CLINICAL STUDY PROTOCOL

A Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex

Investigational Product: Sulbactam-ETX2514 (ETX2514SUL)

Protocol Number: CS2514-2017-0004

EudraCT Number: 2018-002526-23

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SIGNATURE PAGE

STUDY TITLE: A Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
SL LaR, MD	17 DEC 2020

Steven LaRosa, MD
Vice President, Clinical Development
Entasis Therapeutics

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Entasis Therapeutics to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Entasis Therapeutics and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Entasis Therapeutics, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by *Acinetobacter baumannii-calcoaceticus* Complex

PROTOCOL NUMBER: CS2514-2017-0004

INVESTIGATIONAL PRODUCT: Sulbactam-ETX2514 (ETX2514SUL)

PHASE: 3

INDICATION(S): Treatment of serious infections caused by *Acinetobacter baumannii* (*A. baumannii)-calcoaceticus* complex (ABC)

OBJECTIVES:

This is a 2-part study, with Part A being the randomized, controlled portion of the study in patients with ABC hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), or bacteremia. Part B is the single-group portion of the study and includes ABC infections that are resistant to or have failed colistin or polymyxin B treatment, as detailed in the inclusion criteria.

The primary objectives of this study are the following:

- To compare the efficacy of ETX2514SUL plus imipenem/cilastatin to colistin plus imipenem/cilastatin in patients with carbapenem-resistant ABC (CRABC) infections in Part A; and
- To compare the incidence of nephrotoxicity, as measured by the Risk–Injury–Failure–Loss–End-stage renal disease (RIFLE) criteria, of ETX2514SUL to colistin in patients with ABC infections in Part A.

The secondary objectives of this study are the following:

- To compare the efficacy of ETX2514SUL plus imipenem/cilastatin to colistin plus imipenem/cilastatin in all randomized patients in Part A;
- To evaluate the efficacy of ETX2514SUL plus imipenem/cilastatin in patients with colistin- or polymyxin B-resistant ABC infections in Part B;
- To estimate the efficacy of ETX2514SUL plus imipenem/cilastatin for each primary infection site;
- To evaluate and compare the safety of ETX2514SUL and colistin;
- To describe the overall safety profile of ETX2514SUL; and
- To determine the systemic exposure of ETX2514 and sulbactam in a small cohort of severely ill patients administered ETX2514SUL in Part A.

The exploratory objectives of this study are the following:

- To evaluate the efficacy of ETX2514SUL in relation to pharmacokinetics (PK) exposure;
- To evaluate the efficacy of ETX2514SUL in relation to minimum inhibitory concentration (MIC) distribution of ETX2514SUL;
- To evaluate the efficacy of ETX2514SUL in relation to total duration of treatment received; and
- To compare the resource utilization of patients receiving ETX2514SUL plus imipenem/cilastatin to patients receiving colistin plus imipenem/cilastatin.

POPULATION:

The population for this study is male and female patients ≥18 years of age with documented ABC infections.

INCLUSION CRITERIA:

General Inclusion Criteria:

Patients who meet all of the following general inclusion criteria, in addition to the specific inclusion criteria listed below for Parts A and B, will be eligible to participate in the study:

1. A signed informed consent form;

   Note: If a study patient is unable to provide informed consent due to their medical condition, the patient's legally authorized representative may consent on behalf of the study patient, or the decision can be made according to the procedure permitted by local law and institutional Standard Operating Procedures.

2. Male or female ≥18 years of age;
3. A confirmed diagnosis of a serious infection and the expectation, in the judgment of the Investigator, that the patient's infection will require treatment with intravenous (IV) antibiotics;
4. A known infection caused by ABC (bacteremia, HABP, VABP, VP, complicated urinary tract infection [cUTI] or acute pyelonephritis [AP], or surgical or post-traumatic wound infections) as either a single pathogen or member of a polymicrobial infection based on evidence from culture or, if available, rapid diagnostic test from a sample collected within 72 hours prior to randomization (HABP/VABP/VP patients), AND 1 of the following:

   a. Has received no more than 48 hours of potentially effective (ie, Gram negative coverage) antimicrobial therapy prior to the first dose of study drug; OR

   b. Is clinically failing prior treatment regimens (ie, clinical deterioration or failure to improve after at least 48 hours of antibiotic treatment);

   Note: Rapid testing of respiratory specimens utilizing Biofire® FilmArray® 2.0 Pneumonia Panel (BPP) technology should be used to enable early identification of ABC pneumonia. Patients can be randomized based on the results of the BPP rapid test while awaiting results of cultures from the local laboratory. However, if the respiratory sample does not grow ABC in the local microbiology laboratory culture, these patients will be withdrawn from the study drug treatment.

Note: Isolation of ABC from pleural effusion (empyema) is allowed, if concurrent pulmonary infiltrate is confirmed.

5. Acute Physiology and Chronic Health Evaluation (APACHE) II score between 10 and 30, inclusive, OR Sequential Organ Failure Assessment (SOFA) score between 7 and 11, inclusive, at the time of diagnosis of infection. Patients who are not being treated in an intensive care unit and cannot have an APACHE II or SOFA score performed should have a quick SOFA (qSOFA) score ≥2 for enrollment;
6. Expectation, in the judgment of the Investigator, that the patient will benefit from effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study; and
7. Women of childbearing potential (ie, not post-menopausal or surgically sterilized) must have a negative highly sensitive urine or serum pregnancy test before randomization. Participating women of childbearing potential must be willing to consistently use one highly effective method of contraception (ie, condom, combined oral contraceptive, implant, injectable, indwelling intrauterine device, or a vasectomized partner) from Screening until at least 30 days after administration of the last dose of study drug.

Part A-Specific Inclusion Criteria:

In addition to the general inclusion criteria above, patients may enroll in Part A if they meet the criteria below. All patients must be categorized in 1 infection type that is judged to be the primary infection by the Investigator:

1. Diagnosed with HABP, VABP, VP, and/or bacteremia, defined as:

HABP With ABC in Sputum/Respiratory Sample		
All of the following:	**AND signs or symptoms evidenced by at least 2 of the following:**	**AND at least 1 of the following:**
• Onset of symptoms >48 hours after admission or ≤7 days after discharge from an inpatient acute or chronic care facility (eg, LTAC, rehabilitation center, hospital, or skilled nursing home); OR • Admission from LTAC or rehabilitation center, or admission from home <7 days after discharge from an LTAC or rehabilitation center; AND • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.	• A new onset of cough (or worsening of baseline cough); • Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony); • Dyspnea, tachypnea, or respiratory rate >25 breaths/minute; OR • Hypoxemia (oxygen saturation <90% or pO_2 <60 mmHg while breathing room air, or worsening of the oxygen saturation/FiO_2); OR the following ALONE: • New onset need for mechanical ventilation.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC count <4500/mm^3).

1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.

ABC = *Acinetobacter baumannii-calcoaceticus* complex; CT = computed tomography; FiO_2 = fraction of inspired oxygen; HABP = hospital-acquired bacterial pneumonia; LTAC = long-term acute care; MRI = magnetic resonance imaging; pO_2 = partial pressure of oxygen; WBC = white blood cell.

VABP With ABC in Sputum/Respiratory Sample		
All of the following:	**AND signs or symptoms evidenced by at least 2 of the following:**	**AND at least 1 of the following:**
• Onset of symptoms >48 hours after receiving ventilator support via an endotracheal (or nasotracheal) tube; • Requires ventilator support; AND • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.	• Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening oxygen saturation/FiO_2 ratio; • Increased suctioning; OR • Tracheal aspirate change to purulence.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC <4500/mm^3).
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; CT = computed tomography; FiO_2 = fraction of inspired oxygen; MRI = magnetic resonance imaging; VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.		

Ventilated Pneumonia With ABC in Respiratory Sample		
All of the following:	**AND signs or symptoms evidenced by at least 2 of the following:**	**AND at least 1 of the following:**
• Requires ventilator support; AND • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.	• Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation; • Increased suctioning; OR • Tracheal aspirate change to purulence.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC count <4500/mm^3).
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; CT = computed tomography; MRI = magnetic resonance imaging; WBC = white blood cell.		

Bacteremia With ABC	
All of the following:	**AND at least 1 of the following:**
• Isolation of ABC from at least 1 blood culture collected from a peripheral vein OR newly placed intravenous line.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC count <4500/mm^3); • Tachycardia >100 bpm; • Tachypnea >25 breaths/minute; OR • Hypotension, systolic <90 mmHg.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.	
ABC = *Acinetobacter baumannii-calcoaceticus* complex; bpm = beats per minute; WBC = white blood cell.	

Part B-Specific Inclusion Criteria:

Part B will include patients with the following ABC infections: HABP, VABP, VP, or bacteremia who do not qualify for Part A, and cUTI/AP or surgical or post-traumatic wound infections.

1. Patients with HABP, VABP, VP, or bacteremia should be considered for enrollment in Part B if they meet ANY of the following criteria (*a*, *b*, *c,* OR *d*), in addition to the general inclusion criteria above:

   a. Has an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a non-agar based method);

      For known colistin- or polymyxin B-resistant infections, the following must be satisfied:

      - Has a known resistant infection based on evidence from culture and susceptibility testing by a non-agar based method within 72 hours prior to randomization, alone or as a single organism of a polymicrobial infection; AND has received no more than 48 hours of an antimicrobial agent to which the ABC is susceptible prior to the first dose of study drug;

        OR

      - Has documented clinical evidence of failure (ie, clinical deterioration or failure to improve that is attributable to ABC infection) after at least 48 hours of treatment with colistin or polymyxin B; OR

   b. Has known intolerance to colistin;

      Note: Patients whom the Investigator feels may have a potential intolerance to colistin can be enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; OR

   c. Has myasthenia gravis or another neuromuscular syndrome(s) that contraindicates colistin and is not ventilated;

Note: Ventilated patients with myasthenia gravis or other neuromuscular syndromes where, in the opinion of the Investigator, colistin administration is reasonable are permitted for consideration for the study; OR

d. Has acute kidney injury and is receiving renal replacement therapy at study entry;

2. Patients diagnosed with cUTI, AP, or surgical or post-traumatic wound infections may enroll in Part B if they meet the general inclusion criteria as well as either *a*, *b*, *c*, *d,* OR *e* in addition to the indication requirements for *f*:

   a. Has an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a non-agar based method); OR

   b. Has known intolerance to colistin;

      Note: Patients whom the Investigator feels may have a potential intolerance to colistin can be enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; OR

   c. Has myasthenia gravis or another neuromuscular syndrome(s) that contraindicates colistin; OR

   d. Has acute kidney injury and is receiving renal replacement therapy at study entry; OR

   e. Has documented clinical evidence of failure (ie, clinical deterioration or failure to improve) after at least 48 hours of treatment with a polymyxin-based regimen; AND

   f. Is diagnosed with cUTI, AP, or surgical or post-traumatic wound infection, defined as:

cUTI With ABC		
At least 1 of the following:	**AND at least 2 of the following signs and symptoms:**	**AND at least 1 of the following:**
• Indwelling urinary catheter or intermittent bladder catheterization; • Neurogenic bladder with presence or history of urine residual volume of ≥100 mL; • Obstructive uropathy (eg, nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 hours post-randomization; • Azotemia due to intrinsic renal disease; OR • Urinary retention in men due to previously diagnosed benign hypertrophy.	• Chills, rigors, or fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3) or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; OR • Lower abdominal pain or pelvic pain.	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; OR • WBC count ≥10 cells/hpf in urine sediment.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.		

AP With ABC	
Presence of an ascending tract infection including at least 2 of the following signs or symptoms:	**AND at least 1 of the following:**
• Chills, rigors, or fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3) or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Flank pain; OR • Costovertebral angle tenderness on physical examination.	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; OR • WBC count ≥10 cells/hpf in urine sediment.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; AP = acute pyelonephritis; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.	

Surgical Wound Infection With ABC	
Superficial SSI meeting all of the following criteria:	**AND at least 1 of the following regional or systemic signs of infection:**
• Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered); • Involves only the skin or subcutaneous tissue around the incision, does not involve fascia; • Occurs within 30 days after procedure; • Original surgical incision ≥3 cm; AND • Purulent drainage (spontaneous or therapeutic) that is positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2.	• Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI; • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • WBC count ≥10,000/mm^3 or <4000/mm^3; OR • >15% immature neutrophils.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; ABSSSI = acute bacterial skin and skin structure infection; SSI = surgical site infection; WBC = white blood cell.	

Post-Traumatic Wound Infection With ABC	
Post-traumatic wound (including penetrating trauma) characterized by the following within 24 hours of Screening:	**AND at least 1 of the following regional or systemic signs of infection:**
• Purulent drainage (spontaneous or therapeutic) that is positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2.	• Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI; • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • WBC count ≥10,000/mm^3 or <4000/mm^3; OR • >15% immature neutrophils.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; ABSSSI = acute bacterial skin and skin structure infection; WBC = white blood cell.	

EXCLUSION CRITERIA:

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Presence of suspected or confirmed deep-seated infection (eg, lung abscess in patients with pneumonia, skin abscess, or decubitus ulcer) that is not planned on being drained or debrided within 24 hours after randomization;

   Note: Patients with an empyema who will have drainage within 24 hours of Screening and who are expected to be able to be treated with 14 or fewer days of antibiotics are allowed.

2. Evidence of active concurrent pneumonia requiring additional antimicrobial treatment caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, respiratory syncytial virus, influenza and parainfluenza viruses, Middle East respiratory syndrome coronavirus, mycobacteria, aspergillus, mucormycosis, etc;

   Note: If these organisms are identified but it is deemed by the Investigator that no treatment is warranted and their presence does not significantly change the prognosis of the patient, then the patient may be considered for this study.

3. Pulmonary disease that precludes evaluation of a therapeutic response (such as lung cancer resulting in bronchial obstruction or on the same side as the pneumonia, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection, lung abscess, pleural empyema, post obstructive pneumonia, or COVID-19 infection without clinical improvement);

   Note: Patients with an empyema who will have drainage within 24 hours of Screening and who are expected to be able to be treated with 14 or fewer days of antibiotics are allowed.

4. Presence of suspected or confirmed deep seated bacterial infections such as bacterial Gram negative osteomyelitis, endocarditis, or meningitis requiring prolonged therapy, as determined by history and/or physical examination;

5. Acute infective endocarditis due to Gram positive bacteria that require urgent/emergent indication of surgery (ie, heart failure because of valvular insufficiency or septic shock), or

patients in whom surgery is contraindicated due to prohibitive risk for surgery due to comorbidities;

6. Irremovable implantable device or line thought to be the potential source of ABC infection;
7. Sustained shock with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥60 mmHg;

   Note: Patients who can maintain MAP ≥60 mmHg on a reasonable dose of pressors or are weaning off of pressors may be considered. Patients who require more than the maximal dose of 2 vasopressors to maintain MAP ≥60 mmHg are ineligible. If vasopressors are weaned to below these levels, patient enrollment can be reconsidered.

8. For patients to be enrolled with the primary indication of HABP, VABP, or VP, any of the following conditions:
   a. Diagnosis of ventilator-associated tracheobronchitis; or
   b. Inability to provide proper respiratory specimens for culture. Respiratory samples from expectorated or induced sputum should show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100× field;
9. For patients to be enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:
   a. Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (eg, patients with vesico-uretal reflux);
   b. Suspected or confirmed prostatitis;
   c. Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;
   d. Previous or planned cystectomy or ileal loop surgery;
   e. Uncomplicated urinary tract infection (eg, female patients with urinary frequency, urgency, or pain or discomfort without systemic symptoms or signs of infection);
   f. Complete, permanent obstruction of the urinary tract;
   g. Suspected or confirmed perinephric or renal corticomedullary abscess;
   h. Polycystic kidney disease; or
   i. Any recent history of trauma to the pelvis or urinary tract;
10. Pregnant or breastfeeding women;
11. APACHE II score >30 and SOFA score >11 at the time of diagnosis of infection;

    Note: A qSOFA score must be calculated for all patients without an APACHE II score. Glasgow coma score for APACHE II calculation should be the best response prior to initiation of sedation/neuromuscular blockade, even if sedation has been in use for >24 hours.

12. Receiving peritoneal dialysis;
13. Requirement for temporary or acute onset treatment with antiseizure medication that, in the opinion of the Investigator, would prohibit the patient from complying with the protocol. Patients at risk of seizure or requiring prophylactic antiseizure medications during the study

can be considered for enrollment at the discretion of the Investigator. Patients with a history of epilepsy or who are on stable treatment (ie, no recurrent episodes in the past 30 days) and no history of imipenem-associated seizures may be considered for enrollment in the study;

14. Requirement for continuing treatment with probenecid, methotrexate, ganciclovir, valproic acid, or divalproex sodium during the study;
15. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis, hepatic cirrhosis, hepatic failure, chronic ascites, or hepatic encephalopathy;
16. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) AND total bilirubin >2 × ULN at Screening;

    Note: Patients with AST or ALT up to 5 × ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.
17. Requirement at the time of randomization for any reason, or likely to require during the patient's participation in the study (from randomization through the Late Follow-up [LFU] Visit), for additional systemic Gram negative antimicrobial therapy;
18. Requirement for inhaled antibiotics;
19. Known history of human immunodeficiency virus infection and known recent CD4 count <200/mm^3 within the last year or presence of significant immunologic disease or dysfunction, as determined by a current diagnosis of an Acquired Immune Deficiency Syndrome-defining illness;
20. Presence of neutropenia (absolute neutrophil count <500/mm^3) obtained from a local laboratory at Screening;
21. A QT interval corrected using Fridericia's formula ≥480 msec;
22. History of significant hypersensitivity or allergic reaction to any β-lactam (BL), any contraindication to the use of cilastatin based on local approved prescribing information (eg, Summary of Medicinal Product Characteristics), any contraindication to the excipients used in the respective formulations, or any contraindication to the use of BL antibiotics;
23. Participation in a clinical study involving investigational medication or an investigational device within the last 30 days or 5 half-lives, whichever is longer, prior to Day 1;
24. Any condition that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data or require greater than 14 days of treatment with antibiotics;
25. Unable or unwilling, in the opinion of the Investigator, to comply with the protocol;
26. Has previously received ETX2514 in this study; or
27. For Part A only, patients with an infection known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a non-agar based method), with a known intolerance to colistin, or taking any drug that prevents them from receiving colistin.

STUDY DESIGN AND DURATION:

This study is a randomized, active-controlled study to evaluate the safety and efficacy of IV ETX2514SUL in patients with ABC infections. Patients providing informed consent and meeting

all study eligibility criteria will be enrolled in the study and have pretreatment blood and infection site-specific samples obtained and submitted to the local laboratory.

The study will be enrolled in 2 parallel parts, with the PK data from the first approximately 30 patients in Part A (with only 15 patients dosed with ETX2514SUL) reviewed prior to initiating enrollment in Part B:

a. Part A will be the pivotal, assessor-blind, randomized, comparative portion of the study in patients with documented ABC HABP, VABP, VP, or bacteremia. While study drugs will not be masked due to logistical reasons, every attempt will be made to maintain the blind for patients, all staff at the site, and the Sponsor or its designees, except for the treatment physician and other immediate healthcare providers. In Part A, patients will be randomized 1:1 to 1 of the following treatment groups:

   - Group 1: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours every 6 hours (q6h) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h; or
   - Group 2: 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours (q12h) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

   Patients will be enrolled until there are 120 patients in the CRABC Microbiologically Modified Intent-to-Treat (m-MITT) Population in Part A, as determined by the central microbiology laboratory. Approximately 200 patients are expected to be enrolled in Part A, assuming approximately 60% of patients will have CRABC (see the statistical methods for complete details). The HABP/VABP/VP patients who are randomized to Part A based on a positive screening of a respiratory sample for ABC by the BPP, but who subsequently do not have growth of ABC in their respiratory sample culture processed by the local microbiology laboratory, will be withdrawn from the study drug treatment.

   Randomization will be stratified by indication (HABP/VABP/VP versus bacteremia), severity of illness (based on APACHE II [10 to 19 versus 20 to 30], SOFA [7 to 9 versus ≥10], or qSOFA [2 versus 3] score at Screening), and geography (China Mainland versus Rest of World). In the situation where a patient has more than one score reported, the scores will be used in the following order: APACHE, SOFA, and qSOFA.

   Enrollment of HABP, VP, and bacteremia patients will be limited to a total of no more than 40% of patients in Part A, regardless of resistance.

b. Part B will be the open-label, supportive portion of the study that will include patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms that are known to be resistant to colistin or polymyxin B, those failing a colistin or polymyxin B regimen prior to study entry or are on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia, as detailed in the inclusion criteria.

   Any patient who has a qualifying ABC infection and meets study inclusion criteria but has a contraindication to colistin due to underlying conditions, intolerance, or evidence of failing colistin or polymyxin B therapy prior to study entry, and/or has a colistin- or polymyxin B-resistant ABC infection cannot be enrolled in Part A but can be considered for enrollment in Part B (see the inclusion and exclusion criteria for details).

   Patients with ABC infections who are not otherwise eligible for Part A are expected to be enrolled in Part B. Patient enrollment in Part B will continue until Part A enrollment in the

CRABC m-MITT Population is complete. In Part B, patients will receive the following treatment:

- Group 3: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

Transfer from Part A to Part B: Since Part A will be the first time patients in intensive care are receiving ETX2514SUL, PK in the first approximately 30 patients must be verified prior to initiating Part B to ensure the treatment planned in Part B is optimal for the targeted patient population. Patients randomized to either group of Part A can only be transferred to Part B, once Part B is open for enrollment, if the ABC identified from the baseline culture is subsequently determined to be resistant to colistin or polymyxin B by the local microbiology laboratory. If Part B is not yet open for enrollment in a given country and a patient in Part A has a baseline culture determined to be colistin- or polymyxin B-resistant but is responding to therapy, the patient may remain in Part A at the discretion of the Investigator. A patient in Part A whose culture is determined to be colistin- or polymyxin B-resistant and who has not shown improvement or whose condition has worsened will be withdrawn from the study drug treatment. All such cases must be discussed with the Medical Monitor.

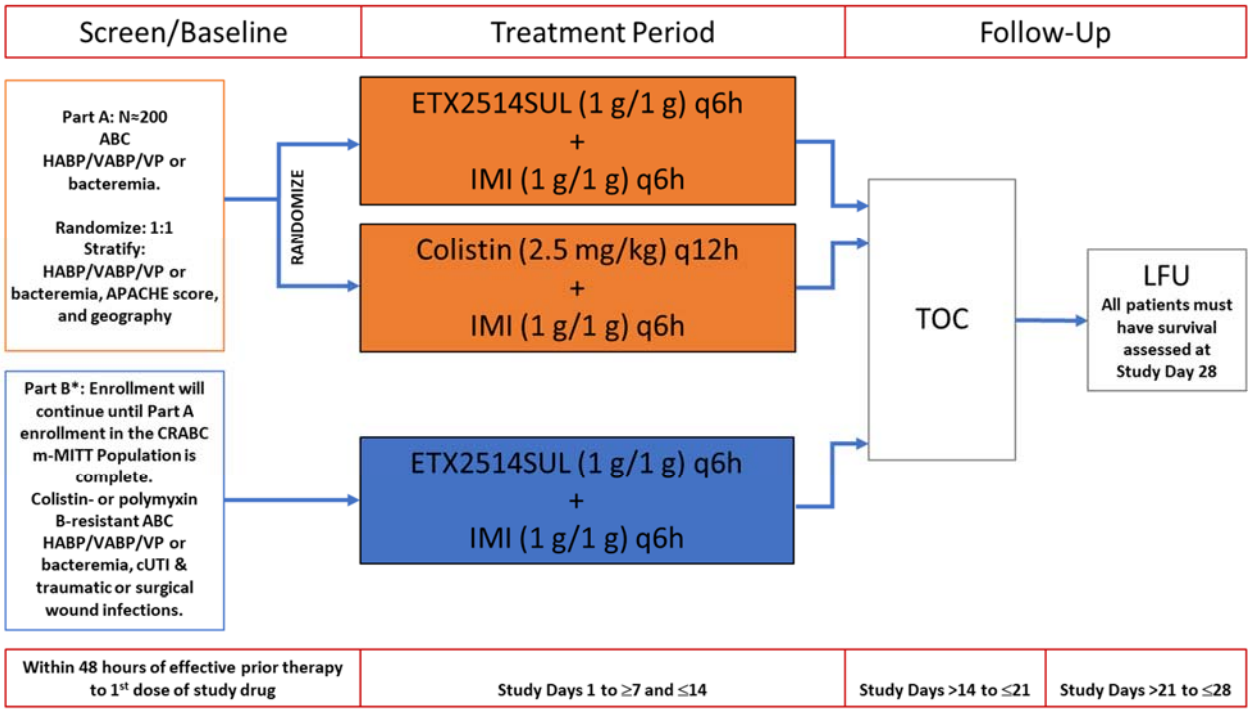
Any organism isolated from the blood or infection site-specific cultures will be identified by genus and species by the local laboratory. Organisms will be cultured and quantified (urine and bronchoalveolar lavage only) at the local laboratory, and susceptibility of the organism(s) will be performed per local laboratory standards. Isolates of pathogens cultured at the local laboratory are to be sent to the central laboratory for confirmation of identification and susceptibility testing.

No dosing regimen changes, other than those specified in the protocol for renal insufficiency or for patients on imipenem who develop a seizure that is thought to be directly related to imipenem, can occur without discussion with the Medical Monitor. Patients with cultures growing organisms with evidence of carbapenem resistance should remain on their assigned treatment regimen; treatment regimen changes can occur after 5 days after discussion with the Medical Monitor. If changes to the regimen are needed due to unsatisfactory clinical response, patients should be classified as clinical failures and discontinued from study drug. All patients should receive at least 48 hours of IV study drug (ie, 8 doses of ETX2514SUL plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in patients without dose adjustments) before the Investigator considers the patient to be a clinical failure and discontinues the patient from study drug therapy.

Note: Patients who experience focal tremors, myoclonus, or seizures at any point during the study should be evaluated neurologically, placed on anticonvulsant therapy (if not already instituted), and the dose of imipenem/cilastatin should be evaluated to determine whether it should be decreased or discontinued.

Day 1 is defined as the first day of study drug administration. The subsequent study days are defined by the number of treatment days thereafter. Treatment days should constitute 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy will be 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated. Refer to the Pharmacy Manual for specifics on dosing for all patients.

The overall study design is shown in the figure below.



*Part B: Part B will be the open-label, supportive portion of the study that will include patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms that are known to be resistant to colistin or polymyxin B, those failing a colistin or polymyxin B regimen prior to study entry or are on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia. The total number of patients enrolled in Part B may be adjusted based on the number needed to be enrolled in Part A to achieve the number needed to be treated in the CRABC m-MITT Population.
ABC = *Acinetobacter baumannii-calcoaceticus* complex; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; CRABC = Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; cUTI = complicated urinary tract infection; ETX2514SUL = sulbactam-ETX2514; HABP = hospital-acquired bacterial pneumonia; IMI = imipenem/cilastatin; LFU = Late Follow-up; m-MITT = Microbiologically Modified Intent-to-Treat; q6h = every 6 hours; q12h = every 12 hours; TOC = Test of Cure; VABP = ventilator-associated bacterial pneumonia; VP = ventilated pneumonia.

Patients who have early discontinuation of study drug dosing should perform all End of Treatment (EOT) Visit procedures and should be followed through the LFU Visit for safety assessments, even if the reason for discontinuation is clinical failure.

In Part A, clinical outcome assessments will be performed by a blinded assessor, in addition to the unblinded Investigator. Whenever possible, the same blinded assessor should complete all clinical outcome assessments for a study patient. If there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor will be used. If there is a missing assessment from either the blinded assessor or unblinded Investigator, the other available assessment will be used. An adjudication committee may be organized for endpoint adjudication should it be deemed necessary as determined by the Data Safety Monitoring Board (DSMB). In such a case, a charter will be developed that describes their activities.

Intense PK sampling will be performed on the first approximately 30 patients randomized in Part A. The purpose of the intense PK sampling is to ensure that exposures observed in this severely ill cohort are comparable to those observed thus far in prior clinical studies. The PK samples will be collected for both treatment groups in Part A to keep the study data blinded. Pharmacokinetic assessment of the initial 15 patients on ETX2514SUL in Part A will be performed by an

independent PK assessor, prior to the opening of enrollment in Part B. To explore the PK profile of the ETX2514SUL combination in Chinese patients with severe infection, the intense PK sample will also be collected from the first approximately 20 patients randomized in Part A at China Mainland sites. All other patients enrolled in the study (Parts A and B) will have samples collected for sparse PK analysis, which will be used to better inform the population PK model.

Patients will be enrolled in the study for approximately 28 days, with a maximum duration of 32 days. Screening laboratory analytes can be performed as standard of care up to 48 hours prior to randomization on Day 1, with the exception of local laboratory serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. The Treatment Period begins on Day 1, and study drug will be administered for 7 days (ie, 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin for those without dose adjustments) with a prolongation of therapy of up to 14 days if clinically indicated. The EOT Visit will be completed on the final dosing day or the following day. The Test of Cure (TOC) Visit will be completed 7 days (±2 days) after the EOT Visit for all patients. The LFU Visit will be completed 14 days (±2 days) after the EOT Visit for all patients. For patients with an LFU Visit occurring before Day 28, a telephone call to assess survival will be made on Day 28 or anytime thereafter. Every attempt must be made to record survival status at Day 28 or anytime thereafter for all randomized patients (including HABP/VABP/VP patients who are randomized to Part A based on a positive BPP rapid test, but who subsequently do not have growth of ABC in their respiratory sample culture), regardless of their status of treatment, as long as the patient has not withdrawn consent from participation in the study.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

In Part A, the following study drugs will be administered in a 1:1 randomized manner:

- Group 1 (experimental group): 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h; or
- Group 2 (control group): 2.5 mg/kg colistin IV infused over 30 minutes q12h (after an initial loading dose of colistin 2.5 to 5 mg/kg) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

In Part B, the following study drugs will be administered:

- Group 3 (experimental group): 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

EFFICACY VARIABLES:

The primary efficacy endpoint for the study is 28-day all-cause mortality in the CRABC m-MITT Population in Part A.

The secondary efficacy endpoints for Part A and Part B include the following:

- 28-day all-cause mortality in the Intent-to-Treat (ITT) Population;
- Clinical cure at TOC in the CRABC m-MITT Population;
- Clinical cure at TOC in the m-MITT, Clinical Evaluable (CE), Microbiologic Evaluable (ME), and CRABC ME Populations;

- Clinical cure at Day 5, Day 7, EOT, and LFU in the m-MITT, CRABC m-MITT, CE, ME, and CRABC ME Populations;
- Microbiological favorable assessment at Day 5, Day 7, EOT, TOC, and LFU in the m-MITT, CRABC m-MITT, ME, and CRABC ME Populations;
- 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations;
- 28-day all-cause mortality in the m-MITT and CRABC ME Populations; and
- PK exposure of ETX2514 and sulbactam in the PK Population.

The exploratory efficacy endpoints include the following:

- Clinical cure based on PK exposure;
- Clinical cure based on MIC distribution of ETX2514SUL;
- Clinical cure based on baseline resistance to ETX2514SUL, carbapenems, or colistin;
- Number of days in the intensive care unit;
- Number of patients transferred to the intensive care unit;
- For patients with VABP, VP, or ventilated HABP, number of days on ventilators;
- Number of days in the hospital; and
- Number of days on study drug treatment.

Outcome Definitions:

Clinical Outcome:

Clinical outcome will be used to determine a response of clinical success for all patients. Based on the assessment of signs and symptoms, the unblinded Investigator will choose 1 of the following clinical outcomes at the Day 5, Day 7, EOT Visit, TOC Visit, LFU Visit, and ET Visit, if applicable. In Part A, in addition to the unblinded Investigator, a blinded assessor will also determine clinical outcome. If there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor will be used. If there is a missing assessment from either the blinded assessor or unblinded Investigator, the other available assessment will be used. An adjudication committee may be organized for endpoint adjudication should it be deemed necessary by the DSMB. In such a case, a charter will be developed that describes their activities.

Clinical cure: complete resolution or significant improvement of signs and symptoms that were present at baseline and no new symptoms, such that no additional Gram negative antimicrobial therapy is warranted.

Clinical failure: symptoms present at study entry have not significantly improved or completely resolved, or new symptoms have developed and require the initiation of a non-study Gram negative antibacterial drug therapy, death, or intolerance to study drug leading to discontinuation from the study treatment.

Clinical indeterminate: determination cannot be made because of missing data or the patient is lost to follow-up.

Microbiologic Outcome:

Microbiologic outcome for bacteremia, complicated urinary tract infection, or acute pyelonephritis:

For patients with bacteremia, cUTI, or AP, per-patient microbiological response will be determined programmatically as 1 of the following outcomes based on the results of blood and/or urine cultures at the Day 5, Day 7, EOT, TOC, and LFU Visits. A microbiological favorable assessment will include eradication and presumed eradications, as detailed below.

Microbiologic eradication:

- For patients with cUTI or AP: the baseline strain of ABC is reduced to $<10^3$ colony-forming units (CFU)/mL on urine culture and negative on repeat blood culture (if positive at baseline); or
- For patients with bacteremia: absence of the baseline strain of ABC on culture.

Microbiologic presumed eradication: no culture was done, and the patient meets clinical criteria for clinical cure.

Microbiologic persistence:

- For patients with cUTI or AP: the demonstration that the urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry and/or a blood culture demonstrates the same baseline pathogen(s); or
- For patients with bacteremia: presence of the baseline strain of ABC on repeat culture.

Patients who are a persistence at EOT will be considered a persistence at TOC.

Microbiologic presumed persistence: no culture was done, and the patient meets clinical criteria for clinical failure.

Microbiologic indeterminate: if clinically indicated (for cUTI and bacteremia only), no follow-up culture is available, the culture cannot be interpreted for any reason, or the culture is considered contaminated.

Microbiologic recurrence:

- For patients with cUTI or AP: the demonstration that the urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry at any time after documented eradication at the TOC Visit up to and including the LFU Visit; or
- For patients with bacteremia: a positive blood culture for ABC at any time after documented eradication at the TOC Visit up to and including the LFU Visit.

Microbiologic outcome for hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, ventilated pneumonia, or surgical or post-traumatic wound infections:

Microbiologic presumed eradication: no culture was done, and the patient meets clinical criteria for clinical cure. For patients with HABP/VABP/VP or surgical or post-traumatic wound infections, where repeat culture samples may not be indicated, presumed eradication based on clinical improvement will be inferred.

Microbiologic presumed persistence: no culture was done, and the patient meets clinical criteria for clinical failure.

SAFETY VARIABLES:

The safety parameters include the incidence, severity, causality, and seriousness of treatment-emergent adverse events (TEAEs) and adverse events of special interest, including nephrotoxicity as measured by RIFLE criteria, and the evaluation of changes from baseline in safety laboratory test results, electrocardiograms (ECGs), vital signs, physical examinations, and chest X-ray/radiology/ultrasound and mechanical ventilator assessments for patients with HABP, VABP, or VP. Newly emergent infections that appear after baseline will be reported as adverse events and summarized separately.

STATISTICAL ANALYSES:

This study is designed to estimate treatment efficacy of ABC infections with a pivotal component in Part A.

Continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized by using the frequency count and the percentage of patients in each category as descriptive statistics.

All comparisons in Part A will be for ETX2514SUL plus imipenem/cilastatin versus colistin plus imipenem/cilastatin. The efficacy endpoints for Part B will be summarized descriptively only and will be used to supplement results in Part A. Listings of individual patient data will be produced.

The ITT Population will include all patients randomized to study drug treatment (ETX2514SUL plus imipenem/cilastatin or colistin plus imipenem/cilastatin) in Part A or enrolled in Part B, regardless of whether the patient actually receives study drug.

The Modified ITT (MITT) Population will include patients in Parts A and B who meet ITT criteria and receive any amount of study drug. The MITT Population will be considered the Safety Population. Patients with HABP/VABP/VP who were randomized to Part A on the basis of a BPP rapid test result but were subsequently withdrawn due to a lack of a culture growing ABC will be counted in the MITT and Safety Populations.

The m-MITT Population will include patients who meet MITT criteria and have an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory. If an isolate for testing at the central laboratory is not available, the local laboratory data can be used to confirm the presence of ABC organism, as long as the local laboratory uses modern methods of diagnosis such as molecular-based tests, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, Vitek, Phoenix, etc (ie, not conventional biochemical or manual phenotypic methods). Patients with HABP/VABP/VP who are enrolled based upon a positive BPP rapid test for ABC, but subsequently are found to have respiratory sample cultures that do not grow ABC (by the local laboratory), will be withdrawn from the study drug treatment. These patients will not be included in the m-MITT Population but will remain in the MITT Population.

The CRABC m-MITT Population will include patients who meet m-MITT criteria and have a baseline ABC organism that is confirmed to be carbapenem-resistant (MIC to imipenem/meropenem ≥8 mg/L) by the central laboratory or by the local laboratory if the central

laboratory is not able to identify the isolate for any reason. Patients will be excluded from the CRABC m-MITT Population if they have isolates that are deemed by the central laboratory to be resistant to ETX2514SUL (MIC >4 mg/L) or colistin (MIC ≥4 mg/L), if their blood culture or respiratory samples are collected more than 72 hours prior to randomization, if they are transferred from Part A to Part B, or if they are enrolled with infections other than ABC pneumonia or bloodstream infection (ie, ABC infections other than HABP, VABP, VP, and bacteremia). A sensitivity analysis for the primary efficacy endpoint will be performed for patients whose eligible culture is >48 hours from the first dose of study drug, as well as for all patients with and without evidence of non-susceptibility to colistin and ETX2514SUL at baseline.

The CE Population will include patients who meet m-MITT criteria and meet evaluability criteria (meet key inclusion criteria, do not have key exclusion criteria, received at least 72 hours of study drug [ie, 12 doses of ETX2514SUL plus 12 doses of imipenem/cilastatin or 6 doses of colistin plus 12 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical cure, received at least 48 hours of study drug [ie, 8 doses of ETX2514SUL plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical failure, received ≥80% of anticipated doses, and did not have a clinical response of indeterminate at the TOC Visit).

The ME Population will include patients who meet m-MITT criteria and CE criteria and have an appropriately collected culture specimen and interpretable culture result when specimen collection is clinically indicated at the TOC Visit.

The CRABC ME Population will include patients who meet ME criteria and who have a baseline ABC organism that is confirmed to be carbapenem-resistant (and susceptible to ETX2514SUL for Parts A and B and susceptible to colistin for Part A).

The PK Population will include patients who receive any amount of study drug and have evaluable PK data.

Efficacy:

The primary efficacy endpoint for the study is 28-day all-cause mortality in the CRABC m-MITT Population in Part A. Patients in the CRABC m-MITT Population who discontinue study drug prematurely in Part A for any reason will be included in the assessment of 28-day all-cause mortality, provided consent has not been withdrawn.

A sensitivity analysis for the primary efficacy endpoint will be performed for patients whose eligible culture is >48 hours from the first dose of study drug, as well as for all patients with and without evidence of non-susceptibility to colistin and ETX2514SUL at baseline.

The non-inferiority assessment will be based on the 2-sided 95% confidence intervals (CIs) for the difference ([ETX2514SUL + imipenem/cilastatin] – [colistin + imipenem/cilastatin]) in 28-day all-cause mortality rates between the treatment groups. Non-inferiority will be concluded if the upper limit of the 2-sided 95% CI is less than +20%.

If non-inferiority is achieved, a test of superiority will be performed.

The analysis of the primary efficacy endpoint 28-day all-cause mortality will also be performed in the ITT Population.

The number and percentage of patients in each response category for the secondary efficacy endpoints will be summarized by treatment group for the populations defined earlier. Two-sided

95% CIs for the difference in outcome rates between the treatment groups in Part A will be provided.

Part B data will be analyzed separately from Part A using descriptive statistics.

Further subgroup analyses will be conducted, and details of the analysis will be described in the Statistical Analysis Plan (SAP).

Exploratory endpoint analysis will be described in the SAP. Exploratory endpoints for health resource utilization difference between treatment groups (such as length of ventilation, intensive care unit stay, hospitalization, additional antibiotic use, etc) will be reported separately. Efficacy analysis for patients with HABP/VABP/VP who are identified as positive for ABC by BPP molecular methodology will be explored.

Pharmacokinetics:

Descriptive statistics will be provided for PK concentration data and PK parameters. All PK analyses will be performed using the PK Population.

For the intense PK group, PK samples will be obtained from the first approximately 30 patients randomized in Part A. The PK samples will be collected for both treatment groups in Part A to keep the study data blinded. The PK samples obtained from the ETX2514SUL group will be analyzed for ETX2514 and sulbactam concentrations using a validated assay by a central bioanalytical laboratory. Pharmacokinetic assessment of the initial 15 patients on ETX2514SUL in Part A will be performed by an independent PK assessor, prior to the opening of enrollment in Part B. The independent PK assessor will conduct sequential PK analysis from patients as they are enrolled. An initial aggregate assessment of PK parameters will be done after enrollment of the first 8 HABP/VABP/VP patients randomized to ETX2514SUL. The independent PK assessor will report results to the DSMB, relative to concentrations projected in the population PK model, once data from all 15 patients on ETX2514SUL is available. However, if the preliminary analysis of the first 8 patients with HABP/VABP/VP on ETX2514SUL reveals evidence of inadequate exposure this will be escalated to the DSMB.

The intense PK sampling will also be performed on the first approximately 20 patients randomized in Part A from China Mainland sites. The PK samples obtained from patients who have received the ETX2514SUL treatment will be analyzed for ETX2514 and sulbactam concentrations, which will be applied to build the population PK model combined with data from the sparse PK group.

For the sparse PK group, PK samples will be obtained from all other patients enrolled in the study (Parts A and B), which will be used to better inform the population PK model.

Analysis of the PK data and incorporation into the population PK analysis and PK/pharmacodynamic model will be described in a separate PK Analysis Plan.

Safety:

All patients who receive any amount of study drug (MITT Population) will be included in the safety analyses. Patients who received the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

A primary analysis of safety will be performed for Part A to assess the proportion of patients with nephrotoxicity, as measured by the RIFLE criteria based on the Safety and CE Populations.

Overall safety will be assessed for Part A and Part B in the Safety Population. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a TEAE for each unique system organ class and preferred term will be tabulated. A TEAE is defined as an adverse event occurring on or after the administration of the first dose of study drug. Treatment-emergent adverse events will also be tabulated by treatment group, severity, and the relationship to study drug as assessed by the Investigator. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a treatment-emergent serious adverse event will be tabulated. The number and percentage of patients (in each treatment group) prematurely discontinuing study drug treatment due to a TEAE will be tabulated by system organ class and preferred term. Adverse events of special interest in Part A will be summarized for all patients by treatment.

Safety laboratory data will be presented by descriptive statistics of the post-baseline value and the change from baseline, as well as the number and percentage of patients with potentially clinically significant laboratory values. Descriptive statistics of vital signs and ECG parameters and the change from baseline will also be presented. An outlier analysis of the ECG parameters will be conducted.

SAMPLE SIZE DETERMINATION:

Patients will be enrolled until there are 120 patients in the CRABC m-MITT Population in Part A. The study will have 80% power to demonstrate non-inferiority between Group 1 and Group 2 using a 20% non-inferiority margin and a 2-sided 95% CI. This assumes a mortality rate in the comparator group (Group 2) of 41% and in the ETX2514SUL group (Group 1) of 36%. To have 120 patients in the CRABC m-MITT Population, Part A will need to enroll approximately 200 patients, assuming 60% of ABC clinical isolates are carbapenem-resistant. Patient enrollment in Part B (Group 3) will continue until Part A enrollment in the CRABC m-MITT Population is complete. Rates of carbapenem resistance among isolates from Part A patients will be monitored by the unblinded data manager/designee at the Clinical Research Organization on an ongoing basis.

SITES: Approximately 100 global sites.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
A. baumannii	*Acinetobacter baumannii*
ABC	*Acinetobacter baumannii-calcoaceticus* complex
ALT	Alanine aminotransferase
AP	Acute pyelonephritis
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
BL	β-lactam
BLI	β-lactamase inhibitor
BPP	Biofire® FilmArray® 2.0 Pneumonia Panel
CBA	Colistin base activity
C. difficile	*Clostridium difficile*
CE	Clinical Evaluable
CFR	Code of Federal Regulations
CFU	Colony-forming units
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CMS	Colistimethate sodium
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CRABC	Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex
CT	Computed tomography
CTA	Clinical trial authorization
cUTI	Complicated urinary tract infection
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
ET	Early Termination
ETX2514SUL	Sulbactam-ETX2514
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HABP	Hospital-acquired bacterial pneumonia
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IU	International unit
IV	Intravenous(ly)
LFT	Liver function test
LFU	Late Follow-up
MAP	Mean arterial pressure
MDR	Multi-drug resistant
ME	Microbiologic Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MITT	Modified Intent-to-Treat
MIU	Million international unit
m-MITT	Microbiologically Modified Intent-to-Treat
MRI	Magnetic resonance imaging
P. carinii	*Pneumocystis carinii*
PD	Pharmacodynamic
PEEP	Positive end-expiratory pressure
PK	Pharmacokinetic(s)
q6h	Every 6 hours
q12h	Every 12 hours
qSOFA	Quick Sequential Organ Failure Assessment
QTcF	QT interval corrected using Fridericia's formula
RIFLE	Risk–Injury–Failure–Loss–End-stage renal disease
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Failure Assessment
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
ULN	Upper limit of normal
US	United States
VABP	Ventilator-associated bacterial pneumonia
VP	Ventilated pneumonia
WBC	White blood cell
WHO	World Health Organization
XDR	Extremely drug resistant

1 INTRODUCTION AND BACKGROUND INFORMATION

There is a significant unmet medical need to identify new agents to treat *Acinetobacter baumannii (A. baumannii)-calcoaceticus* complex (ABC) infections. Sulbactam-ETX2514 (ETX2514SUL) is a novel bactericidal β-lactam (BL)/β-lactamase inhibitor (BLI) combination, which is being developed for the treatment of infections caused by ABC, including multi-drug resistant (MDR) and carbapenem-resistant ABC (CRABC) isolates.

Acinetobacter baumannii, a non-fermenting Gram negative bacterial species, is increasingly being recognized as an important cause of severe infections, particularly in compromised hospital patients. It is a significant public health concern and is classified as a "serious threat" pathogen in the recent United States (US) Centers for Disease Control and Prevention "Antibiotic Resistance Threats in the United States" report[1] and is ranked as "critical" on the World Health Organization (WHO) global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.[2] *Acinetobacter baumannii* causes severe infections that are associated with high mortality. Approximately 2% of healthcare-associated infections are caused by *A. baumannii*.[3] Patients on mechanical ventilators and those with central line-catheters have the highest proportion of infections caused by *A. baumannii*. Serious infections caused by *A. baumannii*, including hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP), ventilated pneumonia (VP), complicated urinary tract infection (cUTI), bacteremia, and wound infections, are estimated to occur in 70,000 patients to 90,000 patients in the United States per year, of which approximately 63% are caused by MDR isolates.[4] Multi-drug resistance in *A. baumannii* is an evolving problem, with some countries in Europe reporting carbapenem resistance rates >50%.[5] Mortality associated with bacteremia and pneumonia caused by *A. baumannii* ranges from 30% to 50%.[6,7] The risk of death associated with infections caused by *A. baumannii* isolates resistant to carbapenems is even higher,[1,7] and MDR *A. baumannii* is an evolving global problem. While most reports focus on *A. baumannii* as the etiological agent of these infections, several very closely related *Acinetobacter* species that are genotypically distinct but phenotypically indistinguishable from *A. baumannii* also cause human disease. Therefore, this group is referred to as the "*Acinetobacter baumannii-calcoaceticus* complex".[8]

In the early 1960s to 1970s, infections due to *A. baumannii* were managed effectively with BL antibiotics, as the rates of resistance to available antimicrobial classes were low.[9,10] However, by the end of the 1970s, resistance to aminoglycosides and BL antibiotics had been reported. In the 1980s, carbapenems such as imipenem became the drug of choice for treatment of *A. baumannii* infections; widespread carbapenem resistance, however, has now been observed in many countries.[1,10]

In the late 1990s to 2000s, the in vitro activity and clinical effectiveness of sulbactam against *A. baumannii* were demonstrated.[9] There has been a steady decline, however, in the in vitro susceptibility of *A. baumannii* to sulbactam. Presently, the majority of *A. baumannii* isolates are MDR, defined as non-susceptible to at least 3 or more antimicrobial categories, and many are extremely drug resistant (XDR), defined as non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories.[11] For example, data from the Healthcare Safety Network summarizing healthcare-associated infections reported that approximately 60% to 70% of *A. baumannii* isolates causing pneumonia or bacteremia were resistant to carbapenems and were identified as MDR.[3]

ETX2514 is a novel, rationally designed diazabicyclooctenone BLI. It is a potent inhibitor of Classes A and C β-lactamases and a broad-spectrum inhibitor of Class D β-lactamases. ETX2514 has no activity against Class B β-lactamases. ETX2514 is not a BL. It displays a covalent, reversible mechanism of inhibition through β-lactamase active-site serine carbamoylation. ETX2514 exhibits intrinsic activity against some *Enterobacteriaceae* but has no significant clinical activity against *A. baumannii*.

Sulbactam is a penicillin derivative and is used widely as an inhibitor of β-lactamases. Although sulbactam is available as a standalone product in a small number of countries (eg, Combactam™, Germany), the vast majority of human use is in combination with BL (eg, Unasyn™, ampicillin/sulbactam). Unasyn is approved by regulatory authorities in the United States, Europe, and the Asia-Pacific region.

Entasis Therapeutics is developing ETX2514SUL for the treatment of serious infections caused by *A. baumannii*. The dose of sulbactam, 1 g once every 6 hours (q6h) (maximum daily dose in patients with normal renal clearance of 4 g), that will be used in combination with ETX2514 is the highest dose approved for human use.

1.1 Nonclinical Experience With ETX2514

Nonclinical data are provided in more detail in the Investigator's Brochure.

The nonclinical safety program for ETX2514 includes toxicology studies up to 14 days duration in rats and dogs, safety pharmacology, and genetic toxicity. These studies demonstrate that ETX2514 was generally well tolerated and was not associated with target organ toxicity when administered in doses up to 2000 mg/kg. ETX2514 did not exhibit high protein binding, and in vitro data did not indicate significant drug-drug interactions via cytochrome P450 pathways or interactions with hepatic or renal transporters. ETX2514 was largely excreted unchanged in the urine. Reproductive toxicology studies are currently ongoing.

1.2 Clinical Experience With ETX2514

A summary of clinical experience is provided in greater detail in the Investigator's Brochure.

ETX2514 has been evaluated both alone and in combination with sulbactam and/or imipenem/cilastatin in a Phase 1 first-in-human study. This study evaluated single ascending doses and multiple ascending doses of ETX2514 to fully characterize the safety and pharmacokinetics (PK) profile of ETX2514. In addition, this study evaluated if there was any clinically significant drug-drug interaction between sulbactam, ETX2514, and imipenem/cilastatin.

Additionally, a Phase 1 study evaluated lung penetration by ETX2514 and sulbactam in 30 healthy volunteers. Administration of single doses of ETX2514SUL was also studied in patients with mild, moderate, or severe renal insufficiency, as well as in hemodialysis patients.

A Phase 2 study in patients with cUTI or acute pyelonephritis (AP) has been completed. The primary objective of this study was to assess the safety of ETX2514SUL in moderately ill hospitalized patients. Study CS2514-2514-2017-0003 was conducted at 20 sites in 4 countries (Belarus, Bulgaria, Russia, and Ukraine). This study was a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of intravenous (IV) ETX2514SUL in patients with cUTIs or AP who were otherwise relatively healthy. Patients providing informed consent and meeting all study eligibility criteria were enrolled and had a pretreatment urine and blood sample obtained and submitted to the local laboratory. Eighty patients were randomized in

a 2:1 ratio (53 patients randomized into the ETX2514SUL group and 27 patients randomized into the placebo group) to receive either 1 g ETX2514/1 g sulbactam IV (infused over 3 hours) or matching placebo q6h, respectively. All patients received background therapy with 500 mg/500 mg IV imipenem/cilastatin q6h (infused over 30 minutes). Therapy was continued for 7 days, with the option to increase for up to 14 days if bacteremia was present.

Key findings from the above studies are summarized below:

- ETX2514 demonstrated linear PK and had no evidence of accumulation.
- ETX2514 did not interact with sulbactam and/or imipenem/cilastatin.
- ETX2514 was predominantly excreted renally and dose adjustments were necessary for patients with moderate or severe renal insufficiency including dialysis. Similarly, higher doses are recommended for patients with augmented renal clearance or receiving continuous renal replacement therapy.
- ETX2514SUL demonstrated good penetration of the lung epithelium.

Efficacy results:

- ETX2514SUL when dosed with imipenem/cilastatin showed comparable efficacy to placebo + imipenem/cilastatin in treatment of hospitalized patients with cUTI or AP. Among patients with imipenem nonsusceptible infections, imipenem combined with ETX2514SUL was able to successfully treat 3 out of 3 infections.

Safety and tolerability results:

- ETX2514 was generally safe and well tolerated when given alone or with sulbactam and/or imipenem/cilastatin.
- To date, there have been no serious adverse drug reactions or deaths in clinical studies.
- The most common adverse events reported were headache and infusion site reactions, including phlebitis and vascular pain at the infusion site.
- Mild reductions in total white blood cell (WBC) and absolute neutrophil counts have been observed with multiple doses of ETX2514, although no events of leukopenia or neutropenia have been observed.
- Asymptomatic, transient increases in hepatic enzymes (unaccompanied by increases in bilirubin) have been observed with ETX2514SUL, and these are thought to be related to known effects of sulbactam.
- Mild to moderate allergic reactions including urticaria have been observed at rates <1% with ETX2514SUL.
- No clinically significant changes in vital signs or electrocardiogram (ECG) parameters have been observed in patients treated with ETX2514SUL. Transient increases in systolic blood pressure within normal ranges were observed in healthy elderly subjects dosed with ETX2514SUL.
- ETX2514, at the studied doses, had no clinically relevant effects on studied ECG parameters in a thorough QT study conducted in healthy volunteers.

1.3 Rationale

Entasis Therapeutics is developing ETX2514SUL for the treatment of serious infections caused by ABC, particularly those that are resistant to carbapenems. The dose of sulbactam, 1.0 g q6h (maximum daily dose in patients with normal renal clearance of 4 g), that will be used in combination with ETX2514 is the highest dose approved for human use, often in combination with ampicillin or cefoperazone.

ETX2514 is a novel diazabicyclooctenone BLI with a spectrum of activity that encompasses clinically important β-lactamases of Ambler Class A and C and broad-spectrum inhibition of Class D β-lactamases. ETX2514 is not a BL. ETX2514 has greater potency than comparator BLIs, including clavulanic acid, tazobactam, and avibactam against all Class A, C, and D enzymes tested. ETX2514 does not inhibit the Class B New Delhi Metallo-β-lactamase 1.

Sulbactam is classified as a BLI but also has intrinsic antibacterial activity against *A. baumannii* due to its inhibition of Penicillin Binding Protein 3, a transpeptidase that is essential for the final step of bacterial peptidoglycan synthesis.[12] Although no breakpoint for *A. baumannii* has been established by the European Committee on Antimicrobial Susceptibility Testing or Clinical and Laboratory Standards Institute (CLSI) for sulbactam alone, sulbactam is used in combination with ampicillin (in a 2:1 ampicillin:sulbactam ratio) in therapy for *A. baumannii*. The CLSI has established breakpoints of 8/4 (ampicillin/sulbactam) mg/L for this agent for *Acinetobacter* species. Because the activity of ampicillin/sulbactam versus *A. baumannii* can be attributed to the sulbactam component alone, the CLSI-defined susceptible breakpoint of 8/4 (ampicillin/sulbactam) mg/L that applies to the combination suggests a susceptible breakpoint of 4 mg/L for sulbactam alone in *A. baumannii*.

The addition of ETX2514 to sulbactam in vitro restores the activity of sulbactam such that the minimum inhibitory concentration (MIC) to inhibit 90% of growth versus a collection of recent *A. baumannii* clinical isolates shifts from >32 mg/L to 2 mg/L in the presence of ETX2514 (held constant at 4 mg/L). In vitro experiments supported a susceptibility-testing paradigm of holding the concentration of ETX2514 constant at 4 mg/L while varying the sulbactam concentration in 2-fold increments. This activity of sulbactam-ETX2514 was consistent across *A. baumannii* isolates from different geographic regions and infection types and did not change in subsets of meropenem-resistant, colistin-resistant, or MDR isolates, nor did it change over time (a total of 3611 isolates collected from 2011 to 2018 were tested). A detailed assessment of human dose projection of sulbactam-ETX2514 was performed utilizing PK parameters from human Phase 1 and Phase 2 data, lung penetration data, PK/pharmacodynamic (PD) targets, and current MIC distribution versus *A. baumannii*. A preliminary probability of target attainment was completed. The result of these analyses suggested a 3-hour infusion of 1.0 g sulbactam/1.0 g ETX2514 administered 4 times a day is predicted to be effective to treat patients infected with *A. baumannii* with MICs ≤4 mg/L. Complete details of this assessment can be found in the Investigator's Brochure.

Current treatment guidelines (Infectious Diseases Society of America/American Thoracic Society) for the treatment of HABP/VABP/VP due to *A. baumannii* recommend the use of carbapenems or ampicillin/sulbactam as first-line agents as long as the isolates are sensitive to these drugs. However, in the event of carbapenem resistance, the current recommended regimens are to use polymyxins such as colistin to treat these infections. This study utilizes a combination of colistin and imipenem as the comparator. The combination of a carbapenem with a polymyxin has been shown to have increased activity in vitro against *A. baumannii*.[13] The selection of the comparator

for this study is challenging. The possibility of utilizing "best-available care" as the comparator was considered, but it was determined that this was not a satisfactory option because of the size of the study and the potential to confound assessment of comparative efficacy. On a world-wide basis, including Europe, the majority of ABC isolates are MDR. Common regimens that are utilized include colistin either alone or plus a carbapenem and tigecycline plus 1 or more agents. It is of interest that tigecycline is not indicated for treatment of patients with pneumonia in Europe or for the treatment of HABP/VABP/VP in the United States.

Based on these considerations, this study will use colistin plus imipenem/cilastatin as the comparator. Imipenem/cilastatin is indicated for the treatment of HABP/VABP/VP and is widely used in this indication. Part A will enroll patients prior to the availability of antibiotic sensitivities, and it is anticipated that approximately 40% of ABC infections could be sensitive to carbapenem. Imipenem/cilastatin would be the drug of choice in this population. For those patients with CRABC infection, colistin would be the drug of choice. Although recent data[14] suggest that the addition of a carbapenem to colistin may not be synergistic in the treatment of CRABC infections, there was no suggestion of a negative effect of this combination. Moreover, discontinuation of imipenem/cilastatin in these patients after randomization will result in unblinding of treatment assignment. Lastly, assessment of efficacy of the combination of ETX2514 with both sulbactam *and* imipenem/cilastatin in the treatment of CRABC infections would entail not discontinuing the carbapenem in the investigational treatment group. Hence, all patients in this study will receive imipenem/cilastatin regardless of the carbapenem sensitivity of the ABC infection.

This is a Phase 3, randomized, active-controlled pivotal study to evaluate the efficacy and safety of IV ETX2514SUL plus imipenem/cilastatin compared to colistin plus imipenem/cilastatin in the treatment of patients with ABC infections. In Part A, all patients will receive imipenem/cilastatin as the best treatment option for HABP, VABP, VP, and/or bacteremia caused by ABC. In addition, the experimental group will receive ETX2514SUL, while the comparator group will receive colistin, both agents targeting drug-resistant ABC. These combinations of drugs should provide all patients with the best treatment options for ABC infections, while anticipating a high rate of drug resistant ABC infections.

Part B will be the open-label, supportive portion of the study that will include patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms that are known to be resistant to colistin or polymyxin B, those failing a colistin or polymyxin B regimen prior to study entry or are on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia. The goal is to gather preliminary efficacy and safety data in the setting of these other infections and provide a salvage option for XDR strains of ABC infections; hence, Part B will not be pivotal and will not have a comparator. The objective of Part B will be to estimate efficacy of the combination of sulbactam and ETX2514 against colistin- or polymyxin B-resistant ABC infecting various sites, as supporting evidence for Part A results. Safety of ETX2514SUL will be assessed as a whole in Part A and Part B.

1.4 Risk/Benefit

No unique contraindications have been determined for ETX2514. Contraindications to the use of sulbactam include a history of hypersensitivity or allergic reactions to sulbactam or any cephalosporin, penicillin, or carbapenem.

ETX2514 was well tolerated in repeat dose animal toxicology studies; no specific safety signals were observed that require special monitoring in human subjects. Reductions in absolute neutrophil count and monocytes were reported in the dog repeat dose toxicity studies and will be monitored by routine hematology assessments in human subjects.

Studies in healthy adult and elderly subjects and in patients with renal impairment or cUTI have revealed no serious adverse drug reactions or deaths to date, and the withdrawal rate due to adverse events has been low (1%). Adverse events have generally been mild to moderate in severity. The most common treatment-emergent adverse events (TEAEs) in both healthy elderly subjects and in patients have included injection site reactions/pain and headache; the less common TEAEs in patients were nausea, diarrhea, and vomiting. Overall, ETX2514SUL has been well tolerated, and only 1 drug-unrelated serious adverse event (SAE) has been reported to date. Doses of ETX2514SUL must be adjusted in patients with impaired renal function. Mild decreases from baseline in mean WBC and neutrophil counts have been observed in subjects receiving ETX2514 alone or multiple doses of ETX2514 with imipenem/cilastatin. Mild increases in alanine aminotransferase (ALT) were observed with administration of ETX2514SUL with imipenem/cilastatin. These findings were not considered clinically significant since mean values remained within the reference range at all time points. However, WBC counts and hepatic function will be monitored closely in ongoing clinical studies. No clinically significant changes in vital signs or ECG parameters have been observed in patients treated with ETX2514SUL with or without imipenem/cilastatin.

Although sulbactam is available as a standalone product in a small number of countries (eg, Combactam, Germany), the vast majority of human use is in combination with BLs (eg, Unasyn, combination of ampicillin/sulbactam). The clinical safety of sulbactam has been established by nearly 30 years of experience with Unasyn. Based on the product label, Unasyn is generally safe and well tolerated. The dose of sulbactam that will be used in combination with ETX2514 is the highest dose approved for human use (1.0 g q6h, maximum daily dose in patients with normal renal clearance of 4.0 g).[15] The most frequently reported adverse events reported with Unasyn are nausea, vomiting, diarrhea, pain at the injection site, and skin rash. Hepatic dysfunction, including hepatitis and cholestatic jaundice, has been associated with the use of sulbactam. Hepatic toxicity is usually reversible; however, deaths have been reported. Routine monitoring of liver function will be conducted at baseline and during and after administration of ETX2514SUL.

Dose adjustments are necessary for severe renal insufficiency and hemodialysis patients. It is expected that the combination of ETX2514SUL with imipenem/cilastatin will have high levels of penetration in the lung and, hence, should show good efficacy in treatment of patients with ABC pneumonia. Reproductive studies for ETX2514 have not yet been completed, so precautions against exposure in pregnant women and avoidance of pregnancy of participants in this study are necessary. Allergic and hypersensitivity reactions are a potential risk, as with all antimicrobials, and patients with serious known allergies to BLs will not be enrolled in the study.

Colistin is now used routinely for Gram negative infections that are resistant to carbapenems, based on treatment guidelines in most countries with high prevalence of such infections. The risk of nephrotoxicity and neurotoxicity are well described in the colistin label and the literature. Dosing of colistin in this trial is weight-based and will be adjusted based on daily calculations of estimated glomerular filtration rate (eGFR). Patients will be monitored for worsening renal function and

signs of neurotoxicity. Patients with contraindications for colistin treatment may be considered for enrollment in Part B of the study.

Imipenem/cilastatin is indicated for a broad variety of infections and has been approved for use for many years for the treatment of serious infections, including those caused by ABC. Key risks, including hypersensitivity and seizures, are well documented in the literature. Dose adjustments for renal insufficiency are being implemented in the dosing of patients in this protocol as a key risk mitigation. Drugs that are contraindicated with the use of imipenem/cilastatin are not allowed for use in this protocol.

2 STUDY OBJECTIVES

This is a 2-part study, with Part A being the randomized, controlled portion of the study in patients with ABC HABP, VABP, VP, or bacteremia. Part B is the single-group portion of the study and includes ABC infections that are resistant to or have failed colistin or polymyxin B treatment, as detailed in the inclusion criteria.

2.1 Primary Objectives

The primary objectives of this study are the following:

- To compare the efficacy of ETX2514SUL plus imipenem/cilastatin to colistin plus imipenem/cilastatin in patients with CRABC infections in Part A; and
- To compare the incidence of nephrotoxicity, as measured by the Risk–Injury–Failure–Loss–End-stage renal disease (RIFLE) criteria, of ETX2514SUL to colistin in patients with ABC infections in Part A.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To compare the efficacy of ETX2514SUL plus imipenem/cilastatin to colistin plus imipenem/cilastatin in all randomized patients in Part A;
- To evaluate the efficacy of ETX2514SUL plus imipenem/cilastatin in patients with colistin- or polymyxin B-resistant ABC infections in Part B;
- To estimate the efficacy of ETX2514SUL plus imipenem/cilastatin for each primary infection site;
- To evaluate and compare the safety of ETX2514SUL and colistin;
- To describe the overall safety profile of ETX2514SUL; and
- To determine the systemic exposure of ETX2514 and sulbactam in a small cohort of severely ill patients administered ETX2514SUL in Part A.

2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To evaluate the efficacy of ETX2514SUL in relation to PK exposure;
- To evaluate the efficacy of ETX2514SUL in relation to MIC distribution of ETX2514SUL;
- To evaluate the efficacy of ETX2514SUL in relation to total duration of treatment received; and
- To compare the resource utilization of patients receiving ETX2514SUL plus imipenem/cilastatin to patients receiving colistin plus imipenem/cilastatin.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This study is a randomized, active-controlled study to evaluate the safety and efficacy of IV ETX2514SUL in patients with ABC infections. Patients providing informed consent and meeting all study eligibility criteria will be enrolled in the study and have pretreatment blood and infection site-specific samples obtained and submitted to the local laboratory.

The study will be enrolled in 2 parallel parts, with the PK data from the first approximately 30 patients in Part A (with only 15 patients dosed with ETX2514SUL) reviewed prior to initiating enrollment in Part B:

a. Part A will be the pivotal, assessor-blind, randomized, comparative portion of the study in patients with documented ABC HABP, VABP, VP, or bacteremia. While study drugs will not be masked due to logistical reasons, every attempt will be made to maintain the blind for patients, all staff at the site, and the Sponsor or its designees, except for the treatment physician and other immediate healthcare providers (see Section 5.4). In Part A, patients will be randomized 1:1 to 1 of the following treatment groups:

   - Group 1: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h; or
   - Group 2: 2.5 mg/kg colistin IV infused over 30 minutes every 12 hours (q12h) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

   Patients will be enrolled until there are 120 patients in the CRABC Microbiologically Modified Intent-to-Treat (m-MITT) Population in Part A, as determined by the central microbiology laboratory. Approximately 200 patients are expected to be enrolled in Part A, assuming approximately 60% of patients will have CRABC (see Section 9 for complete details). The HABP/VABP/VP patients who are randomized to Part A based on a positive screening of a respiratory sample for ABC by the Biofire® FilmArray® 2.0 Pneumonia Panel (BPP), but who subsequently do not have growth of ABC in their respiratory sample culture processed by the local microbiology laboratory, will be withdrawn from the study drug treatment.

   Randomization will be stratified by indication (HABP/VABP/VP versus bacteremia), severity of illness (based on Acute Physiology and Chronic Health Evaluation [APACHE] II [10 to 19 versus 20 to 30], Sequential Organ Failure Assessment [SOFA] [7 to 9 versus ≥10], or quick SOFA [qSOFA] [2 versus 3] score at Screening), and geography (China Mainland versus Rest of World). In the situation where a patient has more than one score reported, the scores will be used in the following order: APACHE, SOFA, and qSOFA.

   Enrollment of HABP, VP, and bacteremia patients will be limited to a total of no more than 40% of patients in Part A, regardless of resistance.

b. Part B will be the open-label, supportive portion of the study that will include patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms that are known to be resistant to colistin or polymyxin B, those failing a colistin or polymyxin B regimen prior to study entry or are on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia, as detailed in Section 4.1.3.

Any patient who has a qualifying ABC infection and meets study inclusion criteria but has a contraindication to colistin due to underlying conditions, intolerance, or evidence of failing colistin or polymyxin B therapy prior to study entry, and/or has a colistin- or polymyxin B-resistant ABC infection cannot be enrolled in Part A but can be considered for enrollment in Part B (see Section 4 for details).

Patients with ABC infections who are not otherwise eligible for Part A are expected to be enrolled in Part B. Patient enrollment in Part B will continue until Part A enrollment in the CRABC m-MITT Population is complete. In Part B, patients will receive the following treatment:

- Group 3: 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

Transfer from Part A to Part B: Since Part A will be the first time patients in intensive care are receiving ETX2514SUL, PK in the first approximately 30 patients must be verified prior to initiating Part B to ensure the treatment planned in Part B is optimal for the targeted patient population. Patients randomized to either group of Part A can only be transferred to Part B, once Part B is open for enrollment, if the ABC identified from the baseline culture is subsequently determined to be resistant to colistin or polymyxin B by the local microbiology laboratory. If Part B is not yet open for enrollment in a given country and a patient in Part A has a baseline culture determined to be colistin- or polymyxin B-resistant but is responding to therapy, the patient may remain in Part A at the discretion of the Investigator. A patient in Part A whose culture is determined to be colistin- or polymyxin B-resistant and who has not shown improvement or whose condition has worsened will be withdrawn from the study drug treatment. All such cases must be discussed with the Medical Monitor.

Any organism isolated from the blood or infection site-specific cultures will be identified by genus and species by the local laboratory. Organisms will be cultured and quantified (urine and bronchoalveolar lavage [BAL] only) at the local laboratory, and susceptibility of the organism(s) will be performed per local laboratory standards. Isolates of pathogens cultured at the local laboratory are to be sent to the central laboratory for confirmation of identification and susceptibility testing.

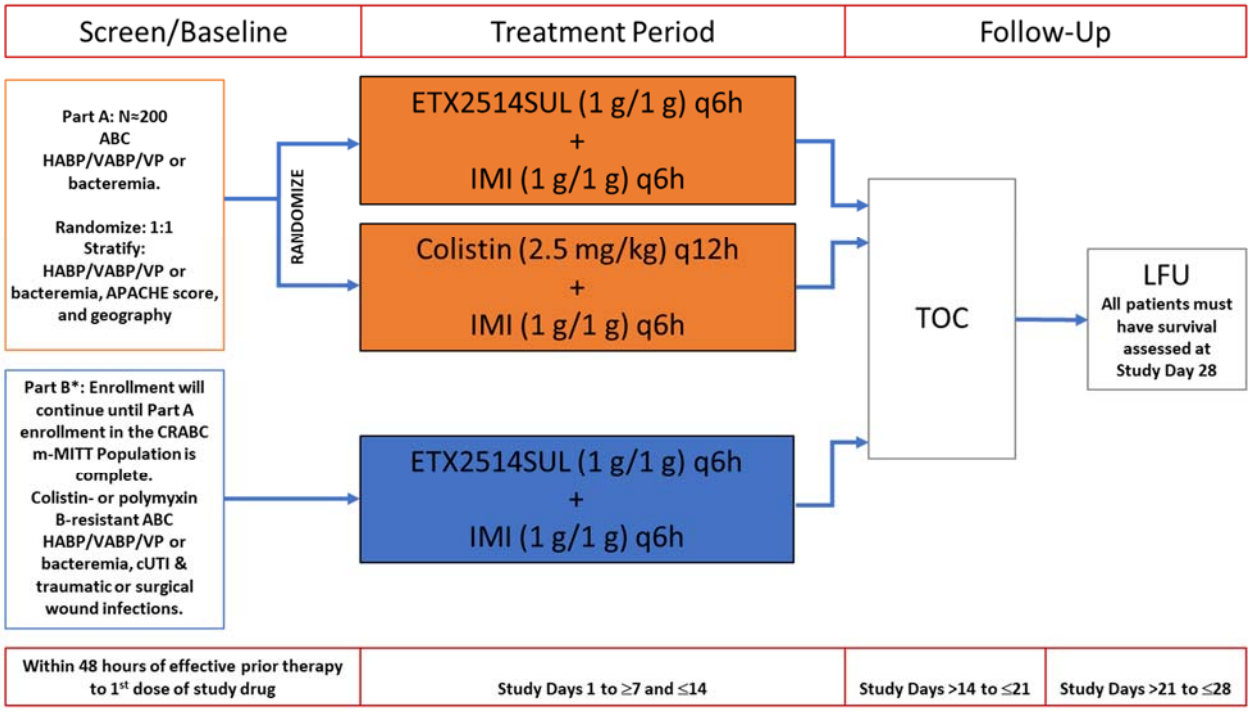
No dosing regimen changes, other than those specified in the protocol for renal insufficiency (see Section 5.3) or for patients on imipenem who develop a seizure that is thought to be directly related to imipenem, can occur without discussion with the Medical Monitor. Patients with cultures growing organisms with evidence of carbapenem resistance should remain on their assigned treatment regimen; treatment regimen changes can occur after 5 days after discussion with the Medical Monitor. If changes to the regimen are needed due to unsatisfactory clinical response, patients should be classified as clinical failures and discontinued from study drug. All patients should receive at least 48 hours of IV study drug (ie, 8 doses of ETX2514SUL plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in patients without dose adjustments) before the Investigator considers the patient to be a clinical failure and discontinues the patient from study drug therapy.

Note: Patients who experience focal tremors, myoclonus, or seizures at any point during the study should be evaluated neurologically, placed on anticonvulsant therapy (if not already instituted), and the dose of imipenem/cilastatin should be evaluated to determine whether it should be decreased or discontinued.

Day 1 is defined as the first day of study drug administration. The subsequent study days are defined by the number of treatment days thereafter. Treatment days should constitute 24 hours of treatment. For those patients with no dose adjustments, the duration of antibiotic treatment with study drug therapy will be 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin (ie, treatment for 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated. Refer to the Pharmacy Manual for specifics on dosing for all patients.

The overall study design is shown in Figure 1.

Figure 1. Study Design



*Part B: Part B will be the open-label, supportive portion of the study that will include patients known to have HABP, VABP, VP, and/or bacteremia infections associated with ABC organisms that are known to be resistant to colistin or polymyxin B, those failing a colistin or polymyxin B regimen prior to study entry or are on acute renal replacement therapy, and patients with infections due to colistin- or polymyxin B-resistant ABC with sources of infection other than HABP, VABP, VP, and/or bacteremia. The total number of patients enrolled in Part B may be adjusted based on the number needed to be enrolled in Part A to achieve the number needed to be treated in the CRABC m-MITT Population.
ABC = *Acinetobacter baumannii-calcoaceticus* complex; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; CRABC = Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; cUTI = complicated urinary tract infection; ETX2514SUL = sulbactam-ETX2514; HABP = hospital-acquired bacterial pneumonia; IMI = imipenem/cilastatin; LFU = Late Follow-up; m-MITT = Microbiologically Modified Intent-to-Treat; q6h = every 6 hours; q12h = every 12 hours; TOC = Test of Cure; VABP = ventilator-associated bacterial pneumonia; VP = ventilated pneumonia.

Patients who have early discontinuation of study drug dosing should perform all End of Treatment (EOT) Visit procedures and should be followed through the Late Follow-up (LFU) Visit for safety assessments, even if the reason for discontinuation is clinical failure.

In Part A, clinical outcome assessments will be performed by a blinded assessor, in addition to the unblinded Investigator. Whenever possible, the same blinded assessor should complete all clinical outcome assessments for a study patient. If there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor will be used. If there is a missing assessment from either the blinded assessor or unblinded Investigator, the

other available assessment will be used. An adjudication committee may be organized for endpoint adjudication should it be deemed necessary as determined by the Data Safety Monitoring Board (DSMB). In such a case, a charter will be developed that describes their activities.

Intense PK sampling will be performed on the first approximately 30 patients randomized in Part A. The purpose of the intense PK sampling is to ensure that exposures observed in this severely ill cohort are comparable to those observed thus far in prior clinical studies. The PK samples will be collected for both treatment groups in Part A to keep the study data blinded. Pharmacokinetic assessment of the initial 15 patients on ETX2514SUL in Part A will be performed by an independent PK assessor, prior to the opening of enrollment in Part B. To explore the PK profile of the ETX2514SUL combination in Chinese patients with severe infection, the intense PK sample will also be collected from the first approximately 20 patients randomized in Part A at China Mainland sites. All other patients enrolled in the study (Parts A and B) will have samples collected for sparse PK analysis, which will be used to better inform the population PK model.

Patients will be enrolled in the study for approximately 28 days, with a maximum duration of 32 days. Screening laboratory analytes can be performed as standard of care up to 48 hours prior to randomization on Day 1, with the exception of local laboratory serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. The Treatment Period begins on Day 1, and study drug will be administered for 7 days (ie, 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin for those without dose adjustments) with a prolongation of therapy of up to 14 days if clinically indicated. The EOT Visit will be completed on the final dosing day or the following day. The Test of Cure (TOC) Visit will be completed 7 days (±2 days) after the EOT Visit for all patients. The LFU Visit will be completed 14 days (±2 days) after the EOT Visit for all patients. For patients with an LFU Visit occurring before Day 28, a telephone call to assess survival will be made on Day 28 or anytime thereafter. Every attempt must be made to record survival status at Day 28 or anytime thereafter for all randomized patients (including HABP/VABP/VP patients who are randomized to Part A based on a positive BPP rapid test, but who subsequently do not have growth of ABC in their respiratory sample culture), regardless of their status of treatment, as long as the patient has not withdrawn consent from participation in the study.

3.2 Study Indication

ETX2514SUL is indicated for the treatment of serious infections caused by ABC.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

4.1.1 General Inclusion Criteria

Patients who meet all of the following general inclusion criteria, in addition to the specific inclusion criteria listed below for Parts A and B, will be eligible to participate in the study:

1. A signed informed consent form (ICF);

   Note: If a study patient is unable to provide informed consent due to their medical condition, the patient's legally authorized representative may consent on behalf of the study patient, or the decision can be made according to the procedure permitted by local law and institutional Standard Operating Procedures in compliance with Section 6.1.

2. Male or female ≥18 years of age;
3. A confirmed diagnosis of a serious infection and the expectation, in the judgment of the Investigator, that the patient's infection will require treatment with IV antibiotics;
4. A known infection caused by ABC (bacteremia, HABP, VABP, VP, cUTI or AP, or surgical or post-traumatic wound infections) as either a single pathogen or member of a polymicrobial infection based on evidence from culture or, if available, rapid diagnostic test from a sample collected within 72 hours prior to randomization (HABP/VABP/VP patients), AND 1 of the following:

   a. Has received no more than 48 hours of potentially effective (ie, Gram negative coverage) antimicrobial therapy prior to the first dose of study drug; OR

   b. Is clinically failing prior treatment regimens (ie, clinical deterioration or failure to improve after at least 48 hours of antibiotic treatment);

   Note: Rapid testing of respiratory specimens utilizing BPP technology (see Section 7.7) should be used to enable early identification of ABC pneumonia. Patients can be randomized based on the results of the BPP rapid test while awaiting results of cultures from the local laboratory. However, if the respiratory sample does not grow ABC in the local microbiology laboratory culture, these patients will be withdrawn from the study drug treatment.

   Note: Isolation of ABC from pleural effusion (empyema) is allowed, if concurrent pulmonary infiltrate is confirmed.

5. APACHE II score between 10 and 30, inclusive, OR SOFA score between 7 and 11, inclusive, at the time of diagnosis of infection. Patients who are not being treated in an intensive care unit and cannot have an APACHE II or SOFA score performed should have a qSOFA score ≥2 for enrollment;
6. Expectation, in the judgment of the Investigator, that the patient will benefit from effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study; and

7. Women of childbearing potential (ie, not post-menopausal or surgically sterilized) must have a negative highly sensitive urine or serum pregnancy test before randomization. Participating women of childbearing potential must be willing to consistently use one highly effective method of contraception (ie, condom, combined oral contraceptive, implant, injectable, indwelling intrauterine device, or a vasectomized partner) from Screening until at least 30 days after administration of the last dose of study drug.

4.1.2 Part A-Specific Inclusion Criteria

In addition to those general inclusion criteria listed in Section 4.1.1, patients may enroll in Part A if they meet the criteria below. All patients must be categorized in 1 infection type that is judged to be the primary infection by the Investigator:

1. Diagnosed with HABP, VABP, VP, and/or bacteremia, defined as:

HABP With ABC in Sputum/Respiratory Sample		
All of the following:	**AND signs or symptoms evidenced by at least 2 of the following:**	**AND at least 1 of the following:**
• Onset of symptoms >48 hours after admission or ≤7 days after discharge from an inpatient acute or chronic care facility (eg, LTAC, rehabilitation center, hospital, or skilled nursing home); OR • Admission from LTAC or rehabilitation center, or admission from home <7 days after discharge from an LTAC or rehabilitation center; AND • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.	• A new onset of cough (or worsening of baseline cough); • Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony); • Dyspnea, tachypnea, or respiratory rate >25 breaths/minute; OR • Hypoxemia (oxygen saturation <90% or pO_2 <60 mmHg while breathing room air, or worsening of the oxygen saturation/ FiO_2); OR the following ALONE: • New onset need for mechanical ventilation.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC count <4500/mm^3).
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; CT = computed tomography; FiO_2 = fraction of inspired oxygen; HABP = hospital-acquired bacterial pneumonia; LTAC = long-term acute care; MRI = magnetic resonance imaging; pO_2 = partial pressure of oxygen; WBC = white blood cell.		

VABP With ABC in Sputum/Respiratory Sample		
All of the following:	**AND signs or symptoms evidenced by at least 2 of the following:**	**AND at least 1 of the following:**
• Onset of symptoms >48 hours after receiving ventilator support via an endotracheal (or nasotracheal) tube; • Requires ventilator support; AND • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.	• Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation, as determined by a worsening oxygen saturation/FiO_2 ratio; • Increased suctioning; OR • Tracheal aspirate change to purulence.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC <4500/mm^3).
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; CT = computed tomography; FiO_2 = fraction of inspired oxygen; MRI = magnetic resonance imaging; VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.		

Ventilated Pneumonia With ABC in Respiratory Sample		
All of the following:	**AND signs or symptoms evidenced by at least 2 of the following:**	**AND at least 1 of the following:**
• Requires ventilator support; AND • New or evolving infiltrate on chest X-ray, MRI, CT scan, or ultrasound obtained within 48 hours prior to randomization. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.	• Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, dullness on percussion, bronchial breath sounds, or egophony); • An acute change in the ventilator support system to enhance oxygenation; • Increased suctioning; OR • Tracheal aspirate change to purulence.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; OR • Leukopenia (total WBC count <4500/mm^3).
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; CT = computed tomography; MRI = magnetic resonance imaging; WBC = white blood cell.		

Bacteremia With ABC	
All of the following:	**AND at least 1 of the following:**
• Isolation of ABC from at least 1 blood culture collected from a peripheral vein OR newly placed intravenous line.	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • Elevated total peripheral WBC count (>10,000/mm^3); • >15% immature neutrophils (bands) regardless of total peripheral WBC count; • Leukopenia (total WBC count <4500/mm^3); • Tachycardia >100 bpm; • Tachypnea >25 breaths/minute; OR • Hypotension, systolic <90 mmHg.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider.	
ABC = *Acinetobacter baumannii-calcoaceticus* complex; bpm = beats per minute; WBC = white blood cell.	

4.1.3 Part B-Specific Inclusion Criteria

Part B will include patients with the following ABC infections: HABP, VABP, VP, or bacteremia who do not qualify for Part A, and cUTI/AP or surgical or post-traumatic wound infections.

1. Patients with HABP, VABP, VP, or bacteremia should be considered for enrollment in Part B if they meet ANY of the following criteria (*a*, *b*, *c,* OR *d*), in addition to the general inclusion criteria listed in Section 4.1.1:

    a. Has an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a non-agar based method);

    For known colistin- or polymyxin B-resistant infections, the following must be satisfied:

    - Has a known resistant infection based on evidence from culture and susceptibility testing by a non-agar based method within 72 hours prior to randomization, alone or as a single organism of a polymicrobial infection; AND has received no more than 48 hours of an antimicrobial agent to which the ABC is susceptible prior to the first dose of study drug;

      OR

    - Has documented clinical evidence of failure (ie, clinical deterioration or failure to improve that is attributable to ABC infection) after at least 48 hours of treatment with colistin or polymyxin B; OR

b. Has known intolerance to colistin;

   Note: Patients whom the Investigator feels may have a potential intolerance to colistin can be enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; OR

c. Has myasthenia gravis or another neuromuscular syndrome(s) that contraindicates colistin and is not ventilated;

   Note: Ventilated patients with myasthenia gravis or other neuromuscular syndromes where, in the opinion of the Investigator, colistin administration is reasonable are permitted for consideration for the study; OR

d. Has acute kidney injury and is receiving renal replacement therapy at study entry;

2. Patients diagnosed with cUTI, AP, or surgical or post-traumatic wound infections may enroll in Part B if they meet the general inclusion criteria listed in Section 4.1.1 as well as either *a*, *b*, *c*, *d,* OR *e* in addition to the indication requirements for *f*:

   a. Has an infection caused by ABC organisms known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a non-agar based method); OR

   b. Has known intolerance to colistin;

      Note: Patients whom the Investigator feels may have a potential intolerance to colistin can be enrolled in Part B on a case-by-case basis after discussion with the Medical Monitor; OR

   c. Has myasthenia gravis or another neuromuscular syndrome(s) that contraindicates colistin; OR

   d. Has acute kidney injury and is receiving renal replacement therapy at study entry; OR

   e. Has documented clinical evidence of failure (ie, clinical deterioration or failure to improve) after at least 48 hours of treatment with a polymyxin-based regimen; AND

   f. Is diagnosed with cUTI, AP, or surgical or post-traumatic wound infection, defined as:

cUTI With ABC		
At least 1 of the following:	**AND at least 2 of the following signs and symptoms:**	**AND at least 1 of the following:**
• Indwelling urinary catheter or intermittent bladder catheterization; • Neurogenic bladder with presence or history of urine residual volume of ≥100 mL; • Obstructive uropathy (eg, nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 hours post-randomization; • Azotemia due to intrinsic renal disease; OR • Urinary retention in men due to previously diagnosed benign hypertrophy.	• Chills, rigors, or fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3) or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; OR • Lower abdominal pain or pelvic pain.	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; OR • WBC count ≥10 cells/hpf in urine sediment.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; cUTI = complicated urinary tract infection; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.		

AP With ABC	
Presence of an ascending tract infection including at least 2 of the following signs or symptoms:	**AND at least 1 of the following:**
• Chills, rigors, or fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]); • Elevated WBC count (>10,000/mm^3) or left shift (>15% immature PMNs); • Nausea or vomiting; • Dysuria, increased urinary frequency, or urinary urgency; • Flank pain; OR • Costovertebral angle tenderness on physical examination.	• Positive LCE on urinalysis; • WBC count ≥10 cells/mm^3 in unspun urine; OR • WBC count ≥10 cells/hpf in urine sediment.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; AP = acute pyelonephritis; hpf = high-power field; LCE = leukocyte esterase; PMN = polymorphonuclear leukocyte; WBC = white blood cell.	

Surgical Wound Infection With ABC	
Superficial SSI meeting all of the following criteria:	**AND at least 1 of the following regional or systemic signs of infection:**
• Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered); • Involves only the skin or subcutaneous tissue around the incision, does not involve fascia; • Occurs within 30 days after procedure; • Original surgical incision ≥3 cm; AND • Purulent drainage (spontaneous or therapeutic) that is positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2.	• Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI; • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • WBC count ≥10,000/mm^3 or <4000/mm^3; OR • >15% immature neutrophils.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; ABSSSI = acute bacterial skin and skin structure infection; SSI = surgical site infection; WBC = white blood cell.	

Post-Traumatic Wound Infection With ABC	
Post-traumatic wound (including penetrating trauma) characterized by the following within 24 hours of Screening:	**AND at least 1 of the following regional or systemic signs of infection:**
• Purulent drainage (spontaneous or therapeutic) that is positive for ABC by culture with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2.	• Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI; • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]); • WBC count ≥10,000/mm^3 or <4000/mm^3; OR • >15% immature neutrophils.
1. Evidence of fever within 24 hours of the Screening Visit is acceptable if observed and documented by a healthcare provider. ABC = *Acinetobacter baumannii-calcoaceticus* complex; ABSSSI = acute bacterial skin and skin structure infection; WBC = white blood cell.	

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Presence of suspected or confirmed deep-seated infection (eg, lung abscess in patients with pneumonia, skin abscess, or decubitus ulcer) that is not planned on being drained or debrided within 24 hours after randomization;

   Note: Patients with an empyema who will have drainage within 24 hours of Screening and who are expected to be able to be treated with 14 or fewer days of antibiotics are allowed.

2. Evidence of active concurrent pneumonia requiring additional antimicrobial treatment caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, respiratory syncytial virus,

influenza and parainfluenza viruses, Middle East respiratory syndrome coronavirus, mycobacteria, aspergillus, mucormycosis, etc;

Note: If these organisms are identified but it is deemed by the Investigator that no treatment is warranted and their presence does not significantly change the prognosis of the patient, then the patient may be considered for this study.

3. Pulmonary disease that precludes evaluation of a therapeutic response (such as lung cancer resulting in bronchial obstruction or on the same side as the pneumonia, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection, lung abscess, pleural empyema, post obstructive pneumonia, or COVID-19 infection without clinical improvement);

   Note: Patients with an empyema who will have drainage within 24 hours of Screening and who are expected to be able to be treated with 14 or fewer days of antibiotics are allowed.

4. Presence of suspected or confirmed deep seated bacterial infections such as bacterial Gram negative osteomyelitis, endocarditis, or meningitis requiring prolonged therapy, as determined by history and/or physical examination;
5. Acute infective endocarditis due to Gram positive bacteria that require urgent/emergent indication of surgery (ie, heart failure because of valvular insufficiency or septic shock), or patients in whom surgery is contraindicated due to prohibitive risk for surgery due to comorbidities;
6. Irremovable implantable device or line thought to be the potential source of ABC infection;
7. Sustained shock with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥60 mmHg;

   Note: Patients who can maintain MAP ≥60 mmHg on a reasonable dose of pressors or are weaning off of pressors may be considered. Patients who require more than the maximal dose of 2 vasopressors to maintain MAP ≥60 mmHg are ineligible. If vasopressors are weaned to below these levels, patient enrollment can be reconsidered.

8. For patients to be enrolled with the primary indication of HABP, VABP, or VP, any of the following conditions:
   a. Diagnosis of ventilator-associated tracheobronchitis; or
   b. Inability to provide proper respiratory specimens for culture. Respiratory samples from expectorated or induced sputum should show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100× field;
9. For patients to be enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:
   a. Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (eg, patients with vesico-uretal reflux);
   b. Suspected or confirmed prostatitis;
   c. Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;
   d. Previous or planned cystectomy or ileal loop surgery;

e. Uncomplicated urinary tract infection (eg, female patients with urinary frequency, urgency, or pain or discomfort without systemic symptoms or signs of infection);

f. Complete, permanent obstruction of the urinary tract;

g. Suspected or confirmed perinephric or renal corticomedullary abscess;

h. Polycystic kidney disease; or

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

10. Pregnant or breastfeeding women;

11. APACHE II score >30 and SOFA score >11 at the time of diagnosis of infection;

    Note: A qSOFA score must be calculated for all patients without an APACHE II score. Glasgow coma score for APACHE II calculation should be the best response prior to initiation of sedation/neuromuscular blockade, even if sedation has been in use for >24 hours.

12. Receiving peritoneal dialysis;

13. Requirement for temporary or acute onset treatment with antiseizure medication that, in the opinion of the Investigator, would prohibit the patient from complying with the protocol. Patients at risk of seizure or requiring prophylactic antiseizure medications during the study can be considered for enrollment at the discretion of the Investigator. Patients with a history of epilepsy or who are on stable treatment (ie, no recurrent episodes in the past 30 days) and no history of imipenem-associated seizures may be considered for enrollment in the study;

14. Requirement for continuing treatment with probenecid, methotrexate, ganciclovir, valproic acid, or divalproex sodium during the study;

15. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis, hepatic cirrhosis, hepatic failure, chronic ascites, or hepatic encephalopathy;

16. Aspartate aminotransferase (AST) or ALT >3 × upper limit of normal (ULN) AND total bilirubin >2 × ULN at Screening;

    Note: Patients with AST or ALT up to 5 × ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.

17. Requirement at the time of randomization for any reason, or likely to require during the patient's participation in the study (from randomization through the LFU Visit), for additional systemic Gram negative antimicrobial therapy. See Section 5.6.3 for a list of antibiotics that are allowed to treat mixed or concurrent infections;

18. Requirement for inhaled antibiotics;

19. Known history of human immunodeficiency virus infection and known recent CD4 count <200/mm^3 within the last year or presence of significant immunologic disease or dysfunction, as determined by a current diagnosis of an Acquired Immune Deficiency Syndrome-defining illness;

20. Presence of neutropenia (absolute neutrophil count <500/mm^3) obtained from a local laboratory at Screening;

21. A QT interval corrected using Fridericia's formula (QTcF) ≥480 msec;

22. History of significant hypersensitivity or allergic reaction to any BL, any contraindication to the use of cilastatin based on local approved prescribing information (eg, Summary of Medicinal Product Characteristics), any contraindication to the excipients used in the respective formulations, or any contraindication to the use of BL antibiotics;
23. Participation in a clinical study involving investigational medication or an investigational device within the last 30 days or 5 half-lives, whichever is longer, prior to Day 1;
24. Any condition that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data or require greater than 14 days of treatment with antibiotics;
25. Unable or unwilling, in the opinion of the Investigator, to comply with the protocol;
26. Has previously received ETX2514 in this study; or
27. For Part A only, patients with an infection known to be resistant to colistin or polymyxin B (defined as MIC ≥4 mg/L by a non-agar based method), with a known intolerance to colistin, or taking any drug that prevents them from receiving colistin.

4.3 Withdrawal and Discontinuation Criteria

Participation of a patient in this clinical study may be withdrawn or study drug discontinued by the patient or Investigator for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Patient develops severe liver-related abnormalities, as detailed below:
  - ALT or AST >10 × ULN;
  - ALT or AST >5 × ULN for more than 2 weeks or progressively increasing transaminases despite clinical improvement of underlying infection;
  - Confirmed values of ALT or AST >3 × ULN and total bilirubin >2 × ULN or international normalized ratio >1.5 (for patients who are not on coumadin) without evidence of an alternative etiology; or
  - Confirmed values of ALT or AST >3 × ULN along with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia [>5%]);
- Pregnancy;
- Requirement of prohibited concomitant medications, including the need for antibiotics that have an overlapping Gram negative coverage other than study drugs;

  Note: Patients who require antibiotic prophylaxis due to immunosuppression (eg, trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis carinii* [*P. carinii*] pneumonia) may participate in the study.

- Patients randomized to Part A based on a positive screening of a respiratory sample for ABC by BPP rapid test, but subsequently do not have growth of ABC in their respiratory sample culture processed by the local microbiology laboratory;
- Patient failure to comply with protocol requirements or study-related procedures, including the need for treatment with study drug beyond 14 days; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason other than withdrawal of consent to participate, study staff should make every effort to complete the full panel of assessments scheduled for the EOT Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF). Even if a patient discontinues study drug and/or the patient is a clinical failure, he/she should remain enrolled in the study, as long as all assessments for the EOT Visit and follow-up visits can be completed. Reasons for discontinuation of study drug must be recorded in the eCRF. ***Every attempt must be made to record survival status at Day 28 or anytime thereafter for all randomized patients (including HABP/VABP/VP patients who are randomized to Part A based on a positive BPP rapid test, but who subsequently do not have growth of ABC in their respiratory sample culture), regardless of their status of treatment, as long as the patient has not withdrawn consent from participation in the study.***

5 STUDY TREATMENTS

5.1 Treatment Groups

In Part A, the following study drugs will be administered in a 1:1 randomized manner:

- Group 1 (experimental group): 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h; or
- Group 2 (control group): 2.5 mg/kg colistin IV infused over 30 minutes q12h (after an initial loading dose of colistin 2.5 to 5 mg/kg) plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

In Part B, the following study drugs will be administered:

- Group 3 (experimental group): 1.0 g ETX2514/1.0 g sulbactam IV infused over 3 hours q6h plus 1.0 g imipenem/1.0 g cilastatin IV infused over 1 hour q6h.

5.2 Rationale for Dosing

The doses of ETX2514 and sulbactam to be evaluated in this study have been selected based on Phase 1 and Phase 2 PK, safety, and efficacy data and extensive PK/PD modeling and probability of target attainment against CRABC in the lung. Data from these studies and details of the PK/PD modeling are provided in more detail in the Investigator's Brochure.

ETX2514 1.0 g was generally well tolerated in all of the clinical studies to date. Sulbactam 1.0 g was generally well tolerated in the Phase 2 study. The total daily dose of sulbactam being used in the current study is consistent with the US Product Circular for Unasyn, in which the maximum approved daily dose in patients with normal renal clearance for sulbactam is 4 g, which is equivalent to 1.0 g sulbactam q6h.

The ETX2514SUL regimen of 1.0 g ETX2514/1.0 g sulbactam should be infused over 3 hours q6h given for 7 days to 14 days (28 doses to 56 doses), depending on the clinical response.

Imipenem/cilastatin will be administered as a 1.0 g/1.0 g dose infused over 1 hour q6h given for the same duration as ETX2514SUL or colistin.

Colistin will be administered at a daily dose of 5 mg/kg of colistin base activity (CBA) divided into 2 doses 12 hours apart. Doses will be adjusted to ideal body weight in obese patients. Patients who weigh <60 kg with normal renal function will receive a flat dose of 300 mg CBA or 9 million international unit (MIU)/day. A single loading dose of 2.5 to 5 mg/kg (total dose not exceeding 300 mg CBA or 9 MIU and following local standard of care) given IV over 3 to 6 minutes (or according to standard of care) will be administered on Day 1. Colistin infusions beyond the loading dose on Day 1 will begin 12 hours after the initial loading dose and will be infused over 30 minutes. Details on dosing for those patients who are on colistin prior to randomization into the study can be found in the Pharmacy Manual.

Details of study drug preparation and administration can also be found in the Pharmacy Manual.

No dosing regimen changes, other than those specified in the protocol for renal insufficiency (see Section 5.3) or for patients on imipenem who develop a seizure that is thought to be directly related to imipenem, can occur without discussion with the Medical Monitor.

5.3 Dosing in Patients With Renal Insufficiency

Estimated creatinine clearance will be determined daily while patients are receiving IV study drug. Principal Investigators will be responsible for testing estimated creatinine clearance daily at the local laboratory per institutional Standard Operating Procedures and must adjust doses of all medications as detailed in Table 1 in order to optimize efficacy and safety. Estimated creatinine clearance and dose adjustment data will be captured in source documents and in the eCRFs. Table 1 summarizes the recommended dosing regimens for patients with renal impairment.[16,17] Of note, patients with estimated creatinine clearance <15 mL/min will only be dosed with imipenem/cilastatin as outlined in Table 1 if renal replacement therapy of acute hemodialysis is planned to be instituted within 48 hours of dosing.

Table 1. Study Drug Dose Adjustments by Renal Function

Estimated Creatinine Clearance, mL/min (Cockcroft-Gault)	ETX2514SUL Dosage Regimen	Colistin Dosage Regimen	Imipenem/Cilastatin Dosage Regimen [1]
130-200 (augmented renal clearance)	1.5/1.5 g q6h	2.5 mg/kg q12h	1.0/1.0 g q6h
90-129 (normal)	1.0/1.0 g q6h	2.5 mg/kg q12h	1.0/1.0 g q6h
60-89 (mild renal impairment)	1.0/1.0 g q6h	1.25 to 1.9 mg/kg q12h	0.75/0.75 g q8h
30-59 (moderate renal impairment)	1.0/1.0 g q6h	1.25 mg/kg q12h or 2.5 mg/kg once daily	0.5/0.5 g q6h
15-29 (severe renal impairment)	1.0/1.0 g q8h	1.5 mg/kg q36h	0.5/0.5 g q12h
0-14 (severe renal impairment) [2]	1.0/1.0 g q12h	1.5 mg/kg q36h	0.5/0.5 g q12h
Intermittent hemodialysis	1.0/1.0 g q12h [4]	Non-dialysis day: CBA dose of 65 mg q12h. Dialysis day supplement: add 40 mg (for 3-hour IHD session) or 50 mg (for 4-hour IHD session) post-dialysis [3]	0.5/0.5 g q12h [4]
Continuous renal replacement therapy	1.5/1.5 g q6h	220 mg q12h	1.0/1.0 g q8h to q12h, depending on ultrafiltration rate

1. Administer doses ≤0.5 g by IV infusion over 20 to 30 minutes. Administer doses >0.5 g by IV infusion over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.
2. Patients with creatinine clearance <15 mL/min should not receive imipenem/cilastatin unless renal replacement therapy of acute hemodialysis is instituted within 48 hours of dosing.
3. The dialysis session should occur toward the end of a colistimethate dosing interval, and the supplement to the baseline (non-dialysis) daily dose should be administered with the next regular dose, after the dialysis session has ended.
4. The dialysis session should occur toward the end of a dosing interval, and the daily dose should be administered after the dialysis session has ended.

CBA = colistin base activity; ETX2514SUL = sulbactam-ETX2514; IHD = intermittent hemodialysis; IV = intravenous; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; q36h = every 36 hours.

5.4 Randomization and Blinding

Qualifying patients enrolling in Part A will be randomized in a 1:1 ratio to receive 1.0 g ETX2514/1.0 g sulbactam q6h plus 1.0 g imipenem/1.0 g cilastatin q6h or 2.5 mg/kg colistin q12h plus 1.0 g imipenem/1.0 g cilastatin q6h via the Interactive Response Technology (IRT) system. Patients enrolled in the study based on the positive BPP rapid test results but are found to not grow

ABC in respiratory specimen cultures by the local microbiology laboratory will be withdrawn from the study drug treatment as detailed in Section 4.3.

Randomization in Part A will be stratified by indication (HABP/VABP/VP versus bacteremia), severity of illness (based on APACHE II [10 to 19 versus 20 to 30], SOFA [7 to 9 versus ≥10], or qSOFA [2 versus 3] score at Screening), and geography (China Mainland versus Rest of World). In the situation where a patient has more than one score reported, the scores will be used in the following order: APACHE, SOFA, and qSOFA. A quick reference guide will be provided that describes the IRT system and includes user instructions. Enrollment of HABP, VP, and bacteremia patients will be limited to a total of no more than 40% of patients in Part A, regardless of resistance.

The study data will be collected and handled as if it were a blinded study. The blinded assessor (see Section 5.4.2), the Sponsor, and the Sponsor's designees involved in medical and safety monitoring, data management, and other aspects of the study (eg, interpretation of the results) will be blinded to treatment assignment. Given the complexity of the regimens, the Principal Investigator, other care givers, the clinical research associate (CRA), and other site personnel (eg, study coordinators and pharmacy staff) will be unblinded (see Section 5.4.1). Patients will not be informed of their treatment assignment, and efforts will be made to keep patients naïve to their treatment throughout the course of the study.

Part B is open-label and not randomized; all patients enrolling in Part B will receive 1.0 g ETX2514/1.0 g sulbactam q6h plus 1.0 g imipenem/1.0 g cilastatin q6h.

5.4.1 Unblinded Investigator

An unblinded Investigator at each site will evaluate criteria for clinical outcomes, conduct causality assessment for adverse events, and assess clinical signs and symptoms at study visits for patients in both Part A and Part B. For patients in Part A, a blinded assessor will also evaluate criteria for clinical outcomes, conduct causality assessment for adverse events, and assess clinical signs and symptoms at study visits. The unblinded Investigator must be a qualified physician, able to perform medical evaluations, and determine medical diagnoses (eg, Principal Investigator, sub-Investigator). For consistency, whenever possible, the same unblinded Investigator should complete all unblinded assessments for a study patient. If there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor will be used. If there is a missing assessment from either the blinded assessor or unblinded Investigator, the other available assessment will be used. An adjudication committee may be organized for endpoint adjudication should it be deemed necessary by the DSMB. In such a case, a charter will be developed that describes their activities.

5.4.2 Blinded Assessor

Study data will be collected and handled as if it were a blinded study.

For patients in Part A, each site will assign a blinded assessor, in addition to the unblinded Investigator, to evaluate criteria for clinical outcomes, conduct causality assessment for adverse events, and assess clinical signs and symptoms at study visits where an endpoint is evaluated (see Appendix A). A blinded assessor must be qualified to perform medical evaluations and determine medical diagnoses (eg, physician, physician's assistant, or nurse practitioner [in the United States]). The blinded assessor may participate in the consenting process and Screening procedures, but once a patient is randomized the blinded assessor should have no other role in the study other than making blinded assessments. For consistency, whenever possible, the same blinded assessor

should complete all blinded assessments for a study patient. All efforts will be made to keep the blinded assessor blinded during the course of the study. The blinded assessor should not have access to sections in the patient's medical record in which treatment group or dosing frequency are documented, should have no role in patient care or treatment, and should be restricted to limited sections of the patient's chart in order to assess clinical outcomes. Data collection by the blinded assessor will be used for entry into the eCRF.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

ETX2514 sodium 500 mg is presented as a sterile lyophilized cake in a sterile 10 mL amber glass vial with a stopper, overseal, and clinical label. Two ETX2514 500 mg vials will be combined to generate the 1.0 g ETX2514 dose.

Sulbactam sodium 1.0 g is presented as a sterile powder in a sterile 30 mL clear glass vial with a stopper, overseal, and clinical label.

Commercially available imipenem/cilastatin and colistin will be provided. Each commercial material will have a clinical label.

Imipenem/cilastatin is presented in fixed dose vials containing 0.5 g imipenem and 0.5 g cilastatin. Two vials will be combined to generate 1.0 g imipenem and 1.0 g cilastatin.

Colistin is presented in vials containing colistimethate sodium (CMS).

For non-US sites, CMS vials containing 2 MIU/vial powder for solution (equivalent to approximately 68 mg of CBA/vial based on microbiological standardization) will be used.

For US sites, CMS equivalent to 150 mg of CBA/vial powder for solution (equivalent to approximately 400 mg or 4.5 MIU of CMS based on microbiological standardization) will be used. To avoid errors in dosing and administration, CMS will be referred to in terms of "international unit" (IU), "CBA", or, simply, "colistin."

Table 2 provides a guide for conversion of IU values to mg of CBA. Greater details of dose calculations and conversion tables can be found in the Pharmacy Manual.

Study drugs will be labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines.

Table 2. Unit Conversion Guidance

Colistin (IU)	Colistin (mg of CBA)
150,000 IU	5 mg
1 MIU	34 mg
4.5 MIU	150 mg
9 MIU	300 mg

CBA = colistin base activity; IU = international unit; MIU = million international unit.
Source: Colistin summary of product characterization

5.5.2 Study Drug Preparation and Dispensing

A pharmacist (or qualified designee) will prepare the study drug according to the requirements outlined in the Pharmacy Manual. The IV bags will be labeled with the date and time of study drug preparation and patient identification number and will be transferred to the study staff for

administration to the patient. Reconstituted study drug should be administered according to the requirements outlined in the Pharmacy Manual.

5.5.3 Study Drug Administration

The pharmacist (or qualified designee) will be responsible for providing study personnel with study drug ready for IV infusion. Patients will receive treatment in accordance with the randomization schedule provided via the IRT system. Patients will receive randomized treatment administered as described in the Pharmacy Manual.

Patients will receive all infusions by programmable infusion pump, or drip infusion in case of failure of the pump, while seated or partially reclined in bed. The times at which each infusion is started and stopped must be recorded. If a dose is interrupted for more than 10 minutes, the interruption and reason for interruption should be noted in the source documents. Any missed dose should also be noted in the source documents with the reason for the missed dose. For patients with normal renal function, study drug infusions will be administered q6h (±15 minutes) for ETX2514SUL and imipenem/cilastatin and q12h (±15 minutes) for colistin. Infusions that fall outside of the q6h (±15 minutes) or q12h (±15 minutes) dosing schedule will be considered protocol deviations. It is critical that administration and infusion time be captured in the eCRF based on actual time. Windows for administration and infusion should be used sparingly, and the patient should remain on schedule based on the q6h administration requirement.

Dosing time is relative to the start of infusion. For additional information on study drug product dilution, infusion volumes, and dispensing instructions, refer to the Pharmacy Manual.

5.5.4 Treatment Compliance

The infusion date and start and stop times will be recorded in the source documents and eCRFs. Treatment compliance will be calculated based on the number of doses received and expected as detailed in the Statistical Analysis Plan (SAP).

5.5.5 Storage and Accountability

The pharmacist or designated study personnel will ensure that all study drugs are stored in a locked, secure area with limited access. Study drugs will be stored under recommended storage conditions per the label and in accordance with the Pharmacy Manual.

The date and time of preparation of study drug will be recorded on the IV bags. Refer to the Pharmacy Manual for additional information.

The Investigator is responsible for maintaining a current record of inventory/drug accountability. Vials may not be discarded until inventory and drug accountability are performed by the monitor. Study drugs must only be used for this protocol.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Treatment with any of the following concomitant medications or procedures is prohibited:

- Probenecid;
- Methotrexate;

- Ganciclovir;
- Valproic acid or divalproex sodium;
- Any additional or adjunctive non-study-specific Gram negative antibiotic therapy administered with the intention of treating HABP, VABP, VP, bacteremia, cUTI, AP, or other infection; and/or

  Note: Patients who require antibiotic prophylaxis due to immunosuppression (eg, trimethoprim-sulfamethoxazole for prophylaxis against *P. carinii* pneumonia) may participate in the study.
- For patients with cUTI or AP, bladder irrigations with any antiseptic or antibiotic.

5.6.2 Restricted Medications and/or Procedures

- For patients with surgical or post-traumatic wounds, topical antibiotics are prohibited. For all other patients, topical antibiotics are permitted; and
- For patients with all indications being considered for Part A, curariform muscle relaxants (eg, tubocurarine) and other drugs, including ether, succinylcholine, gallamine, decamethonium, and sodium citrate, that potentiate the neuromuscular blocking effect should be used with extreme caution in patients being treated with colistin.

5.6.3 Allowed Medications and/or Procedures

Unless specifically restricted per the protocol, medications and procedures for the management of the patient are permitted per standard of care. Patients who require antibiotic prophylaxis due to immunosuppression (eg, trimethoprim-sulfamethoxazole for prophylaxis against *P. carinii* pneumonia) may participate in the study. Additionally, treatment with any of the following concomitant antibiotics is allowed for treatment of Gram positive bacteria or *Clostridium difficile* (*C. difficile*) infections.

Permitted medications include the following:

- Agents with Gram positive only coverage, including the following:
  - Vancomycin;
  - Linezolid;
  - Daptomycin;
  - Oritavancin;
  - Tedizolid; and
  - Dalbavancin;
- Agents for treatment of *C. difficile* infections, including the following:
  - Metronidazole;
  - Oral vancomycin;
  - Rifaximin; and
  - Fidaxomicin.

5.6.4 Documentation of Prior and Concomitant Medication Use

Reasonable effort will be made to determine all relevant treatments (including all antibiotics, prescription and non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and non-pharmacologic treatments) received within 14 days before the first dose of study drug and during the study. The name, route of administration, dose, frequency, indication, and duration of the treatment will be recorded in the eCRF. The date and time of start and stop of any antibiotic therapy received within 14 days before the first dose of study drug and during the study will also be recorded.

Patients cannot participate in any other investigational medication study while participating in this study or have taken any investigational product within 30 days or 5 half-lives, whichever is longer, prior to Day 1 in this study.

6 STUDY PROCEDURES

A detailed schedule of procedures is provided in Appendix A.

6.1 Informed Consent

Informed consent must be obtained before any study procedures are performed. An ICF of limited scope may be signed prior to Screening to perform only BPP rapid testing of respiratory specimens. A comprehensive ICF, which will include all study procedures, will be signed at Screening. Patients will participate as much as possible in the informed consent procedure; however, as permitted by local law and institutional Standard Operating Procedures, in cases of a lack of decision-making capacity, informed consent on behalf of the patient may be provided by a legally authorized representative, independent physician, or consortium of independent physicians. These patients, upon return of their capacity, will be consented and allowed to make their own informed medical decisions.

6.2 Screening Visit (-48 Hours to Day 1)

Screening can occur up to 48 hours before the first dose of study drug. All Screening procedures must be performed prior to randomization and the first dose of study drug (Day 1). All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours before the first dose of study drug.

The following procedures will be performed at Screening:

- Obtain informed consent;
- Review all inclusion and exclusion criteria;
- Only for patients suspected to have HABP/VABP/VP, perform rapid testing of respiratory specimens using BPP to detect ABC infection as specified in Section 7.7.1 and the Laboratory Manual;
    - For patients who only signed the limited scope ICF (which only allows rapid testing on a respiratory sample):
        - If the BPP rapid test is negative or indeterminate for ABC, the patient should be screen failed;
        - If the BPP is indeterminate, the Investigator may opt to wait and repeat the test within 24 hours before screen failing the patient;

          Note: The Investigator should review the local culture result from the respiratory sample once available. If the local culture result is positive for ABC, the patient may be re-screened under a new patient number, beginning with the main ICF and ensuring all eligibility criteria are met.
    - For patients who signed the main ICF (including all study procedures):
        - If the BPP rapid test result is negative for ABC, the patient should not be screen failed immediately, instead the Investigator should wait for the local culture result. In case the local culture result is positive for ABC, the Investigator should proceed with the Screening procedures;

  - Patients with suspected HABP/VABP/VP with a positive BPP rapid test for ABC of their respiratory specimen must meet all other enrollment criteria in order to be randomized. The respiratory specimen should be sent to the local laboratory for culture and susceptibility. If culture of the respiratory specimen by the local microbiology laboratory subsequently does not show growth with ABC, this patient must be withdrawn from the study treatment as they no longer meet eligibility criteria (see Section 4.3);

- Obtain medical/surgical history;
- Record prior and concomitant medications;
- Obtain demographics, including sex, age, race, and ethnicity;
- Perform a complete physical examination, including weight and height;
- Calculate APACHE II, SOFA, or qSOFA score;

  Note: An APACHE II or SOFA score will be calculated prior to randomization for patients in Part A only. For patients who are not being treated in an intensive care unit and cannot have an APACHE II or SOFA score performed, and for all patients in Part B, a qSOFA score should be calculated.

  Note: An APACHE II, SOFA, or qSOFA score that was calculated as part of standard of care within 24 hours of Screening may be used and does not need to be repeated.

- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP);
- Perform/review chest X-ray, magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasound within 72 hours of Screening (HABP, VABP, and VP patients only). For images obtained >48 hours prior to randomization, repeat imaging is required. Findings should be consistent with the screening image and diagnosis of pneumonia, in the Investigator's judgment; otherwise, the patient is no longer eligible;

  Note: If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours.

- Assess clinical signs and symptoms (see Section 7.5);
- Perform a highly sensitive urine or serum pregnancy test for women of childbearing potential only;
- Collect blood samples for serum chemistry, serum creatinine, hematology, and baseline blood cultures;
- Collect urine sample for urinalysis;
- Collect infection site-specific culture specimens based on diagnosis. Cultures obtained within 72 hours prior to randomization that are positive for ABC are acceptable for enrollment, but site-specific culture samples should be repeated within 24 hours prior to randomization (see Section 7.7);

- Perform 12-lead ECG and consult the study Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF ≥480 msec); and
- Assess adverse events.

6.3 Treatment Period – Day 1 Through End of Treatment

All patients will receive IV treatment for a minimum of 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin (ie, 7 days of antibiotics for those without dose adjustments). Patients can receive up to 14 days of IV treatment if clinically indicated. Time of discontinuation of antibiotics will be determined on achievement of clinical cure (see Section 7.6). Additionally, at any time during the study, if a patient develops signs and symptoms of disease worsening, cultures from all appropriate sites should be collected and sent to the central laboratory.

6.3.1 Day 1

The following procedures will be performed at Day 1:

- Record concomitant medications;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Collect predose blood samples for:
  - Serum chemistry;
  - Serum creatinine;
  - Hematology; and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect predose urine sample for urinalysis;
- Calculate APACHE II, SOFA, or qSOFA score prior to randomization;

  Note: An APACHE II or SOFA score will be calculated prior to randomization for patients in Part A only. For patients who are not being treated in an intensive care unit and cannot have an APACHE II or SOFA score performed, and for all patients in Part B, a qSOFA score should be calculated.
- Randomize patient to study drug via IRT;
- Administer study drug;
- For intense PK sampling, collect PK samples after the second infusion at the end of the infusion after the infusion pump is turned off (+15 minutes), 1.5 hours (±15 minutes) after the end of the infusion, and immediately prior to the start of the next infusion;

- For sparse PK sampling, collect PK samples after the second infusion, immediately prior to the start of the next infusion. The patient should have received at least 2 infusions before this schedule is implemented;

  Note: When possible, PK samples should be collected after the second infusion on Day 1. If the second infusion happens during the night and it is not possible to collect the PK sample after the infusion, the same procedures could be done after the third infusion on Day 1. The PK sample should be taken after the patient received at least 2 infusions on Day 1.

- Perform 12-lead ECG at the end of the first infusion of study drug for all patients, and consult the study Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF ≥480 msec after the end of infusion and after the patient has been in a supine position for at least 10 minutes); and
- Assess adverse events.

6.3.2 Day 2

The following procedures will be performed at Day 2:

- Record concomitant medications;
- Perform a limited physical examination, if needed;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Collect blood samples for:
  - Serum creatinine; and
  - Blood cultures in patients with bacteremia, if applicable;
- Administer study drug; and
- Assess adverse events.

6.3.3 Day 3

The following procedures will be performed at Day 3:

- Record concomitant medications;
- Perform a complete physical examination, including weight;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Collect blood sample for:
  - Serum chemistry;
  - Serum creatinine;

  - Hematology; and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect urine sample for urinalysis;
- Administer study drug;
- For intense PK sampling, if PK samples will not be collected on Day 4, collect PK samples at the end of any infusion after the infusion pump is turned off (+15 minutes), and immediately prior to the start of the next infusion;
- For sparse PK sampling, if PK samples will not be collected on Day 4, collect PK samples after the end of infusion, immediately prior to the start of the next infusion;

  Note: When possible, PK samples should be collected on Day 4. If collection on Day 4 is not possible, post-dose PK samples may be collected on Day 3 or Day 5 instead of Day 4, at the discretion of the Investigator.
- If PK samples are collected, repeat 12-lead ECG as close as possible following the end of the infusion of study drug administration associated with the PK samples, if clinically indicated; and
- Assess adverse events.

6.3.4 Day 4

The following procedures will be performed at Day 4:

- Record concomitant medications;
- Perform a limited physical examination, if needed;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Collect blood samples for:
  - Serum creatinine; and
  - Blood cultures in patients with bacteremia, if applicable;
- Administer study drug;
- For intense PK sampling, collect PK samples at the end of any infusion after the infusion pump is turned off (+15 minutes), and immediately prior to the start of the next infusion;
- For sparse PK sampling, collect PK samples after the end of infusion, immediately prior to the start of the next infusion;

  Note: When possible, PK samples should be collected on Day 4. If collection on Day 4 is not possible, post-dose PK samples may be collected on Day 3 or Day 5 instead of Day 4, at the discretion of the Investigator.

- If PK samples are collected, repeat 12-lead ECG as close as possible following the end of the infusion of study drug administration associated with the PK samples, if clinically indicated; and
- Assess adverse events.

6.3.5 Day 5

The following procedures will be performed at Day 5:

- Record concomitant medications;
- Perform a complete physical examination, including weight;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Assess clinical outcome. In Part A, clinical outcome will be assessed by the blinded assessor, in addition to the unblinded Investigator (see Section 7.6);
- Collect blood sample for:
  - Serum chemistry;
  - Serum creatinine;
  - Hematology; and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect urine sample for urinalysis;
- Collect infection site-specific cultures based on diagnosis if clinically indicated (see Section 7.7);
- Administer study drug;
- For intense PK sampling, if PK samples were not collected on either Day 3 or Day 4, collect PK samples at the end of any infusion after the infusion pump is turned off (+15 minutes), and immediately prior to the start of the next infusion;
- For sparse PK sampling, if PK samples were not collected on either Day 3 or Day 4, collect PK samples after the end of infusion, immediately prior to the start of the next infusion;

  Note: When possible, PK samples should be collected on Day 4. If collection on Day 4 is not possible, post-dose PK samples may be collected on Day 3 or Day 5 instead of Day 4, at the discretion of the Investigator.
- If PK samples are collected, repeat 12-lead ECG as close as possible following the end of the infusion of study drug administration associated with the PK samples, if clinically indicated; and
- Assess adverse events.

6.3.6 Day 6

The following procedures will be performed at Day 6:

- Record concomitant medications;
- Perform a limited physical examination, if needed;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Collect blood sample for:
  - Serum creatinine; and
  - Blood cultures in patients with bacteremia, if applicable;
- Administer study drug; and
- Assess adverse events.

6.3.7 Day 7 to Day 14 and End of Treatment Visit

Patients will be treated with 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin (ie, 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated.

If EOT occurs on Day 7, Day 7 study procedures may be considered the EOT Visit study procedures. If EOT occurs after Day 7, the EOT Visit activities should be completed within 24 hours after the last dose of study drug. Day 7 to Day 14 study procedures are only required if the patient receives IV study drug treatment on Day 7 to Day 14. If EOT has already occurred, study procedures are not required to be performed.

The following procedures will be performed at Day 7 to Day 14 and at the EOT Visit:

- Record concomitant medications;
- Perform a complete physical examination, including weight (Day 7 and EOT Visit only);
- Perform a limited physical examination, if needed (Day 8 to Day 14 only);
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Assess clinical outcome. In Part A, clinical outcome will be assessed by the blinded assessor, in addition to the unblinded Investigator (see Section 7.6) (Day 7 and EOT Visit only);
- Perform a highly sensitive urine or serum pregnancy test for women of childbearing potential only (EOT Visit only);
- Collect blood sample for:
  - Serum chemistry (Day 7 and EOT Visit only);
  - Serum creatinine;

  - Hematology (Day 7 and EOT Visit only); and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect urine sample for urinalysis (Day 7 and EOT Visit only);
- Perform 12-lead ECG and consult the study Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF ≥480 msec) (EOT Visit only);
- Collect infection site-specific cultures based on diagnosis if clinically indicated (see Section 7.7) (Day 7 and EOT Visit only);
- Administer study drug; and
- Assess adverse events.

6.4 Test of Cure Visit

The TOC Visit will occur 7 days (±2 days) after the EOT Visit.

The following procedures will be performed at the TOC Visit:

- Record concomitant medications;
- Perform a limited physical examination, if needed;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- For patients with HABP, VABP, or VP, perform chest X-ray, MRI, or CT scan;
- Assess clinical signs and symptoms (see Section 7.5);
- Assess clinical outcome. In Part A, clinical outcome will be assessed by the blinded assessor, in addition to the unblinded Investigator (see Section 7.6);

  Note: If a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC Visit and LFU Visit, and the assessment of clinical response by the Investigator should be listed as "failure at EOT or TOC."
- Collect blood samples for:
  - Serum chemistry;
  - Serum creatinine;
  - Hematology; and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect urine sample for urinalysis;
- Collect infection site-specific cultures based on diagnosis if clinically indicated (see Section 7.7); and
- Assess adverse events.

6.5 Late Follow-Up and Day 28 Visit

The LFU Visit will occur 14 days (±2 days) following the EOT Visit. The LFU Visit should be performed as an in-person visit; however, if the patient is unable to attend the LFU Visit at the site, the patient may be contacted by telephone call for follow-up assessment of concomitant medications, clinical signs and symptoms, and adverse events. ***All patients who are alive and have not withdrawn consent for participation in the study must be contacted at Day 28 or anytime thereafter to assess survival if their LFU Visit is prior to Day 28.***

The following procedures will be performed at the LFU Visit:

- Record concomitant medications;
- Perform a limited physical examination, if needed;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Assess clinical outcome. In Part A, clinical outcome will be assessed by the blinded assessor, in addition to the unblinded Investigator (see Section 7.6);

  Note: If a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC Visit and LFU Visit, and the assessment of clinical response by the Investigator should be listed as "failure at EOT or TOC."
- Collect blood samples for:
  - Serum chemistry;
  - Serum creatinine;
  - Hematology; and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect urine sample for urinalysis;
- Collect infection site-specific cultures based on diagnosis if clinically indicated (see Section 7.7); and
- Assess adverse events.

6.6 Early Termination Visit/Withdrawal Procedures

For patients who are withdrawn from the study prior to completion of study drug treatment or discontinue study drug prematurely, an Early Termination (ET) Visit should be completed at the time of study withdrawal or study drug discontinuation. Patients who discontinue study drug prematurely but are not withdrawn from the study should complete TOC and LFU Visits. Patients who are randomized to Part A based on a positive screening of a respiratory sample for ABC by BPP rapid test, but subsequently do not have growth of ABC in their respiratory sample culture processed by the local microbiology laboratory, will be considered withdrawn from the study drug treatment. For patients who are withdrawn from the study after the EOT Visit but prior to completion of the study, the next scheduled visit (either the TOC Visit or LFU Visit) should be completed at the time of study withdrawal. An assessment of all-cause mortality at Day 28 or

anytime thereafter must be made for all patients initially randomized to the study (including HABP/VABP/VP patients who are randomized to Part A based on a positive BPP rapid test, but who subsequently do not have growth of ABC in their respiratory sample culture), regardless of the duration of study drug received, as long as there has been no withdrawal of consent. See Section 4.3 for complete details on criteria for withdrawal and/or discontinuation.

The following procedures will be performed at the ET Visit:

- Record concomitant medications;
- Perform a complete physical examination, including weight;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP;
- Assess clinical signs and symptoms (see Section 7.5);
- Assess clinical outcome. In Part A, clinical outcome will be assessed by the blinded assessor, in addition to the unblinded Investigator (see Section 7.6);
- Perform a highly sensitive urine or serum pregnancy test for women of childbearing potential only;
- Collect blood sample for:
  - Serum chemistry;
  - Serum creatinine;
  - Hematology; and
  - Blood cultures in patients with bacteremia, if applicable;
- Collect urine sample for urinalysis;
- Perform 12-lead ECG and consult the study Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF ≥480 msec);
- Collect infection site-specific cultures based on diagnosis if clinically indicated (see Section 7.7); and
- Assess adverse events.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint for the study is 28-day all-cause mortality in the CRABC m-MITT Population in Part A.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for Part A and Part B include the following:

- 28-day all-cause mortality in the Intent-to-Treat (ITT) Population;
- Clinical cure at TOC in the CRABC m-MITT Population;
- Clinical cure at TOC in the m-MITT, Clinical Evaluable (CE), Microbiologic Evaluable (ME), and CRABC ME Populations;
- Clinical cure at Day 5, Day 7, EOT, and LFU in the m-MITT, CRABC m-MITT, CE, ME, and CRABC ME Populations;
- Microbiological favorable assessment at Day 5, Day 7, EOT, TOC, and LFU in the m-MITT, CRABC m-MITT, ME, and CRABC ME Populations;
- 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations;
- 28-day all-cause mortality in the m-MITT and CRABC ME Populations; and
- PK exposure of ETX2514 and sulbactam in the PK Population.

7.3 Other Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Clinical cure based on PK exposure;
- Clinical cure based on MIC distribution of ETX2514SUL;
- Clinical cure based on baseline resistance to ETX2514SUL, carbapenems, or colistin;
- Number of days in the intensive care unit;
- Number of patients transferred to the intensive care unit;
- For patients with VABP, VP, or ventilated HABP, number of days on ventilators;
- Number of days in the hospital; and
- Number of days on study drug treatment.

7.4 Assessment of 28-Day Survival

Every attempt must be made to record survival status at Day 28 or anytime thereafter for all randomized patients (including HABP/VABP/VP patients who are randomized to Part A based on a positive BPP rapid test, but who subsequently do not have growth of ABC in their respiratory sample culture), regardless of their status of treatment, as long as the patient has not withdrawn consent from participation in the study. An in-person assessment is preferred; however, this assessment may also be performed via a telephone call if an in-person visit is not possible.

For patients with an LFU Visit occurring before Day 28, a telephone call to assess survival will be made on Day 28 or anytime thereafter.

7.5 Assessment of Clinical Signs and Symptoms

Clinical signs and symptoms of the presenting indication will be assessed at Screening, daily during IV treatment beginning on Day 1, at the EOT Visit, at the TOC Visit, at the LFU Visit, and at the ET Visit, if applicable, by the blinded assessor and the unblinded Investigator for Part A and by the unblinded Investigator for Part B. When possible, the same study personnel should complete the assessments at approximately the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single treatment day) will be recorded. Body temperature may be taken per the site's preferred method, as specified in Table 3, and will be recorded in the appropriate eCRF. The same method of measuring a patient's body temperature should be used throughout the study.

Each sign and/or symptom of the presenting indication will be assigned a classification of absent, mild, moderate, or severe. Findings from the assessment of signs and symptoms will be captured on the appropriate eCRF and should not be documented as adverse events. The signs and symptoms by indication are presented in Table 3.

Table 3. Signs and Symptoms for Presenting Indications

Presenting Indication	Signs and Symptoms	
HABP/VABP/VP mechanically ventilated patients	• Rales; • Dullness on percussion; • Bronchial breath sounds; • Egophony; • Purulent secretion; and	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]).
HABP/VABP/VP non-mechanically ventilated patients	• Cough; • Rales; • Dullness on percussion; • Bronchial breath sounds; • Egophony; • Dyspnea;	• Respiratory rate >25 breaths/minute; and • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]).
Bacteremia	• Heart rate >100 bpm; • Respiratory rate >25 breaths/minute; • Systolic blood pressure <90 mmHg; and	• Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]).
cUTI or AP	• Urinary frequency; • Urinary urgency; • Dysuria; • Nausea; • Vomiting; • Abdominal pain; • Supra-pubic pain or discomfort;	• Flank pain; • Costovertebral angle tenderness on examination; and • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]).
Surgical and post-traumatic wound infections	• Purulent drainage; • Erythema; • Warmth; • Exudation; • Odor; • Pain;	• Leukocytosis; and • Fever [1] (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]) OR hypothermia (rectal/core temperature <35°C [<95°F]).

1. Maximum daily temperature on a single treatment day will be recorded. Note: Axial temperature is not allowed.
AP = acute pyelonephritis; bpm = beats per minute; cUTI = complicated urinary tract infection; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia; VP = ventilated pneumonia.

7.6 Clinical Outcome

Clinical outcome will be used to determine a response of clinical success for all patients. Based on the assessment of signs and symptoms, the unblinded Investigator will choose 1 of the following clinical outcomes at the Day 5, Day 7, EOT Visit, TOC Visit, LFU Visit, and ET Visit, if applicable. In Part A, in addition to the unblinded Investigator, a blinded assessor will also determine clinical outcome. If there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator, the assessment from the blinded assessor will be used. If there is a missing assessment from either the blinded assessor or unblinded Investigator, the other available assessment will be used (see Section 5.4.1). An adjudication committee may be organized for endpoint adjudication should it be deemed necessary by the DSMB. In such a case, a charter will be developed that describes their activities.

Clinical cure: complete resolution or significant improvement of signs and symptoms that were present at baseline and no new symptoms, such that no additional Gram negative antimicrobial therapy is warranted.

Clinical failure: symptoms present at study entry have not significantly improved or completely resolved, or new symptoms have developed and require the initiation of a non-study Gram negative antibacterial drug therapy, death, or intolerance to study drug leading to discontinuation from the study treatment.

Clinical indeterminate: determination cannot be made because of missing data or the patient is lost to follow-up.

7.7 Microbiologic Assessments

To assess the primary indication and follow-up of the primary indication, all specimens will be sent to the local laboratory for culture and susceptibility testing per institutional standards. Pure cultures of isolated pathogens will be shipped from the local laboratory to the central laboratory for confirmation of species identification, susceptibility testing, and possible molecular characterization, as detailed in the Microbiology Laboratory Manual. Definitions of resistance for purposes of this protocol are detailed in Section 9.1 and in the Microbiology Laboratory Manual.

Rapid diagnosis of ABC HABP/VABP/VP will utilize the BPP to detect ABC in respiratory specimens. Details of the test and its use will be included in the Laboratory Manual. The test results will be recorded in the eCRF.

All patients must have a specimen sample from the site of infection (ie, respiratory secretion, blood, urine, or wound) and 2 sets of blood culture samples from 2 separate venipuncture sites collected at Screening. Screening respiratory specimens for patients with suspected HABP/VABP/VP should be subjected to BPP rapid diagnostic testing as detailed above, where available, and submitted to the local microbiology laboratory for culture and susceptibility testing. In these cases, if the local microbiology laboratory culture does not grow ABC, the patient will be withdrawn from the study drug treatment.

If the screening sample for culture that is growing ABC is taken per standard of care before the patient or patient's legally authorized representative signs informed consent, that isolate may be used for baseline eligibility and sent to the central laboratory once consent is obtained, as long as the sample was collected within 72 hours prior to randomization. Additional samples for baseline culture should be collected again within 24 hours prior to randomization, at the time points specified in the Schedule of Procedures (Appendix A), and if clinically indicated. Patients who are failing their current treatment as evidenced by worsening clinical condition may enroll in the study, provided they meet all other requisites. However, additional samples must be taken from the site of infection within 24 hours prior to randomization and sent to the local laboratory for culture.

The local laboratory will culture each sample for species identification, quantification (urine and BAL only), and susceptibility testing. Any organism isolated from the culture will be identified by genus and species by the local laboratory. Potential pathogen(s) cultured at the local laboratory, including species isolated from mixed infections with other Gram positive or Gram negative organisms, will be sent to a designated central laboratory for confirmation of species identification, susceptibility testing results, and potential molecular characterization.

All organisms identified on culture at the local laboratory and the local laboratory assessment of susceptibility testing for each organism will be captured in the eCRF.

Enrollment in Part A can occur after ABC is identified in the blood and/or other respiratory tract specimens but prior to establishing the resistance profile. If local laboratory susceptibility testing reveals colistin resistance after a patient has been randomized to Part A, the patient must be transferred to Part B, regardless of the treatment group assignment in Part A, once Part B is open for enrollment. If Part B is not open for enrollment, patients will be withdrawn from the study drug treatment.

Patients who are randomized to Part A based on a positive screening of a respiratory sample for ABC by BPP rapid test, but subsequently do not have growth of ABC in their respiratory sample culture processed by the local microbiology laboratory, will be withdrawn from the study drug treatment. The need for continued standard of care treatment should be assessed by the Investigator.

When a patient's culture grows Gram positive organisms but the patient is clinically improving, the patient may remain on study drug without additional Gram positive antibiotic coverage at the Investigator's discretion. Patients who are not clinically improving or need adjustment in antimicrobial therapy that is not allowed per the protocol should be discontinued from study drug at the discretion of the Investigator, but should remain in the study to complete all study assessments. Additional cultures and all EOT procedures should be performed at the time of discontinuation and every attempt must be made to collect survival data at Day 28 or anytime thereafter.

7.7.1 Respiratory Tract Specimens

For patients with HABP, VABP, or VP, the BPP rapid diagnostic testing at Screening should be conducted using BAL-like specimens (BAL or mini-BAL) or endotracheal aspirate by Protected Endotracheal Catheter specimens, as applicable. See the Laboratory Manual for further details.

For patients with HABP, VABP, or VP that were diagnosed with a positive BPP rapid test of their respiratory specimen at Screening, respiratory specimens for culture and susceptibility testing must be collected again at Screening. All HABP/VABP/VP patients should have additional specimens collected on Day 5, Day 7, EOT, TOC, LFU, and ET Visits from the respective sites as clinically indicated.

Acceptable specimens for culture and susceptibility testing should include at least 1 positive pretreatment sample (ie, sample obtained prior to study drug dosing) obtained by Protected Specimen Brush with BAL or mini-BAL, by non-bronchoscopic BAL, by Protected Endotracheal Catheter suction, or from culture of lung tissue or pleural fluid obtained prior to randomization and treatment. Non-ventilated patients may have specimens obtained via deep expectoration or expectorated/induced sputum or culture of pleural fluid or lung tissue.

All respiratory specimens, even if positive by BPP rapid test for ABC, should be sent to the local microbiology laboratory for Gram stain (expectorated sputum only), culture and pathogen identification, susceptibility testing, and quantification (BAL only).

To be adequate, respiratory samples from expectorated or induced sputum should show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100 × field. Specimens should be cultured regardless of determination of adequacy. However, if the specimen is deemed to be inadequate, another respiratory sample should be collected and cultured.

Gram stains will be conducted per institutional standards, and Gram stain data should be captured in source documents. Colony counts are not expected to be performed on expectorated or induced

sputum or endotracheal aspirate. If the sputum is cultured, isolates of all pathogens exhibiting significant growth identified by the site laboratory's routine procedures should be sent to the central laboratory, even if the organisms are from a specimen that does not meet the specimen adequacy criteria described above. Culture-purified isolates of pathogens from respiratory samples will be sent to the central laboratory for confirmation of identification and susceptibility testing.

7.7.2 Blood Specimens

Two sets of samples from 2 separate venipuncture sites are required for blood cultures in all patients. Each set of blood culture samples will be collected from a separate venipuncture site and will consist of 1 aerobic and 1 anaerobic blood culture bottle (an additional aerobic bottle is allowed if an anaerobic culture is not standard practice at the site). Each set of blood cultures should be collected by direct venipuncture from independent sites approximately 15 minutes to 30 minutes apart. A positive blood culture for ABC within 72 hours prior to randomization can be used for enrollment of a patient as long as the sample was drawn from a peripheral vein or through a newly inserted catheter; however, 2 sets of blood cultures, as outlined above, must be repeated within 24 hours prior to randomization. For a patient to meet criteria for catheter-related bloodstream infection, please see the necessary sampling procedures described in Part A-Specific Inclusion Criterion 1 (Section 4.1.2). If Screening/baseline blood cultures are positive for ABC, repeat blood cultures should be obtained daily until negative or the patient is a treatment failure. To avoid unnecessary blood draws, the Investigator may wait until the result of the prior blood culture is known before performing the next blood culture.

Additional blood cultures, including blood cultures taken during fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]), may also be collected at the Investigator's discretion.

Isolates of pathogens (eg, not considered to be a contaminant as outlined in the Microbiology Laboratory Manual) from each individual positive blood culture will be sent to the central laboratory.

7.7.3 Urine Specimens

For patients with cUTI or AP, urine samples will be collected at Screening, Day 5, Day 7, EOT, TOC, LFU, and ET Visits by 1 of the following methods that minimizes the risk of bacterial contamination:

- Clean-catch mid-stream;
- Newly inserted Foley catheter (bag specimens are not permitted);
- Bladder needle aspiration;
- Suprapubic catheter;
- Ureter aspiration; or
- Nephrostomy tube.

Urine cultures will be performed by the local laboratory. The local laboratory will culture each sample for species identification, quantification, and susceptibility testing. Any organism isolated from the urine will be identified by genus and species by the local laboratory. Culture-purified isolates of potential pathogens isolated at baseline and all post-baseline organisms culture-purified

at the local laboratory and not considered to be contaminants as outlined in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification and susceptibility results. A urine sample taken to support diagnosis or to treat a medical condition within 48 hours prior to the first dose of study drug can be used for baseline microbiologic assessments if the organism(s) cultured was obtained and stored for shipment to the designated central laboratory. Otherwise, a repeat urine sample for baseline microbiologic assessments is required.

Baseline urine cultures must grow 1 or 2 defined bacterial pathogens, each at $\geq 10^5$ colony-forming units (CFU)/mL. If a patient grows ≥3 organisms in the urine, the urine culture will be considered contaminated unless ≥1 of the organisms also grows in a concurrently obtained blood culture.

For post-baseline urine cultures, only those potential pathogens that grow at $\geq 10^3$ CFU/mL and deemed not to be contaminants as outlined in the Microbiology Laboratory Manual will be culture-purified and sent to the central laboratory for confirmation of identification and susceptibility testing.

7.7.4 Surgical or Post-Traumatic Wound Specimens

For patients with surgical or post-traumatic wound infections, an adequate clinical specimen for microbiologic evaluation will be collected at Screening, Day 5, Day 7, EOT, TOC, LFU, and ET Visits as long as clinically indicated (ie, as long as there is material to send for culture). Clinical specimens include pus from a wound or abscess and aspirate from the leading edge of cellulitis.

All specimens should be sent to the local laboratory for Gram stain, species identification, and susceptibility testing.

Isolates of potential pathogen(s) culture-purified at the local laboratory will be sent to the central laboratory for confirmation of identification and susceptibility testing results.

7.8 Microbiologic Outcome

7.8.1 Microbiologic Outcome for Bacteremia, Complicated Urinary Tract Infection, or Acute Pyelonephritis

For patients with bacteremia, cUTI, or AP, per-patient microbiological response will be determined programmatically as 1 of the following outcomes based on the results of blood and/or urine cultures at the Day 5, Day 7, EOT, TOC, and LFU Visits. A microbiological favorable assessment will include eradication and presumed eradications, as detailed below.

Microbiologic eradication:

- For patients with cUTI or AP: the baseline strain of ABC is reduced to $<10^3$ CFU/mL on urine culture and negative on repeat blood culture (if positive at baseline); or
- For patients with bacteremia: absence of the baseline strain of ABC on culture.

Microbiologic presumed eradication: no culture was done, and the patient meets clinical criteria for clinical cure.

Microbiologic persistence:

- For patients with cUTI or AP: the demonstration that the urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry and/or a blood culture demonstrates the same baseline pathogen(s); or
- For patients with bacteremia: presence of the baseline strain of ABC on repeat culture.

Patients who are a persistence at EOT will be considered a persistence at TOC.

Microbiologic presumed persistence: no culture was done, and the patient meets clinical criteria for clinical failure.

Microbiologic indeterminate: if clinically indicated (for cUTI and bacteremia only), no follow-up culture is available, the culture cannot be interpreted for any reason, or the culture is considered contaminated.

Microbiologic recurrence:

- For patients with cUTI or AP: the demonstration that the urine culture grew $\geq 10^3$ CFU/mL of the baseline strain of ABC identified at study entry at any time after documented eradication at the TOC Visit up to and including the LFU Visit; or
- For patients with bacteremia: a positive blood culture for ABC at any time after documented eradication at the TOC Visit up to and including the LFU Visit.

7.8.2 Microbiologic Outcome for Hospital-Acquired Bacterial Pneumonia, Ventilator-Associated Bacterial Pneumonia, Ventilated Pneumonia, or Surgical or Post-Traumatic Wound Infections

Microbiologic presumed eradication: no culture was done, and the patient meets clinical criteria for clinical cure. For patients with HABP/VABP/VP or surgical or post-traumatic wound infections, where repeat culture samples may not be indicated, presumed eradication based on clinical improvement will be inferred.

Microbiologic presumed persistence: no culture was done, and the patient meets clinical criteria for clinical failure.

7.9 Pharmacokinetic Assessments

7.9.1 Intense Pharmacokinetic Sampling

The first approximately 30 patients randomized in Part A will have samples collected for intense PK analysis to ensure that exposures observed in this severely ill cohort are comparable to those observed thus far in prior clinical studies. Intense PK sampling will also be performed on the first approximately 20 patients randomized in Part A at sites in China Mainland.

Samples for intense PK analysis will be collected on Day 1, preferably after the second infusion, as follows:

- At the end of the infusion after the infusion pump is turned off (+15 minutes);
- 1.5 hours (±15 minutes) after the end of infusion; and
- Immediately prior to the start of the next infusion.

When possible, PK samples should be collected after the second infusion on Day 1. If the second infusion happens during the night and it is not possible to collect the PK sample after the infusion, the same procedures could be done after the third infusion on Day 1. The PK sample should be taken after the patient received at least 2 infusions on Day 1.

Additional samples for intense PK analysis will be collected on Day 4 (±1 day) as follows:

- At the end of any infusion after the infusion pump is turned off (+15 minutes); and
- Immediately prior to the start of the next infusion.

Table 4 shows the sampling times for intense PK assessments.

Table 4. Sampling Times for Intense Pharmacokinetic Assessments

PK Sampling Time	Day 1 [1]	Day 4 (±1 Day)
End of infusion (+15 minutes) [2]	X	X
1.5 hours (±15 minutes) after end of infusion	X	
Immediately prior to the start of the next infusion	X	X

1. PK sample should be taken preferably after the second infusion on Day 1.
2. PK sample should be taken at the end of the infusion after the infusion pump is turned off.

PK = pharmacokinetic.

7.9.2 Sparse Pharmacokinetic Sampling

All other patients enrolled in the study (Parts A and B) will have samples collected for sparse PK analysis. Samples for sparse PK analysis will be collected on Day 1, preferably after the second infusion, and on Day 4 as follows:

- On Day 1, immediately prior to the start of the next infusion; and
- On Day 4 (±1 day), immediately prior to the start of the next infusion.

When possible, PK samples should be collected after the second infusion on Day 1. If the second infusion happens during the night and it is not possible to collect the PK sample after the infusion, the same procedures could be done after the third infusion on Day 1. The PK sample should be taken after the patient received at least 2 infusions on Day 1. Table 5 shows the sampling times for sparse PK assessments.

Table 5. Sampling Times for Sparse Pharmacokinetic Assessments

PK Sampling Time	Day 1 [1]	Day 4 (±1 Day)
Immediately prior to the start of the next infusion	X	X

1. PK sample should be taken preferably after the second infusion on Day 1.

PK = pharmacokinetic.

The PK samples will be collected for both treatment groups in Part A to keep the study data blinded. The PK samples obtained from the ETX2514SUL group will be analyzed for ETX2514 and sulbactam concentrations using a validated assay by a central bioanalytical laboratory.

The PK plasma samples will be used to estimate PK parameters using non-compartmental methods, such as area under the concentration-time curve, maximum plasma concentration, time to maximum plasma concentration, drug clearance, half-life, minimum plasma concentration, and

steady-state volume of distribution for ETX2514SUL. Population PK and PK/PD modeling will be performed and reported separately. The results will not be included in the clinical study report.

Additional PK sampling may be performed as needed for patients with eGFR >130 mL/min/m^2 undergoing acute hemodialysis or renal replacement therapy utilizing the trough sampling approach.

The actual PK sampling times will be captured on the eCRF. Actual dosing time will also be captured on the eCRF. Actual sampling time will be used for the PK calculations.

See the Laboratory Manual for more details about PK sampling.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of the main informed consent (not the limited scope ICF) until study participation is complete. This is to be understood that Investigators should report any adverse event occurring from the time the main ICF (including all study procedures) was signed. Investigators are not required to report adverse events occurring for patients who only signed the limited scope ICF (which only allows rapid testing on a respiratory sample). Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning at enrollment, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

Newly emergent infections that appear after baseline will be reported as adverse events and summarized separately. Clinical failures should not be considered adverse events and should not be reported as such.

8.1.1 Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Response” to a medicinal product means that a causal

relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For ETX2514SUL, the reference safety information is included in the Investigator's Brochure currently in force.

8.1.3 Assessment of Adverse Events by the Investigator

The unblinded Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe. In Part A, in addition to the unblinded Investigator, a blinded assessor will also be responsible for the causality assessment, and as detailed below.

Assessment of severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed by the blinded assessor and the unblinded Investigator for Part A and by the unblinded Investigator for Part B, according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
  - The known PK properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

Adverse events of special interest will be analyzed, summarized, and reported in the clinical study report. Statistical comparisons will be made between the investigational and control groups in Part A.

Adverse events of special interest and their definitions include the following:

- Allergic and hypersensitivity reactions: Severe and serious adverse drug reactions from the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Queries of allergy and hypersensitivity;
- Nephrotoxicity: Using the RIFLE criteria for the duration of the study (see Table 6);[18] and
- Emergent infections and superinfections: All serious and severe events in the MedDRA system organ class of infections and infestations other than the indication infection (ie, ABC).

Table 6. Definition of RIFLE Criteria

Term	Definition
Risk (R)	Increased creatinine level 1.5× or GFR decrease >25%
Injury (I)	Increased creatinine level 2× or GFR decrease >50%
Failure (F)	Increased creatinine level 3×, GFR decrease >75%, or creatinine level ≥4 mg/dL
Loss (L)	Persistent acute renal failure or complete loss of function for >4 weeks
ESKD (E)	ESKD for >3 months

ESKD = end-stage kidney disease; GFR = glomerular filtration rate; RIFLE = Risk–Injury–Failure–Loss–End-stage renal disease.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

  Note: An adverse event or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations. Adverse events recorded for a patient who is hospitalized for treatment of the underlying illness, do not necessarily meet serious criterion of hospitalization.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or

- An important medical event.

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of the main informed consent (not the limited scope ICF) or randomization until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). This is to be understood that Investigators should report any SAE occurring from the time the main ICF (including all study procedures) was signed. Investigators are not required to report SAEs occurring for patients who only signed the limited scope ICF (which only allows rapid testing on a respiratory sample). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor. All SAEs should be reported as if it were a blinded study and without evidence of treatment assignment on the report.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (telephone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – US:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com
Medpace SAE reporting line – Rest of World:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
E-mail: medpace-safetynotification@medpace.com

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 120 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early study termination procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

Given that all-cause mortality is the primary efficacy endpoint in the study, all death cases will not be automatically unblinded by the case processing team. Death cases, where there is a plausible cause of death that is related to study drug administration, will be treated as potential suspected unexpected serious adverse reactions and processed as such and reported as needed. The DSMB

will periodically monitor deaths in aggregate, analyzed by treatment group, as detailed in the DSMB charter.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

8.6 Clinical Laboratory Evaluations

Standard clinical laboratory profiles for chemistry will be evaluated at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, the LFU Visit, and the ET Visit. Serum creatinine will be evaluated daily while the patient is receiving study drug and will be analyzed at the local laboratory to assess the need for dose adjustments. All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours before the first dose of study drug. All other samples are to be sent to the central laboratory. The Day 5 safety chemistry panel will be performed at the local laboratory and sent to the central laboratory.

Standard clinical laboratory profiles for hematology including complete blood count (with red blood cell count, total white blood cell count with differential counts, platelet count, hemoglobin, and hematocrit) will be performed at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, the LFU Visit, and the ET Visit.

A urinalysis including urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH will be performed at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, the LFU Visit, and the ET Visit.

A highly sensitive urine or serum pregnancy test will be performed at Screening, the EOT Visit, and the ET Visit for women of childbearing potential.

See Appendix B for a list of central clinical laboratory analytes.

Standard of care safety laboratory profiles should also be performed by the local laboratory. Abnormal values of laboratory parameters must be followed up to normalization or stabilization at the discretion of the Investigator.

In China all sites will perform all laboratory tests at the local laboratory, following the timepoints outlined above.

8.7 Vital Signs

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP) will be taken after at least 5 minutes in a seated or supine position. Vital signs will be recorded at Screening, all days that the patient receives study drug treatment, the EOT Visit, the TOC Visit, the LFU Visit, and the ET Visit. Vital signs should be collected at the same time as assessments of signs and symptoms.

8.8 Medical/Surgical History Assessments

Medical and surgical history will be obtained and evaluated at Screening to confirm the patient's eligibility to enroll in the study.

8.9 Electrocardiograms

Twelve-lead ECGs will be performed for all patients at Screening, at the end of the first infusion of study drug on Day 1, at EOT, and at the ET Visit. If clinically indicated, the 12-lead ECGs will be repeated as close as possible following the end of the infusion of study drug on the day on which the post-dose PK samples are drawn (Day 4 [±1 day]; day selected at the discretion of the Investigator). All 12-lead ECGs will be performed after the end of the infusion and after the patient has been in a supine position for at least 10 minutes. The value at Screening will be used for assessing the QTcF exclusion criterion. All 12-lead ECGs will be performed and read locally. The following ECG parameters will be recorded:

- Heart rate;
- QRS interval;
- PR interval;
- RR interval;
- QT interval; and
- QTc interval.

All ECGs will be evaluated for the presence of abnormalities by a qualified local physician. The ECGs will be classified as 1 of the following:

- Normal;
- Having a not clinically significant abnormality; or
- Having a clinically significant abnormality.

An example of a clinically significant abnormality may be a corrected QTcF ≥480 msec.

8.10 Physical Examinations

A complete physical examination will be performed at Screening, Day 3, Day 5, Day 7, at the EOT Visit, and at the ET Visit. A limited physical examination will be performed, if needed, at Day 2, Day 4, Day 6, Day 8 to Day 14 (if EOT has not already occurred), at the TOC Visit, and at the LFU Visit.

A complete physical examination must include source documentation of weight, skin, head and neck, heart, lung, abdomen, extremities, back/flank/costovertebral angle tenderness, and neuromuscular assessments. Height will only be collected at Screening. Limited physical examinations are symptom-based. When clinically indicated, a prostate exam can be performed, at the discretion of the Investigator.

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

8.11 Chest X-Ray/Radiology/Ultrasound

Chest X-rays, MRIs, or CT scans will be performed in patients with HABP, VABP, or VP at Screening and the TOC Visit, and as clinically indicated to evaluate for the presence of infiltrates. Ultrasounds may also be performed for patients with HABP, VABP, or VP at Screening. If an ultrasound is performed, a confirmatory X-ray or CT scan should be performed within 24 hours. Imaging should be conducted per institutional guidelines and results recorded in the source documents and the eCRF.

8.12 Mechanical Ventilator Assessments

Patients whose primary indication for enrollment into the study is HABP, VABP, or VP and who require mechanical ventilation support will be managed by the study Investigators per institutional guidelines. Data regarding mechanical ventilation settings will be captured in the source documents and the eCRFs.

8.13 Safety Monitoring and Assessment of Abnormal Liver Function Tests

Management and discontinuation criteria for abnormal liver function tests (LFTs) have been designed to ensure patient safety and evaluate liver event etiology.[19] Safety monitoring for LFTs will occur from randomization until 30 days following the last administration of study drug; however, any abnormal LFT will be monitored according to the Safety Monitoring Plan. Investigators should evaluate standard of care laboratory reports in addition to study laboratory reports when monitoring for LFTs.

Abnormal liver chemistry criteria:

The Investigator or sub-Investigator must review patient laboratory reports to identify if they meet the following criteria:

- Moderate abnormality that happened after study drug administration:
  - AST or ALT >2 × baseline or evidence of progressively increasing levels despite improvement of underlying infection; or
  - Total bilirubin >2 × baseline or evidence of progressively increasing levels despite improvement of underlying infection.
- Severe abnormality:
  - Confirmed values of AST or ALT >3 × ULN **and** total bilirubin >2 × ULN or evidence of acute hepatic insufficiency or failure, as evidenced by progression of Child-Pugh score to B or C; or
  - Persistently high values of AST or ALT > 5 × ULN for 14 days.

Action to be taken by Investigator:

If any 1 of the abnormal liver chemistry criteria is met, the Investigator or sub-Investigator must do the following:

- Obtain a detailed history of symptoms and prior or concurrent diseases. The Investigator should ensure that the medical history form captures any preexisting illness that may be relevant in assessing hepatic function;
- Obtain a history of concomitant drug use (including over-the-counter/herbal/dietary supplements);
- Obtain a history of exposure to environmental chemical agents;
- Following the initial observed elevation, every effort should be made to have the patient reassessed within 24 hours to 48 hours. Repeat LFTs will be performed and sent to the central laboratory. Liver function tests may also be repeated via the local laboratory at the discretion of the Investigator;
- Patients who have an Investigator-assessed, study drug-related elevation of their LFTs must be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, alkaline phosphatase, and total bilirubin) completely return to normal range or return to the baseline level and associated clinical signs and symptoms return to baseline levels. If the elevation of LFTs is attributed to a non-study drug-related issue (eg, chronic hepatitis, chronic cholestasis, concomitant treatments, cardiovascular causes, etc), the patient should be monitored until the LFTs stabilize or return to the patient's baseline level and associated clinical signs and symptoms return to baseline levels. The Investigator should contact the Medical Monitor to discuss additional management and follow-up of patients with elevation of LFTs;
- The event must be reported to Medpace within 48 hours to 72 hours after its occurrence on a Liver Event Form;
- Consider a consultation with a specialist such as a hepatologist; and
- Consider performing liver imaging (ie, MRI, CT, or ultrasound).

Hy's Law definition:

The definition of Hy's Law is as follows:

1. AST or ALT >3 × ULN;
2. Total bilirubin >2 × ULN;
3. No evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's Syndrome; and
4. No evidence of any other reason for increase in transaminases as noted above.

If the first 3 criteria of Hy's Law are met in a concurrent blood sample, the case must be reported as an SAE.

Criteria for study drug discontinuation (severe hepatic abnormalities):

In the absence of an explanation for increased liver enzymes, the patient should be discontinued from the study drug. Discontinuation should be considered if:

- ALT or AST >10 × ULN;
- ALT or AST >5 × ULN for more than 2 weeks or progressively increasing transaminases despite clinical improvement of underlying infection;
- AST or ALT >3 × ULN and total bilirubin >2 × ULN or international normalized ratio >1.5 (for patients who are not on coumadin);
- AST or ALT >3 × ULN along with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia [>5%]); or
- Close monitoring for a patient with moderate hepatic laboratory test abnormality is not possible.

Follow-up examination:

If any abnormal liver chemistry criteria are met, the following assessments should be obtained at the LFU Visit and documented in a Liver Event Form:

- Clinical symptoms course;
- Concomitant medications: over-the-counter/herbal/dietary supplements (start and stop dates);
- Alcohol use;
- Risk factors for non-alcoholic steatohepatitis, such as diabetes, obesity, and hypertriglyceridemia;
- Autoimmune hepatitis/cholangitis;
- Wilson's disease; and
- Laboratory assessments. Based on the patient's history, other testing may be appropriate, including:
    - Acute viral hepatitis (A, B, C, D, E, or other infectious agents); and
    - Other laboratory tests, including international normalized ratio and direct bilirubin.

9 STATISTICS

9.1 Analysis Populations

This study is designed to estimate treatment efficacy of ABC infections, with a pivotal component in Part A.

The ITT Population will include all patients randomized to study drug treatment (ETX2514SUL plus imipenem/cilastatin or colistin plus imipenem/cilastatin) in Part A or enrolled in Part B, regardless of whether the patient actually receives study drug.

The Modified ITT (MITT) Population will include patients in Parts A and B who meet ITT criteria and receive any amount of study drug. The MITT Population will be considered the Safety Population. Patients with HABP/VABP/VP who were randomized to Part A on the basis of a BPP rapid test result but were subsequently withdrawn due to a lack of a culture growing ABC will be counted in the MITT and Safety Populations.

The m-MITT Population will include patients who meet MITT criteria and have an ABC organism isolated as the qualifying culture specimen, as confirmed by the central and/or local microbiology laboratory. If an isolate for testing at the central laboratory is not available, the local laboratory data can be used to confirm the presence of ABC organism, as long as the local laboratory uses modern methods of diagnosis such as molecular-based tests, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, Vitek, Phoenix, etc (ie, not conventional biochemical or manual phenotypic methods). Patients with HABP/VABP/VP who are enrolled based upon a positive BPP rapid test for ABC, but subsequently are found to have respiratory sample cultures that do not grow ABC (by the local laboratory), will be withdrawn from the study drug treatment as detailed in Section 4.3. These patients will not be included in the m-MITT Population but will remain in the MITT Population.

The CRABC m-MITT Population will include patients who meet m-MITT criteria and have a baseline ABC organism that is confirmed to be carbapenem-resistant (MIC to imipenem/meropenem ≥8 mg/L) by the central laboratory or by the local laboratory if the central laboratory is not able to identify the isolate for any reason. Patients will be excluded from the CRABC m-MITT Population if they have isolates that are deemed by the central laboratory to be resistant to ETX2514SUL (MIC >4 mg/L) or colistin (MIC ≥4 mg/L), if their blood culture or respiratory samples are collected more than 72 hours prior to randomization, if they are transferred from Part A to Part B, or if they are enrolled with infections other than ABC pneumonia or bloodstream infection (ie, ABC infections other than HABP, VABP, VP, and bacteremia). A sensitivity analysis for the primary efficacy endpoint will be performed for patients whose eligible culture is >48 hours from the first dose of study drug, as well as for all patients with and without evidence of non-susceptibility to colistin and ETX2514SUL at baseline.

The CE Population will include patients who meet m-MITT criteria and meet evaluability criteria (meet key inclusion criteria, do not have key exclusion criteria, received at least 72 hours of study drug [ie, 12 doses of ETX2514SUL plus 12 doses of imipenem/cilastatin or 6 doses of colistin plus 12 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical cure, received at least 48 hours of study drug [ie, 8 doses of ETX2514SUL plus 8 doses of imipenem/cilastatin or 4 doses of colistin plus 8 doses of imipenem/cilastatin in patients without dose adjustments] to be a clinical failure, received ≥80% of anticipated doses, and did not have a clinical response of indeterminate at the TOC Visit).

The ME Population will include patients who meet m-MITT criteria and CE criteria and have an appropriately collected culture specimen and interpretable culture result when specimen collection is clinically indicated at the TOC Visit.

The CRABC ME Population will include patients who meet ME criteria and who have a baseline ABC organism that is confirmed to be carbapenem-resistant (and susceptible to ETX2514SUL for Parts A and B and susceptible to colistin for Part A).

The PK Population will include patients who receive any amount of study drug and have evaluable PK data.

9.2 Statistical Methods

Continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized by using the frequency count and the percentage of patients in each category as descriptive statistics.

All comparisons in Part A will be for ETX2514SUL plus imipenem/cilastatin versus colistin plus imipenem/cilastatin. The efficacy endpoints for Part B will be summarized descriptively only and will be used to supplement results in Part A. Listings of individual patient data will be produced. A complete analysis of efficacy and safety data will be performed and detailed in the SAP.

9.2.1 Patient Population and Characteristics

The number of patients randomized, treated, completed, and discontinued early from the study and the reasons for discontinuation will be summarized descriptively. In addition, reasons leading to study discontinuation will be summarized for each treatment group. The number and percentage of randomized patients included in each analysis population will also be presented.

Summary statistics will be provided by treatment group for demographics (eg, age, gender, race, and ethnicity) and for baseline characteristics.

9.2.2 Analysis of Efficacy

9.2.2.1 Primary efficacy analysis

The primary efficacy endpoint for the study is 28-day all-cause mortality in the CRABC m-MITT Population in Part A. Patients in the CRABC m-MITT Population who discontinue study drug prematurely in Part A for any reason will be included in the assessment of 28-day all-cause mortality, provided consent has not been withdrawn.

A sensitivity analysis for the primary efficacy endpoint will be performed for patients whose eligible culture is >48 hours from the first dose of study drug, as well as for all patients with and without evidence of non-susceptibility to colistin and ETX2514SUL at baseline. Details of the sensitivity analysis will be described in the SAP.

The non-inferiority assessment will be based on the 2-sided 95% confidence intervals (CIs) for the difference ([ETX2514SUL + imipenem/cilastatin] – [colistin + imipenem/cilastatin]) in 28-day all-cause mortality rates between the treatment groups. Non-inferiority will be concluded if the upper limit of the 2-sided 95% CI is less than +20%.

If non-inferiority is achieved, a test of superiority will be performed.

The analysis of the primary efficacy endpoint 28-day all-cause mortality will also be performed in the ITT Population.

9.2.2.2 Secondary efficacy analysis

The number and percentage of patients in each response category for the secondary efficacy endpoints will be summarized by treatment group for the populations defined earlier. Two-sided 95% CIs for the difference in outcome rates between the treatment groups in Part A will be provided.

Part B data will be analyzed separately from Part A using descriptive statistics.

Further subgroup analyses will be conducted, and details of the analysis will be described in the SAP.

9.2.2.3 Exploratory efficacy analysis

Exploratory endpoint analysis will be described in the SAP. Exploratory endpoints for health resource utilization difference between treatment groups (such as length of ventilation, intensive care unit stay, hospitalization, additional antibiotic use, etc) will be reported separately. Efficacy analysis for patients with HABP/VABP/VP who are identified as positive for ABC by BPP molecular methodology will be explored.

9.2.3 Pharmacokinetic Analysis

Descriptive statistics will be provided for PK concentration data and PK parameters. All PK analyses will be performed using the PK Population.

Intense pharmacokinetic group:

Pharmacokinetic samples will be obtained from the first approximately 30 patients randomized in Part A on a schedule detailed in Section 7.9. The PK samples will be collected for both treatment groups in Part A to keep the study data blinded. The PK samples obtained from the ETX2514SUL group will be analyzed for ETX2514 and sulbactam concentrations using a validated assay by a central bioanalytical laboratory. Pharmacokinetic assessment of the initial 15 patients on ETX2514SUL in Part A will be performed by an independent PK assessor, prior to the opening of enrollment in Part B. The independent PK assessor will conduct sequential PK analysis from patients as they are enrolled. An initial aggregate assessment of PK parameters will be done after enrollment of the first 8 HABP/VABP/VP patients randomized to ETX2514SUL. The independent PK assessor will report results to the DSMB, relative to concentrations projected in the population PK model, once data from all 15 patients on ETX2514SUL is available. However, if the preliminary analysis of the first 8 patients with HABP/VABP/VP on ETX2514SUL reveals evidence of inadequate exposure this will be escalated to the DSMB.

China Mainland intense pharmacokinetic group:

The intense PK sampling will also be performed on the first approximately 20 patients randomized in Part A from China Mainland sites. The PK samples obtained from patients who have received the ETX2514SUL treatment will be analyzed for ETX2514 and sulbactam concentrations, which will be applied to build the population PK model combined with data from the sparse PK group.

Sparse pharmacokinetic group:

All other patients enrolled in the study (Parts A and B) will have a sparse PK sampling, which will be used to better inform the population PK model.

Analysis of the PK data and incorporation into the population PK analysis and PK/PD model will be described in a separate PK Analysis Plan.

9.2.4 Analysis of Safety

All patients who receive any amount of study drug (MITT Population) will be included in the safety analyses. Patients who received the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

A primary analysis of safety will be performed for Part A to assess the proportion of patients with nephrotoxicity, as measured by the RIFLE criteria based on the Safety and CE Populations.

Overall safety will be assessed for Part A and Part B in the Safety Population. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a TEAE for each unique system organ class and preferred term will be tabulated. A TEAE is defined as an adverse event occurring on or after the administration of the first dose of study drug. Treatment-emergent adverse events will also be tabulated by treatment group, severity, and the relationship to study drug as assessed by the Investigator. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a treatment-emergent SAE will be tabulated. The number and percentage of patients (in each treatment group) prematurely discontinuing study drug treatment due to a TEAE will be tabulated by system organ class and preferred term. Adverse events of special interest in Part A will be summarized for all patients by treatment.

Safety laboratory data will be presented by descriptive statistics of the post-baseline value and the change from baseline, as well as the number and percentage of patients with potentially clinically significant laboratory values. Descriptive statistics of vital signs and ECG parameters and the change from baseline will also be presented. An outlier analysis of the ECG parameters will be conducted.

9.2.5 Sample Size Determination

Patients will be enrolled until there are 120 patients in the CRABC m-MITT Population in Part A. The study will have 80% power to demonstrate non-inferiority between Group 1 and Group 2 using a 20% non-inferiority margin and a 2-sided 95% CI. This assumes a mortality rate in the comparator group (Group 2) of 41% and in the ETX2514SUL group (Group 1) of 36%. To have 120 patients in the CRABC m-MITT Population, Part A will need to enroll approximately 200 patients, assuming 60% of ABC clinical isolates are carbapenem-resistant. Patient enrollment in Part B (Group 3) will continue until Part A enrollment in the CRABC m-MITT Population is complete. Rates of carbapenem resistance among isolates from Part A patients will be monitored by the unblinded data manager/designee at the Clinical Research Organization on an ongoing basis.

Table 7 demonstrates the mortality rates in the ETX2514SUL plus imipenem/cilastatin treatment group required to demonstrate non-inferiority or superiority with no less than 80% power in the CRABC m-MITT Population relative to various 28-day all-cause mortality rates in the colistin plus imipenem/cilastatin treatment group, given 120 patients in the CRABC m-MITT Population.

The sample size of 120 patients in the CRABC m-MITT Population was calculated based on a 41% mortality rate in the colistin plus imipenem/cilastatin treatment group.

Table 7. 28-Day All-Cause Mortality Rates in the CRABC m-MITT Population Required to Demonstrate Non-Inferiority and Superiority

ETX2514SUL+IMI	Colistin+IMI	95% CI for Treatment Difference [1]	Power	Test
39%	45%	(-0.24, 0.12)	82%	Demonstrate NI
21%	45%	(-0.40, -0.08)	80%	Demonstrate superiority
35%	40%	(-0.22, 0.12)	80%	Demonstrate NI
17%	40%	(-0.39, -0.07)	80%	Demonstrate superiority
30%	35%	(-0.22, 0.12)	83%	Demonstrate NI
13%	35%	(-0.37, -0.07)	81%	Demonstrate superiority
26%	30%	(-0.20, 0.12)	83%	Demonstrate NI
9%	30%	(-0.35, -0.07)	83%	Demonstrate superiority

1. 95% CIs for treatment difference ([ETX2514SUL + IMI] – [colistin + IMI]) were calculated using a normal approximation to the binomial distribution.

CI = confidence interval; CRABC = Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; ETX2514SUL = sulbactam-ETX2514; IMI = imipenem/cilastatin; m-MITT = Microbiologically Modified Intent-to-Treat; NI = non-inferiority.

9.3 Data Safety Monitoring Board

An independent DSMB will review the safety data periodically. The DSMB will also review SAEs and deaths on an ongoing basis. They will make recommendations to the Sponsor based on the safety data. The PK assessment report of data from the initial cohort of patients in Part A from the independent PK assessor will be submitted to the DSMB for its approval of continued enrollment and initiation of Part B. Further details regarding the DSMB guidelines will be described in the DSMB Charter.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the US Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest) for medical history and adverse events; and
- WHO Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (ie, Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the Institutional Review Board (IRB) prior to its use and must be in compliance with all International Council for Harmonisation (ICH) GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. An ICF of limited scope may be signed prior to Screening to perform only BPP rapid testing of respiratory specimens. A comprehensive ICF, which will include all study procedures, will be signed at Screening. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. Patients will participate as much as possible in the informed consent procedure; however, as permitted by local law and institutional Standard Operating Procedures, in cases of a lack of decision-making capacity, informed consent on behalf of the patient may be provided by a legally authorized representative, independent physician, or consortium of independent physicians. These patients, upon return of their capacity, will be consented and allowed to make their own informed medical decisions.

The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Patient Card

On enrollment in the study, the patient will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research study, type of treatment, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who give their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study will be submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 End of Study

End of Study in this study is defined as the last visit or last study-related contact (whichever comes last) of the last patient worldwide.

12.3 Address List

12.3.1 Sponsor

Entasis Therapeutics
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12.3.2 Contract Research Organization

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12.3.3 Serious Adverse Event Reporting

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Medpace Clinical Safety – Rest of World
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E-mail: medpace-safetynotification@medpace.com

12.3.4 Biological Specimens

Medpace Reference Laboratories, LLC
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APPENDIX A: SCHEDULE OF PROCEDURES (PARTS A & B)

	Screening	Treatment Period									TOC	LFU	
Procedure [1]	**-48 Hours to Day 1 [2]**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7 [3]**	**Days 8 to 14 [3]**	**EOT (+1 day) [3,4]**	**EOT +7 (±2) Days [5]**	**EOT +14 (±2) Days and Day 28 [5]**	**ET [6]**
Informed consent [7]	X												
Inclusion/exclusion criteria	X												
Medical/surgical history	X												
Prior/concomitant medications	X [8]	X	X	X	X	X	X	X	X	X	X	X	X
Demographics [9]	X												
Complete physical examination [10]	X			X		X		X		X			X
Limited physical examination [10]			X		X		X		X		X	X	
Vital signs [11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray, MRI, CT scan, or ultrasound [12]	X										X		
Assess clinical signs/symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess clinical outcome [13,14]						X		X		X	X [13]	X [13]	X
Rapid diagnostic test [15]	X												
APACHE II, SOFA, or qSOFA score [16]	X [17]	X											
Randomization [18]		X											
Pregnancy test [19]	X									X			X
Serum chemistry [20]	X	X [25]		X		X [22]		X		X	X	X	X
Serum creatinine [21]	X	X [25]	X	X	X	X	X	X	X	X	X	X	X
Hematology [20,23]	X	X [25]		X		X		X		X	X	X	X
Urinalysis [20,24]	X	X [25]		X		X		X		X	X	X	X
12-lead ECG [26]	X	X [27]			X [27]					X			X
Blood cultures [28]	X	X [25]	X	X	X	X	X	X	X	X	X	X	X
Infection site-specific cultures [29]	X [30]					X		X		X	X	X	X
Administer study drug [31]		X	X	X	X	X	X	X	X	X			
Assessment of adverse events [32]	X	X	X	X	X	X	X	X	X	X	X	X	X
PK samples [33]		X			X								

1. All the procedures for Part B will be the same as Part A, unless otherwise specified.
2. Screening can occur up to 48 hours before the first dose of study drug. All Screening procedures must be performed prior to randomization and the first dose of study drug (Day 1). All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours before the first dose of study drug.
3. Day 7 to Day 14 study procedures are only required if the patient receives IV study drug treatment on Day 7 to Day 14. If EOT has already occurred, study procedures are not required to be performed.
4. Patients will be treated for 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin (ie, 7 days for those without dose adjustments), with a prolongation of therapy up to 14 days if clinically indicated. If EOT occurs on Day 7, Day 7 study procedures may be considered the EOT Visit study procedures. If EOT occurs after Day 7, the EOT Visit activities should be completed within 24 hours after the last dose of study drug.
5. The TOC Visit must occur 7 days (±2 days) after the EOT for all patients. The LFU Visit must occur 14 days (±2 days) after the EOT for all patients. **The LFU Visit should be performed as an in-person visit; however, if the patient is unable to attend the LFU Visit at the site, the patient may be contacted by telephone call for follow-up assessment of concomitant medications, clinical signs and symptoms, and adverse events. All patients who are alive and have not withdrawn consent for participation in the study must be contacted at Day 28 or anytime thereafter to assess survival if their LFU Visit is prior to Day 28.**
6. For patients who are withdrawn from the study prior to completion of study drug or discontinue study drug prematurely, complete an ET Visit at the time of study withdrawal or study drug discontinuation. Patients who discontinue study drug prematurely but are not withdrawn from the study should complete TOC and LFU Visits. For patients who are withdrawn from the study after the EOT Visit but prior to completion of the study, complete the next scheduled visit (either the TOC Visit or LFU Visit) at the time of study withdrawal.
7. Informed consent must be obtained before any study procedures are performed. An ICF of limited scope may be signed prior to Screening to perform only BPP rapid testing of respiratory specimens. A comprehensive ICF, which will include all study procedures, will be signed at Screening.
8. Reasonable effort will be made to determine all relevant treatments (including all antibiotics, prescription and non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and non-pharmacologic treatments) received within 14 days before the first dose of study drug and during the study.
9. Demographic data will be collected, including sex, age, race, and ethnicity.
10. The Screening complete physical examination includes weight and height. A limited, symptom-based physical examination will be performed at the indicated visits. If a patient does not display symptoms, no limited physical examination needs to be performed.
11. Vital signs include blood pressure, heart rate, and respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including FiO_2 and PEEP.
12. For patients with HABP, VABP, or VP only. A chest X-ray, MRI, CT scan, or ultrasound done within 72 hours of Screening is acceptable. For images obtained >48 hours prior to randomization, repeat imaging is required. Note: If an ultrasound is performed, a confirmatory X-ray or CT scan must be performed within 24 hours. Findings should be consistent with the screening image and diagnosis of pneumonia, in the Investigator's judgment; otherwise, the patient is no longer eligible.
13. If a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC and LFU Visits, and the assessment of clinical response by the Investigator should be listed as "failure at EOT or TOC."
14. In Part A, all clinical outcome assessments will be performed by a blinded assessor, in addition to the unblinded Investigator.
15. A respiratory specimen for BPP rapid diagnostic testing should only be collected for patients suspected to have HABP, VABP, or VP.
16. An APACHE II or SOFA score will be calculated at Screening and prior to randomization for patients in Part A only. For patients who are not being treated in an intensive care unit and cannot have an APACHE II or SOFA score performed, and for all patients in Part B, a qSOFA score should be calculated.
17. An APACHE II, SOFA, or qSOFA score that was calculated as standard of care within 24 hours of Screening may be used and does not need to be repeated at Screening.
18. Via IRT.
19. A highly sensitive urine or serum pregnancy test will be performed at Screening, EOT Visit, and ET Visit for women of childbearing potential.
20. Screening laboratories will be performed by the local laboratory within 48 hours of randomization. Subsequent laboratory samples will be collected, processed, and sent to the central laboratory for analysis.
21. While the patient is receiving study drug, serum creatinine will be collected daily and analyzed at the local laboratory to assess the need for dose adjustments. Screening serum creatinine will be collected at the local laboratory within 24 hours before the first dose of study drug.
22. The Day 5 safety chemistry panel will be performed at the local laboratory and sent to the central laboratory.
23. Hematology includes complete blood count (with red blood cell count, total white blood cell count with differential counts, platelet count, hemoglobin, and hematocrit).
24. Urinalysis includes urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH.

25. Predose.
26. The 12-lead ECGs will be performed after the end of infusion, except for at Screening, and all 12-lead ECGs will be performed after the patient has been in a supine position for at least 10 minutes. Consult the Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF ≥480 msec).
27. The 12-lead ECG will be performed for all patients at the end of the first infusion of study drug on Day 1. If clinically indicated, the 12-lead ECGs will be repeated as close as possible following the end of the infusion of study drug administration on the day on which post-dose PK samples are drawn (Day 3, Day 4, or Day 5). The day on which the post-dose PK samples are drawn is at the discretion of the Investigator.
28. Two sets of samples from 2 separate venipuncture sites are required for blood cultures in all patients. Each set of blood culture samples will be collected from a separate venipuncture site and will consist of 1 aerobic and 1 anaerobic blood culture bottle (an additional aerobic bottle is allowed if an anaerobic culture is not standard practice at the site). If Screening/baseline blood cultures are positive for ABC, repeat blood cultures should be obtained daily until negative or the patient is a treatment failure. To avoid unnecessary blood draws, the Investigator may wait until the result of the prior blood culture is known before performing the next blood culture.
29. After screening, collect samples only as clinically indicated. To assess the primary indication and follow-up of the presenting indication, all specimens will be sent to the local laboratory for culture and susceptibility testing per institutional standards. Pure cultures of isolated pathogens will be shipped from the local laboratory to the central laboratory for confirmation of species identification, susceptibility testing, and possible molecular characterization.
30. If the screening sample for culture that is growing ABC is taken per standard of care before the patient or patient's legally authorized representative signs informed consent, that isolate may be used for baseline eligibility and sent to the central laboratory once consent is obtained, as long as the sample was collected within 72 hours prior to randomization. Additional samples for baseline culture should be collected again within 24 hours prior to randomization, at the specified time points and if clinically indicated.
31. All patients will receive IV treatment for a minimum of 28 doses of ETX2514SUL plus 28 doses of imipenem/cilastatin or 14 doses of colistin plus 28 doses of imipenem/cilastatin (ie, 7 days for those without dose adjustments), as described in the protocol. For patients with normal renal function, study drug infusions will be administered q6h (±15 minutes) for ETX2514SUL and imipenem/cilastatin and q12h (±15 minutes) for colistin.
32. Adverse events should be captured as described in the protocol.
33. Intense PK samples will be collected for the first approximately 30 patients randomized in Part A, after the patient received at least 2 infusions on Day 1, at the end of the infusion after the infusion pump is turned off (+15 minutes), 1.5 hours (±15 minutes) after the end of the infusion, and immediately prior to the start of the next infusion, and on Day 4 (±1 day) at the end of the infusion after the infusion pump is turned off (+15 minutes), and immediately prior to the start of the next infusion. Sparse PK samples will be collected for all other patients enrolled in the study (Parts A and B) immediately prior to the start of the next infusion on Day 1 and Day 4 (±1 day). The patient should have received at least 2 infusions before this schedule is implemented. In addition, the intense PK sampling will also be performed on the first approximately 20 patients randomized from China Mainland sites in Part A, following the same procedure as described above.

ABC = *Acinetobacter baumannii-calcoaceticus* complex; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; BPP = Biofire® FilmArray® 2.0 Pneumonia Panel; CT = computed tomography; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; ETX2514SUL = sulbactam-ETX2514; FiO_2 = fraction of inspired oxygen; HABP = hospital-acquired bacterial pneumonia; ICF = informed consent form; IRT = interactive response technology; IV = intravenous; LFU = Late Follow-up; MRI = magnetic resonance imaging; PEEP = positive end-expiratory pressure; PK = pharmacokinetic; q6h = every 6 hours; q12h = every 12 hours; qSOFA = quick Sequential Organ Failure Assessment; QTcF = QT interval corrected using Fridericia's formula; SOFA = Sequential Organ Failure Assessment; TOC = Test of Cure; VABP = ventilator-associated bacterial pneumonia; VP = ventilated pneumonia.

APPENDIX B: CENTRAL CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea/Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

Hematology

Basophils	Eosinophils
Hematocrit	Hemoglobin
Lymphocytes	Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration	Mean corpuscular volume
Monocytes	Neutrophils
Platelet count	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Catalase	Glucose
Ketones	Leukocyte esterase
Microscopic evaluation [1]	Nitrite
pH	Protein
Specific gravity	Urobilinogen

1. Microscopic evaluation is performed only as needed based on positive dipstick test results.

A highly sensitive urine or serum (beta human chorionic gonadotropin) pregnancy test will be performed for female patients of childbearing potential only.

Screening Only

All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours before the first dose of study drug. All other samples are to be sent to the central laboratory. The Day 5 safety chemistry panel will be performed at the local laboratory and sent to the central laboratory.