Center for Anti-Infective Research and Development
Hartford Hospital

Protocol

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Pharmacokinetics of Imipenem/Cilastatin/Relebactam in Critically Ill Patients Receiving Extracorporeal Membrane Oxygenation (ECMO)

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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	**1.0 PROTOCOL AMENDMENT 1: July 7, 2021** 1. Section 2.5 exclusion criteria #5 modified to remove valproic acid. 2. Section 2.5 addition of criteria #6 excluding patients currently receiving or anticipated to receive valproic acid. The change in criteria 5 and 6 will allow for patients to receive imipenem-cilastatin-relebactam despite a prior recent history of valproic acid use. 3. Section 2.5 screening/baseline: removal of urine analysis with microscopy due to unnecessary test not relating to patient safety. **2.0 OBJECTIVES** 1. To determine the pharmacokinetics of imipenem and relebactam in critically ill adult patients supported by ECMO **2.1.1 HYPOTHESES** 1. Imipenem and relebactam pharmacokinetics in critically ill patients receiving ECMO support will be consistent with parameters previously defined in critically ill adult patients not supported by ECMO
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Extracorporeal membrane oxygenation (ECMO) is a mechanical circulatory support device used temporary in critically ill patients with heart and/or respiratory failure unresponsive to maximal conventional therapy. Briefly, ECMO is a form of cardiopulmonary life-support where blood is extracted from the vascular system (i.e., peripheral or central vein) and circulated by a mechanical pump while it is oxygenated and re-infused into the patient's circulation. ECMO can be used in two different configurations depending on the patient's requirement: veno-venous (VV-ECMO) when only respiratory support is needed and veno-arterial (VA-ECMO) for cardiac and/or respiratory support (1). Although controversial until 2009, the clinical benefit of ECMO therapy was substantiated when the CESAR study, a multicenter, randomized controlled trial that included adult patients with respiratory failure, demonstrated an increased survival without disability at 6-month follow-up (2). Since then, ECMO has been increasingly used worldwide in pediatric and adult patients, and remarkable technological improvements (e.g., innovative device design, cannula, oxygenators) have been made, resulting in improved clinical outcomes (3). At our large tertiary care trauma center, we perform VV-ECMO or VA-ECMO in an increasing number of critically ill adult patients each year (n=60 in 2019). With more adult patients receiving ECMO support, there is a need to understand how ECMO circuits affect the pharmacokinetics (PK) and disposition of drugs. ECMO is not a disease-modifying treatment, and its effectiveness relies on the effect of other interventions, such as antibiotics in patients with severe infections where optimal exposure is crucial for treatment success. It is well known that critically ill patients may experience alterations in antibiotic PK, and as a result, dosing modifications are generally required (4). Multiple *in vitro* and *in vivo* studies have shown that ECMO may further alter the PK of certain antibiotics by resulting in lower plasma concentrations unable to achieve pharmacodynamic thresholds (5). Intrinsic drug properties such as lipophilicity and protein binding appear to be predictive of this artificial loss, presumably due to drug adsorption and sequestration within the oxygenator circuit, increases in compensatory volume of distribution and even changes in total body clearance (6-9). However, these specific drug properties may

	not always be predictive; a recent *ex vivo* study with ceftolozane observed 92% loss in the circuit over 24 hours even though this antibiotic is neither lipophilic nor highly protein bound (10). Other factors related with the ECMO circuit itself such as the type of pump and presence of oxygenator have been also associated with antibiotic loss (9,10). In contrast, some investigators largely conclude that antibiotic exposures are minimally altered by ECMO and thus antibiotic dosing should be consistent with critically ill patients not supported by ECMO (11-13). In light of this inconsistent data, the sequestration and clinical PK of individual antibiotics should be assessed to confirm optimal dosing in this patient population. Imipenem/cilastatin/relebactam (Recarbrio®, Merck & Co, Inc, Kenilworth, NJ) is a novel carbapenem/β-lactamase inhibitor combination recently approved by the U.S. Food and Drug Administration (FDA). Imipenem/cilastatin/relebactam has enhanced activity against multidrug resistant Gram-negative bacteria, including imipenem resistant strains (14). As a result of its potent activity against multidrug-resistant pathogens, it is reasonable to surmise that imipenem/cilastatin/relebactam will be prescribed to treat serious infections in critically ill patients, including those who are supported on ECMO. Optimizing the dosing regimen in critically ill patients receiving ECMO will be paramount to achieving successful clinical response and minimizing the risk of resistance development. Both imipenem and relebactam have low protein binding (~20%) and low octanoal/partition coefficients (Log *P*: -3.8 to -0.86 and -3.1 to -1.1, respectively), which suggests that drug disposition should be minimally affected by ECMO (15-17). However, Jaruratanasirikul and colleagues compared imipenem PK parameters between 10 critically ill patients on ECMO and 18 similarly ill patients not supported by ECMO (18). They observed that ECMO, or the underlying physiological state produced by it, resulted in a significantly higher total volume of distribution (33.4 ± 13.9 L vs. 21.3 ± 15.0 L) and significantly lower total body clearance (10.0 ± 10.5 L/h vs. 21.5 ± 9.6 L/h). The authors suggest that these alterations may require dosing modifications (i.e., 1 g q6h) to maintain optimal pharmacodynamic exposure. It should be noted, however, that the PK parameters in the studied ECMO patients were within the range of imipenem PK values observed in other critically ill patients without ECMO, suggesting that the patients may not have been evenly matched for comparison (19). Moreover, there are currently no data evaluating the disposition of relebactam in patients supported by ECMO. We propose a clinical pharmacokinetic study to determine imipenem and relebactam exposure in critically ill patients supported by ECMO.
2.3 Study Design	The study will be a prospective, open-label, single-center, phase 1b PK study of imipenem/cilastatin/relebactam in eight critically ill adult patients receiving ECMO support at Hartford Hospital. PK analyses will be conducted to assess exposure attainment in these eight ECMO patients. The study protocol and informed consent documents will be reviewed and approved by the Institutional Review Board (IRB) at Hartford Healthcare. All study subjects, or their next of kin, will be required to provide written consent in order to participate in the study. Imipenem/cilastatin/relebactam will not be given as a treatment. Therefore, all patients will receive other antibiotics as necessary to treat any ongoing infection if present.
2.4 Study Flowchart	Not Applicable
2.5 Study Procedures	**Study Location** This study will take place at Hartford Hospital, an 867 bed, tertiary care hospital in Hartford, CT. ECMO is prescribed in approximately 60 critically ill adult patients each year, split between use of VV-ECMO and VA-ECMO. We anticipate that the

majority of patients with sepsis who qualify for this study to be receiving VV-ECMO.

Study population

The study population will include eight critically ill adult patients (>/= 18 years of age) receiving ECMO support in the medical or surgical intensive care units at Hartford Hospital. Patients with documented or presumed infection are eligible. Any patient with infection will be treated with standard antibiotics by the attending provider. To ensure representation of patients across the renal function spectrum to be included in the study, half of the enrolled patients with have a creatinine clearance ≥60 ml/min at screening and half will have a value between 15 and 59 ml/min.

Inclusion Criteria: Patients eligible to participate in the study must meet all of the following criteria prior to any study-related procedure:

- Age 18 years or older;
- On support with VV- or VA-ECMO;
- Documented infection or presumed infection as confirmed by the presence of at least one of the following criteria within the past 72 hours:
    - Documented fever (oral, rectal, tympanic, or core temperature > 38.5° C)
    - Hypothermia (oral, rectal, tympanic, or core temperature < 35.0° C)
    - An elevated white blood cell (WBC) count ≥ 12,000 cells/mm^3

Exclusion Criteria: Patients will be considered ineligible if they meet any of the following criteria:

- If female, currently pregnant or breast feeding;
- History of any moderate or severe hypersensitivity or allergic reaction to any β-lactam agent (a history of mild rash to a β-lactam followed by uneventful re-exposure is not a contraindication);
- Severe renal dysfunction defined as a creatinine clearance < 15 mL/min (calculated by the Cockcroft-Gault equation using actual body weight) or requirement for continuous renal replacement therapy or hemodialysis;
- Hemoglobin less than 8 mg/dL at baseline;
- Use of probenecidor imipenem within 3 days before study drug infusion;
- Current use of valproic acid or anticipated use during study enrollment.
- 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;
- Any rapidly-progressing disease or immediately life-threatening illness (defined as imminent death within 48 hours in the opinion of the investigator);
- Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the patient or the quality of study data;

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 ECMO settings
- 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, and aspartame aminotransferase. 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

Imipenem/cilastatin/relebactam Administration

Imipenem/cilastatin/relebactam will be dosed according to current prescribing information based on creatinine clearance (20). Four to six doses of imipenem/cilastatin/relebactam, each infused over 0.5 hours, will be administered to achieve steady-state. 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, 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

- 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 imipenem/cilastatin/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 samples will be collected as described below.

Study Day 2

- Participants will receive imipenem/cilastatin/relebactam as described above. Exact start and stop times will be recorded in military time.
- Blood samples will be collected as described below.
- Concomitant medications will be recorded.
- 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 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.

Sample Collection

Blood samples (4 mL) will be collected in K_2EDTA vacutainers before the first imipenem/cilastatin/relebactam dose (i.e., blank), and at 0.5 and 6 hours following the first dose, and then at 0, 0.5, 0.75, 1, 2, 4, 5, and 6 hours after the start of the final dose, when concentrations are expected to be at steady-state. All blood samples will be collected pre-oxygenator. Additionally, protein binding will be determined at the 0.5 hour time point of the final dose. 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 the end of infusion and should be collected as close to the end of the infusion as possible.

Processing of clinical samples

Blood samples will be immediately stored on ice and centrifuged within 30 minutes of collection at 4º C and 1300 x g for 10 minutes to separate the plasma. Immediately after centrifugation, 1.0 mL of plasma from each sample will be transferred (using a 1.0 mL pipette) to a previously labeled cryovial containing 1.0 mL of plasma stabilizer (2-(N-morpholino) ethanesulfonic acid (MES)). A second 1.0 mL of plasma will be added to a second cryovial (labeled with stabilizer) to have a back-up sample. Thereafter, cryovials will be capped and inverted at least six times to mix the plasma with the stabilizer. The cryovials will be stored at -80º C until concentration determination. No more than 60 minutes should elapse between the blood draw and freezing of plasma sample.

	Protein Binding determination An additional 10ml blood sample will be collected for imipenem and relebactam protein binding determination at time points described above. 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 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 (%).
2.6 Study Duration	IRB Submission and Contracting: 2 months Patient Enrollment: 8 months Data Analyses: 2 months Final Report: 2 months
2.7 Statistical Analysis and Sample Size Justification	**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. **Imipenem and Relebactam Concentration Determination** 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 co-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), calculated CrCL, and ECMO flow rate will be analyzed for correlation with pharmacokinetic parameters (i.e., CL and volume of distribution). By including a similar proportion of participants with creatinine clearance above and below 60 ml/min, a variable range of clearance values will be represented in the population analyses. *Pharmacodynamic Analysis* The free imipenem and relebactam concentration of each of the eight participants will be assessed for free time above the MIC (*f*T>MIC, applied for imipenem) and free area under the curve to MIC (*f*AUC/MIC, applied for relebactam) exposure using the imipenem susceptibility breakpoint of 2 µg/mL for *Pseudomonas aeruginosa*. **Sample Size** No target sample size is provided statistically as this will be a descriptive and exploratory study. Therefore, this study will enroll eight critically ill adult patients on ECMO support based primarily on empirical considerations and feasibility. This number is considered sufficient to meet the study objectives.
2.8 Specific Drug Supply Requirements	Recarbrio® (Imipenem/cilastatin/relebactam) 1.25g vials (n=50 vials)
2.9 Adverse Experience Reporting	**Safety and Adverse Event Monitoring** Participants will be monitored for any sign or symptom of adverse events (AE) 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. Fraser JF, Shekar K, Diab S et al. ECMO - the clinician's view. ISBT Science Series 2012;7:82-88. 2. Peek GJ, Mugford M, Tiruvoipati R et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. The Lancet 2009;374:1351-1363. 3. Makdisi G, Wang IW. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis 2015;7:E166-76. 4. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37:840-51; quiz 859. 5. Dzierba AL, Abrams D, Brodie D. Medicating patients during extracorporeal membrane oxygenation: the evidence is building. Crit Care 2017;21:66. 6. Shekar K, Roberts JA, McDonald CI et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care 2012;16:R194. 7. Shekar K, Roberts JA, McDonald CI et al. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care 2015;19:164. 8. Shekar K, Roberts JA, Barnett AG et al. Can physicochemical properties of antimicrobials be used to predict their pharmacokinetics during extracorporeal membrane oxygenation? Illustrative data from ovine models. Crit Care 2015;19:437. 9. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med 2010;36:2109-16. 10. Cies JJ, Moore WS, 2nd, Giliam N, Low T, Enache A, Chopra A. Oxygenator Impact on Ceftolozane and Tazobactam in Extracorporeal Membrane Oxygenation Circuits. Pediatr Crit Care Med 2019. 11. Abdul-Aziz MH, Roberts JA. Antibiotic dosing during extracorporeal membrane oxygenation: does the system matter? Curr Opin Anaesthesiol 2020;33:71-82. 12. Dhanani JA, Lipman J, Pincus J et al. Pharmacokinetics of Total and Unbound Cefazolin during Veno-Arterial Extracorporeal Membrane Oxygenation: A Case Report. Chemotherapy 2019;64:115-118. 13. Argudo E, Riera J, Luque S et al. Effects of the extracorporeal membrane oxygenation circuit on plasma levels of ceftolozane. Perfusion 2019:267659119864813. 14. Lapuebla A, Abdallah M, Olafisoye O et al. Activity of Imipenem with Relebactam against Gram-Negative Pathogens from New York City. Antimicrob Agents Chemother 2015;59:5029-31. 15. Rizk ML, Rhee EG, Jumes PA et al. Intrapulmonary Pharmacokinetics of Relebactam, a Novel beta-Lactamase Inhibitor, Dosed in Combination with Imipenem-Cilastatin in Healthy Subjects. Antimicrob Agents Chemother 2018;62. 16. Imipenem Monohydrate. https://www.drugbank.ca/salts/DBSALT002429.

	17. Relebactam. https://www.drugbank.ca/drugs/DB12377. 18. Jaruratanasirikul S, Vattanavanit V, Samaeng M, Nawakitrangsan M, Sriwiriyajan S. Pharmacokinetics of Imipenem in Critically Ill Patients with Life-threatening Severe Infections During Support with Extracorporeal Membrane Oxygenation. Clin Drug Investig 2019;39:787-798. 19. Goncalves-Pereira J, Povoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 2011;15:R206. 20. Recarbrio (Imipenem-relebactam) for Injection. Full Prescribing Information 2019;Merck Sharp & Dohme Corp.
2.12 Publication Plan	The Center for Anti-Infective Research and Development will provide a Final Report at the completion of the study in format acceptable for submission to peer review literature. Target journals include Antimicrobial Agents and Chemotherapy and Journal of Antimicrobial Chemotherapy. An abstract will also be generated for presentation at international meeting such as IDWeek, ASM Microbe or ECCMID.
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 to Visiontracker at https://msd.envisionpharma.com/vt_msd/ Non U.S. protocols should be submitted to the MSD office by the investigators.