be the lowest concentration observed for the concentration time profile of each participant that occurs after the observed C_{max}. Lambda (λ_z) will be the resulting slope of the regression line

	of best fit. Half-life ($T_{1/2}$) will be calculated as $\ln(2)/\lambda_z$. Area under the curve for the dosing interval ($AUC_{0-\tau}$) will be calculated by the linear/log trapezoidal rule (linear during increasing concentrations, log during decreasing concentrations), where τ is the dosing interval for the drug studied. The AUC to infinity (AUC_{INF}) will be calculated as the AUC extrapolated to infinity by the equation: AUC + C_{last}/λ_z. Clearance (CL) will be estimated by Dose/$AUC_{0-\tau}$. The volume of distribution based on the terminal elimination phase (V_z) will be estimated by Dose/(λ_z*$AUC_{0-\tau}$). *Population Pharmacokinetic Analyses* Imipenem and relebactam concentrations will be modeled using the non-parametric adaptive grid program (NPAG) with adaptive gamma in the Pmetrics package for R (Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA) using either a one or two compartment model. Appropriate model selection will be based on visual inspection, observed versus predicted plots, and Akaike Information Criterion (AIC). The effect of specific body size descriptors (actual body weight, ideal body weight, body mass index, body surface area) and both calculated and measured CrCL will be analyzed for correlation with pharmacokinetic parameters (i.e., CL and volume of distribution). *Monte Carlo Simulation* Using the population pharmacokinetic model, a 5000 patient Monte Carlo simulation will be conducted for the standard imipenem and relebactam dosing regimen to determine probability of achieving pharmacodynamic thresholds, as defined by Sponsor, at the imipenem susceptibility breakpoint of 2 µg/mL. Observed fraction unbound estimates from the protein-free ultrafiltrate studies in these patients will be incorporated into simulations. In the scenario that the probability of target attainment (PTA) is less than 90%, a higher dose and longer infusion time (e.g., 2-3 hours) will be simulated to determine a dose that achieves at least 90% PTA. Analyses will also be conducted using contemporary MIC distributions of *P. aeruginosa* and KPC producing *K. pneumoniae*. <u>Power/Sample Size:</u> Based upon relebactam single dose pharmacokinetic data from healthy volunteers receiving the drug with or without imipenem (3), clearance across all doses was 8.6 L/h with a standard deviation of 1.2 L/h. Eight in the ARC group would provide 80% power at an alpha of 0.05 to detect a 40% difference in total body clearance from the historical healthy volunteer data; this also assumes an increase in coefficient of variability (CV) to 25%, which is expected in critically ill patients. Since some patients with calculated CrCL via Cockcroft-Gault will not have 8 hour urine CrCL of at least 130 ml/min/1.73 m^2, this study will enroll up to 12 patients to have complete data for 8 patients with ARC. Enrollment will stop once complete data for 8 patients who meet the definition of ARC is confirmed or a maximum of 12 patients complete the study, whichever occurs first.
2.8 Specific Drug Supply Requirements	Imipenem-Cilastatin-Relebactam 1.25 gram vials (n=15 vials)

2.9 Adverse Experience Reporting	Participants will be monitored for any sign or symptom of adverse events throughout the course of the study. Unanticipated, life-threatening or fatal adverse events will be reported to the IRB, the manufacturer, and the Food and Drug Administration according to federal guidelines. All adverse events requiring medical attention will be treated by the study physician and will be recorded by the investigator. For the purpose of this study, an adverse event will be defined as any pathologic or unintended change in the structure (signs), function (symptoms), or chemistry (laboratory values) of the body associated with the use of the study drug, whether or not considered drug related, and will be categorized as one of the following: • MILD – present, but easily tolerated • MODERATE – discomfort that interferes with usual activities • SEVERE – incapacitating, inability to work or do usual activities Relationship of the AE to the study medication (i.e., causality) will be evaluated according to the investigator's opinion, as one of the following: • Concurrent condition – unrelated to study drug • REMOTE adverse drug event – little or no temporal relationship to study drug • POSSIBLE adverse drug event – temporal relationship to study drug • PROBABLE adverse drug event – commonly associated with study drug • DEFINTE adverse drug event – reappeared on re-challenge of study drug All SAEs will be reported to the Institutional Review Board, sponsor, and the Food and Drug Administration according to Federal and local guidelines. A serious adverse event will be defined as any adverse event that results in death, is immediately life-threatening, requires or prolongs hospitalization, or is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the previously mentioned outcomes.
2.10 Itemized Study Budget	See Proposed Budget
2.11 References	1. Zhanel GC, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M, Lagace-wiens PRS, Walkty A, Denisuik A, Golden A, Gin AS, Hoban DJ, Lynch JP, Karlowsky JA. Imipenem-relebactam and meropenem-vaborbactam: two novel carbapenem-beta-lactamase inhibitor combinations. Drugs 2018;78:65-98. 2. Lob SH, Hackel MA, Kazmierczak KM, Young K, Motyl MR, Karlowsky JA, Sahm DF. In vitro activity of imipenem-relebactam against gram-negative ESKAPE pathogens isolated by clinical laboratories in the United states in 2015 (results from the SMART global surveillance program). Antimicrob Agents Chemother 2017;61:e02209-16. 3. Rhee EG, Rizk ML, Calder N, Nefliu M, Warrington SJ, Schwartz MS, Mangin E, Boundy K, Bhagunde P, Colon-Gonzalez F, Jumes P, Liu Y, Butterton JR. Pharmacokinetcs, safety, and tolerability of single and multiple doses of relebactam, a beta-lactamase inhibitor, in combination with imipenem and cilastatin in healthy participants. Antimicrob Agents Chemother 2018;62:e00280. 4. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine

	concentrations: identifying at-risk patients. Crit Care 2013;17:R35. 5. Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, Boots RJ, Lipman J. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 2014;42:520-7. 6. Troger U, Drust A, Martens-Lobenhoffer J, Tanev I, Braun-Dullaeus RC, Bode-Boger SM. Decreased meropenem levels in intensive care unit patients with augmented renal clearance: benefit of therapeutic drug monitoring. Int J Antimicrob Agents 2012;40:370-2. 7. Carler M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E, Depuydt P, Decruyenaere J, Lipman J, Wallis SC, De Waele JJ. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 2013;17:R84. 8. De Waele JJ, Lipman J, Akova M, Bassetti M, Dimopoulos G, Kaukonen M, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Udy AA, Starr T, Wallis SC, Roberts JA. Risk factors for target non-attainment during empirical treatment with β-lactam antibiotics in critically ill patients. Intensive Care Med 2014;40:1340-51. 9. Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, Daali Y, Pugin J, Karmime A, Fathi M, Lew D, Harbarth S. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents 2015;45:385-92. 10. Bergen PJ, Bulitta JB, Kirkpatrick CMJ, Rogers KE, McGregor MJ, Wallis SC, Paterson DL, Nation RL, Lipman J, Roberts JA, Landersdorfer CB. Substantial impact of altered pharmacokinetics in critically ill patients on the antibacterial effects of meropenem evaluated via the dynamic hollow-fiber infection model. Antimicrob Agents Chemother 2017;61:e02642-16.
2.12 Publication Plan	The results of this study would be presented at an international congress such as the ASM Microbe Meeting, IDWeek, ECCMID, or SCCM. A final publication would be submitted to a peer reviewed journal such as Antimicrobial Agents and Chemotherapy or Journal of Antimicrobial Chemotherapy.
2.13 Curriculum Vitae	Investigator should provide curriculum vitae in English and a listing of references to MSD.
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.