Statistical Analysis Plan
(SAP)

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

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SAP APPROVAL FORM

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	*Acinetobacter baumannii*-c*alcoaceticus* complex
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Acute pyelonephritis
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic class
BMI	Body Mass Index
BPP	Biofire FilmArray Pneumonia Panel
CE	Clinical Evaluable
CFU	Colony-forming units
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CRABC	Carbapenem-resistant *Acinetobacter baumannii*-c*alcoaceticus* complex
CSR	Clinical Study Report
CT	Computed tomography
cUTI	Complicated urinary tract infection
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of Treatment
ESKD	End-stage kidney disease
ET	Early Termination
ETX2514SUL	Sulbactam-ETX2514
FiO2	Fraction of inspired oxygen
GFR	Glomerular filtration rate
HABP	Hospital-acquired bacterial pneumonia
ICF	Informed consent form
ICU	Intensive-care units
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LFT	Liver function test
LFU	Late Follow-up
LLN	Lower limit of normal

Abbreviation	Definition
ME	Microbiologic Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MITT	Modified Intent-to-Treat
m-MITT	Microbiologically Modified Intent-to-Treat
MRI	Magnetic resonance imaging
PCS	Potentially clinically significant
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
SOC	System organ class
SOFA	Sequential Organ Failure Assessment
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TOC	Test of Cure
ULN	Upper limit of normal
VABP	Ventilator-associated bacterial pneumonia
VP	Ventilated pneumonia
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol CS2514-2017-0004 (version 4.0, 17 December 2020) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. STUDY OBJECTIVES

This is a 2-part study, with Part A being the randomized, controlled portion of the study in patients with *Acinetobacter baumannii-calcoaceticus* Complex (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 treatment 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 Sulbactam-ETX2514 (ETX2514SUL) plus imipenem/cilastatin to colistin plus imipenem/cilastatin in patients with carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (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 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.

3. STUDY DESIGN

3.1. General 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. 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 at least 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 Biofire FilmArray 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.

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

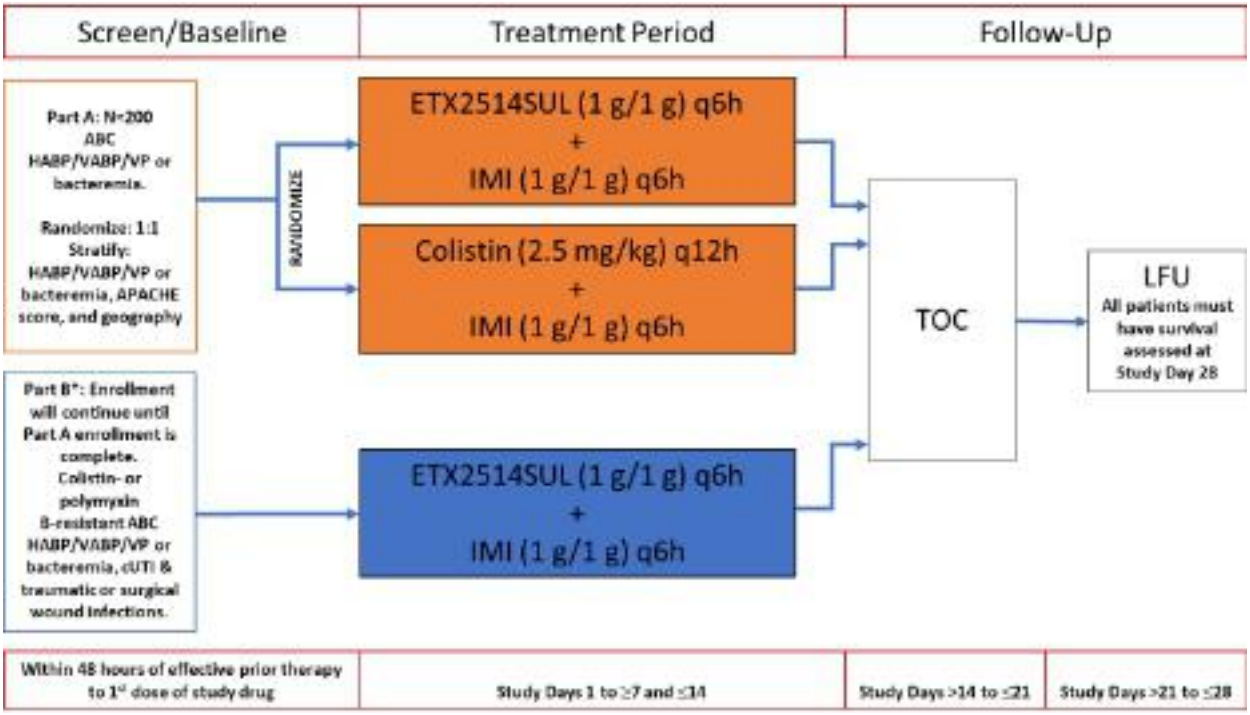
with evidence of carbapenem resistance should remain on their assigned treatment regimen; treatment regimen changes can occur after 5 days after discussion with the Medical Monitor. If changes to the regimen are needed due to unsatisfactory clinical response, patients should be classified as clinical 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.

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.

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 be assessed for 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 Population

The population for this study is male and female patients ≥18 years of age with documented ABC infections. Inclusion and exclusion criteria are listed in the protocol.

3.3. 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 Protocol 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.

The study data will be collected and handled as if it were a blinded study. The blinded assessor (see Section 3.3.2), 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 3.3.1). 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.

3.3.1. 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.

3.3.2. 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. 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 electronic case report form (eCRF).

3.4. Study Assessments

Table 1 presents the visit schedule and procedures of the study to be conducted at each visit.

Table 1. Schedule of Procedures (Parts A & B)

	Screening	Treatment									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 using the same technique 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.

4. SAMPLE SIZE JUSTIFICATION

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.

5. EFFICACY ENDPOINTS AND ASSESSMENT

5.1. 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.

5.2. 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 EOT, and LFU in the m-MITT, CRABC m-MITT, CE, ME, and CRABC ME Populations;
- Microbiological favorable assessment at 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.

5.3. Other Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Clinical cure based on MIC distribution of ETX2514SUL;
- Clinical cure based on MIC distribution of colistin;
- Clinical cure based on baseline resistance to ETX2514SUL, carbapenems, or colistin;

- Microbiologic favorable assessment based on MIC distribution of ETX2514SUL;
- Microbiologic favorable assessment based on MIC distribution of colistin;
- Microbiologic favorable assessment 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.

5.4. 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.

5.5. Efficacy Assessments

5.5.1. 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 Investigator will choose 1 of the following clinical outcomes at the Day 5, Day 7, EOT, TOC, LFU and ET Visits, 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.

5.5.2. Microbiologic Outcome

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

For patients with bacteremia, complicated urinary tract infection (cUTI), or acute pyelonephritis (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 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.

5.5.2.2. 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.

6. SAFETY ASSESSMENTS

6.1. Adverse Events

An adverse event (AE) 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 AE 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 AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0).

6.2. Laboratory Assessments

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.

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.

6.3. Vital Signs

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and, for ventilated patients, oxygen therapy and respiratory settings including fraction of inspired oxygen [FiO2] and positive end-expiratory pressure [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.

6.4. 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.

6.5. Electrocardiograms

Twelve-lead electrocardiograms (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 QT interval corrected using Fridericia's formula (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.

6.6. Physical Examinations

A complete physical examination will be performed at Screening, Day 3, Day 5, Day 7, the EOT Visit, and 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), the TOC Visit, and the LFU Visit.

A complete physical examination must include source documentation of weight, skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral 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.

6.7. Chest X-Ray/Radiology

Chest X-rays, magnetic resonance imaging (MRI), or computed tomography (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.

6.8. 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.

6.9. Safety Monitoring and Assessment of Abnormal Liver Function Tests (LFT)

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.

6.10. Data Safety Monitoring Board (DSMB)

An independent DSMB will review the safety data periodically. The DSMB will also review serious adverse events (SAE) 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.

7. PHARMACOKINETIC ASSESSMENTS

Intense and sparse PK samples will be collected as outlined in Table 1. The PK samples obtained from the ETX2514SUL group will be analyzed for ETX2514 and sulbactam concentrations using a validated assay by an approved bioanalytical laboratory.

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.

7.1. Intense Pharmacokinetic Sampling

As described in Section 9.2.3 of the protocol, approximately 30 patients randomized in Part A had 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.

The intense PK sampling will also be performed on the first approximately 20 patients randomized in Part A from China Mainland sites.

7.2. Sparse Pharmacokinetic Sampling

All other patients enrolled in the study (Parts A and B) will have samples collected for sparse PK analysis.

8. ANALYSIS POPULATIONS

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

8.1. Intent-to-Treat Population (ITT)

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.

8.2. Modified Intent-to-Treat Population (MITT)

The 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.

8.3. Microbiologically Modified Intent-to-Treat Population (m-MITT)

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, MALDITOF, 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.

8.4. Carbapenem-resistant ABC m-MITT Population (CRABC m-MITT)

For Part A, 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, 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 treatment, as well as for all patients with and without evidence of non-susceptibility to colistin and ETX2514SUL at baseline.

For Part B, 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 their blood culture or respiratory samples are collected more than 72 hours prior to randomization.

8.5. Clinical Evaluable Population (CE)

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).

8.6. Microbiologic Evaluable Population (ME)

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.

8.7. Carbapenem-resistant ABC Microbiologic Evaluable Population (CRABC ME)

The CRABC ME Population will include patients who meet both ME criteria and CRABC m-MITT criteria.

8.8. Pharmacokinetic (PK) Population

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

9. STATISTICAL ANALYSIS

9.1. General Statistical Considerations

9.1.1. General Analysis Approach

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 separately and will be used to supplement results in Part A. Listings of individual patient data will be produced.

Data from central microbiology laboratory will be used for microbiological analysis. If the data from central microbiology laboratory is not available, the data from local microbiology laboratory will be used.

9.1.2. Handling of Withdrawals and Missing Data

For the clinical outcome, patients with missing data or who are lost to follow-up will be considered as an indeterminate outcome and are included in the denominator for the calculation of clinical cure rate. Thus, patients with an indeterminate outcome are considered as failures for the analysis. A clinical failure occurring at an earlier time point will be carried forward to the subsequent visits.

In cases of missing or incomplete dates (e.g. AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data analyses and summaries.

9.1.3. Baseline Definition

For microbiological data, baseline pathogen(s) are determined from the specimens collected prior to the first dose of study drug.

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first dose of study drug.

For safety endpoints, patients who were randomized into Part A then transferred into Part B will be included in both Part A and Part B, baseline is defined as the last measurement or assessment prior to the first dose of study drug of Part A for both Part A and Part B safety analysis.

For efficacy endpoints, patients who were randomized into Part A then transferred into Part B will be included in Part B only, baseline is defined as the last measurement or assessment prior to the first dose of study drug of Part A for Part B efficacy analysis.

9.2. Study Subjects

9.2.1. Subject Disposition

The number of patients randomized, treated, completed, and discontinued early from the study and the reasons for discontinuation will be summarized descriptively by treatment group for Part A and Part B in the ITT Population.

The following subject disposition categories will be included in the summary:

- Patients who were randomized,
- Patients who were randomized and treated,
- Patients who were randomized and not treated,
- Patients who completed the study treatment,
- Patients who did not complete the study treatment,
- Patients who did not complete the study treatment related to Coronavirus Disease 2019 (COVID-19);
- Patients who completed the study,
- Patients who did not complete the study, and
- Patients who did not complete the study related to COVID-19

For patients who did not complete the treatment, and patients who did not complete the study, a summary will be provided by reason of discontinuation. In addition, the number of patients in each analysis population and the reason(s) for exclusion from an analysis population (m-MITT, CRABC m-MITT, CE, ME, and CRABC ME) will be summarized by treatment group and a corresponding listing will be provided showing each patient's inclusion/exclusion from each population and reason(s) for exclusion.

9.2.2. Protocol Deviations

The number of patients with at least one reportable protocol deviation, and the number of patients with at least one reportable deviation in each category will be presented by treatment group for Part A and Part B in the ITT Population. In addition, the protocol deviations related to COVID-19 will be categorized and summarized separately.

9.2.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics including age (as a continuous variable and categorized as <65, 65-75 and >75 years), sex, race, ethnicity, weight, body mass index (BMI) (as a continuous variable and categorized as <25, 25-<30, 30-<35 and ≥35), creatinine clearance (as a continuous variable and categorized as <15 mL/min, 15-<30 mL/min, 30-<60 mL/min, 60-<90 mL/min and ≥90 mL/min), Charlson Comorbidity Index <3 or ≥3, septic shock status at baseline, mechanical ventilation status at baseline, infection type (bacteremia, HABP, VABP, VP, cUTI, AP, surgical wound infection, and post-traumatic wound infection), APACHE II score [<10, 10 to 19, 20 to 30 and >30], SOFA score [<7, 7 to 9 and ≥10], qSOFA score [<2, 2, 3 and >3], severity of illness (APACHE II [10-19]/SOFA [7-9]/qSOFA [2] and APACHE II [20-30]/SOFA [≥10]/qSOFA [3]) will be summarized by treatment group and baseline infection type (Overall, Bacteremia, HABP, VABP, VP, cUTI, AP, Surgical Wound Infection, and Post-traumatic Wound Infection) in the ITT, m-MITT, and CRABC m-MITT Populations. The demographics and baseline characteristics will be summarized for all regions and repeated for Mainland Chinese patients.

9.2.4. Baseline Pathogens

The pathogenic organisms identified from the baseline culture will be summarized by genus and species and regions (Overall, North America, Europe, Latin America, Asia-Pacific, and China) and by treatment group for the m-MITT, CRABC m-MITT, ME, and CRABC ME Populations. The number and percentage of patients with a monomicrobial ABC, polymicrobial ABC + other Gram-negative, or polymicrobial ABC + Gram-positive (with or without Gram-negative) infections will also be provided.

For the patients with cUTI or AP, the pathogen(s) cultured from urine at $\geq 10^5$ CFU/mL or the same pathogen present in concurrent blood and urine cultures regardless of CFU values will be considered the baseline pathogen(s). If ≥3 bacterial isolates are identified from urine, the culture will be considered contaminated regardless of colony count unless 1 of the isolates that grows in the urine is also isolated from a blood culture.

For each treatment group, the MIC summary data (MIC_{50}, MIC_{90}, and MIC_{range} and number of unique pathogens tested) for baseline pathogens will be summarized by region (Overall, North America, Europe, Latin America, Asia-Pacific, and China) and by treatment group in the m-MITT, CRABC m-MITT, ME, and CRABC ME Populations. The MIC_{50} and MIC_{90} will only be calculated for pathogens isolated from at least 10 patients within either treatment group.

The summary of susceptibility (susceptible and resistant) to ETX2514SUL and colistin for ABC baseline pathogen by region (Overall, North America, Europe, Latin America, Asia-Pacific, and China) will also be provided. For ABC baseline pathogens, ETX2514SUL susceptible is defined as MIC ≤4 mg/L and ETX2514SUL resistant is defined as MIC >4 mg/L. For ABC baseline pathogens, colistin susceptible is defined as MIC <4 mg/L and colistin resistant is defined as MIC ≥4 mg/L.

9.2.5. Medical and Surgical History

Medical and surgical history terms will be coded using MedDRA (Version 21.0). Medical and

surgical history will be summarized by treatment group and MedDRA system organ class (SOC) and preferred term in the Safety Population.

All Medical and surgical history will be listed by patient.

9.2.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Global B2 September 2018). Prior medications will include medications used before the first dose of study drug. Any medications used on or after the first dose of study drug will be included as concomitant medications.

The number and percentage of patients taking prior antibiotics within 14 days prior to the first dose of study drug and other prior medications within 14 days prior to the first dose of study drug will be summarized in the m-MITT, and CRABC m-MITT Populations by Anatomical Therapeutic Chemical (ATC) class and preferred term for each treatment group. In addition, the number and percentage of patients taking prior antibiotics within 72 hours prior to the first dose of study drug will be summarized in the m-MITT, and CRABC m-MITT Populations for each treatment group. The number and percentage of patients taking prior antibiotics within 24 hours prior to the first dose of study drug will also be summarized in the m-MITT, and CRABC m-MITT Populations for each treatment group.

The number and percentage of patients taking concomitant medications will be summarized in the same manner.

All prior and concomitant medications and procedures will be listed by patient.

9.2.7. Dosing and Treatment Exposure

Descriptive statistics for the duration of treatment will be summarized by treatment group for Part A and Part B for the Safety, m-MITT, and CRABC m-MITT Populations. Duration of treatment will be calculated as the last dose date - the first dose date + 1 day. Contingency table will be provided to show the number and percentage of patients in each treatment group with duration of treatment in the following categories: 1-3 days, 4-7 days, 8-10 days, and > 10 days. The total number of doses of study drug received will also be summarized by treatment group using descriptive statistics.

The compliance rate of study drug will be calculated as the total number of doses received divided by the total number of doses expected then multiplied by 100. The total number of expected doses is the number of medication days multiplied by the number of expected doses per day. Number of medication days is the total number of days from the date of the first dose of study drug to the date of the last dose of study drug.

Percent compliance to study drug will be calculated using the following formula:

$$\%\text{compliance} = \frac{\text{no. of doses received*100}}{\text{total no. of doses expected}}$$

Percent compliance will be summarized by treatment group for the Safety, m-MITT, and CRABC m-MITT Populations. In addition, contingency tables will be provided to show the number and percentage of patients in each treatment group with compliance in the following categories: <80% and ≥80%.

9.3. Efficacy Analyses

The efficacy analyses will be analyzed for Part A and Part B separately. Patients who were randomized into Part A and stayed in Part A will be summarized/analyzed only for Part A. Patients who were randomized into Part A but then transferred into Part B will be summarized/analyzed only for Part B.

9.3.1. Primary Efficacy Analyses

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 mortality, provided consent has not been withdrawn. Patients who withdraw consent from the survival status will be excluded from the analysis. Patients who have missing survival status will be treated as death. Patients who were randomized into Part A but then transferred into Part B will not be included in Part A analysis.

The non-inferiority assessment will be based on the 2-sided 95% confidence intervals (CIs) computed using a continuity-corrected Z-statistic 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, the superiority will be investigated. Superiority will be concluded if the upper limit of the 2-sided 95% CI is less than 0.

Sensitivity Analyses

Sensitivity analyses of the primary efficacy endpoint will be conducted as follows:

- Analysis of the primary efficacy endpoint will be performed for patients whose eligible culture is >48 hours prior to the first dose of treatment in the CRABC m-MITT Population.
- Analysis of the primary efficacy endpoint will be performed for patients whose eligible culture is ≤48 hours prior to the first dose of treatment in the CRABC m-MITT Population.
- Analysis of the primary efficacy endpoint will be performed for patients with ABC pathogens susceptible to ETX2514SUL and colistin at baseline in the CRABC m-MITT Population.
- Analysis of the primary efficacy endpoint will be performed for patients without ABC susceptibility results for ETX2514SUL or colistin at baseline in the CRABC m-MITT Population.
- Analysis of the primary efficacy endpoint will be performed including the patients who were randomized into Part A but then transferred into Part B in the ITT Population.
- Analysis of the primary efficacy endpoint will be performed excluding the patients who have missing survival status in the CRABC m-MITT Population.

Analysis of the primary efficacy endpoint and the sensitivity analysis will be repeated including the patients who withdraw consent from the survival status.

9.3.2. Secondary Efficacy Analyses

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

- 28-day all-cause mortality in the 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 EOT, and LFU in the m-MITT, CRABC m-MITT, CE, ME, and CRABC ME Populations;
- Microbiological favorable assessment at EOT, TOC, and LFU by overall, monomicrobic infection and polymicrobic infection in the m-MITT, CRABC m-MITT, ME, and CRABC ME Populations. Monomicrobic infection is defined as subjects with only ABC pathogens isolated at Baseline, Polymicrobic infection is defined as subjects with both ABC pathogens and non-ABC pathogens isolated at Baseline;
- 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations; and
- 28-day all-cause mortality in the m-MITT and CRABC ME Populations.

All secondary efficacy analyses will be analyzed including the patients who withdraw consent from the survival status.

In addition, the primary analysis will be repeated for 28-day all-cause mortality in the ITT, m-MITT and CRABC ME Populations excluding the patients who withdraw consent from the survival status for Part A. 14-day all-cause mortality in the CRABC m-MITT and m-MITT Populations will be performed in a same manner excluding the patients who withdraw consent prior to Day 14 for Part A.

Similarly, the analysis of clinical response and the microbiologic response will be repeated excluding patients who withdraw consent from the survival status in the CRABC m-MITT Population for Part A.

The number and percentage of patients in each response category for the secondary efficacy endpoints will be summarized by treatment group. Two-sided 95% CIs computed using a continuity-corrected Z-statistic for the difference in outcome rates between the treatment groups in Part A will be provided. Patients who initially randomized to Part A and transferred to Part B will not be included in Part A analysis and will be included in Part B analysis from the time point of transfer. Patients with a missing secondary efficacy value, the efficacy variable will be considered as non-responder. In addition, time to death will be analyzed using log rank test between the treatment groups for Part A.

In Part A, if there is a discrepancy between the assessment of the blinded assessor and unblinded Investigator for clinical outcome, 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.

Part B data will be summarized separately from Part A using descriptive statistics. Patients who transfer from Part A to Part B, Part B data will be summarized from the time point of transfer.

9.3.3. Exploratory Efficacy Analyses

The following exploratory efficacy endpoints will be summarized by treatment group for the CRABC m-MITT Population for Part A and Part B:

- Clinical cure based on baseline ABC pathogen MIC distribution of ETX2514SUL by overall, monomicrobic infection and polymicrobic infection;
- Clinical cure based on baseline ABC pathogen MIC distribution of colistin by overall, monomicrobic infection and polymicrobic infection;
- Microbiological favorable assessment (including microbiologic eradication and microbiologic presumed eradication) based on baseline ABC pathogen MIC distribution of ETX2514SUL by overall, monomicrobic infection and polymicrobic infection;
- Microbiological favorable assessment (including microbiologic eradication and microbiologic presumed eradication) based on baseline ABC pathogen MIC distribution of colistin by overall, monomicrobic infection and polymicrobic infection;
- Number of days in the intensive care unit (ICU);
- Number of patients transferred to the ICU;
- Number of days on ventilators for patients with VABP, VP, or ventilated HABP, number of days on ventilators;
- Number of days in the hospital;
- Number of days on study drug treatment.

The following exploratory efficacy endpoints will be summarized by treatment group for the m-MITT Population for Part A:

- Clinical cure based on baseline ABC pathogen resistance to ETX2514SUL, carbapenems, or colistin by overall, monomicrobic infection and polymicrobic infection;
- Microbiological favorable assessment (including microbiologic eradication and microbiologic presumed eradication) based on baseline ABC pathogen resistance to ETX2514SUL, carbapenems, or colistin by overall, monomicrobic infection and polymicrobic infection.

Monomicrobic infection is defined as subjects with ABC pathogens only isolated at Baseline. Polymicrobic infection is defined as subjects with both ABC pathogens and non-ABC pathogens isolated at Baseline.

Exploratory endpoints for health resource utilization difference between treatment groups will be reported separately.

9.3.4. Subgroup Analyses

The following subgroups based on baseline characteristics will be used for subgroup analyses for the primary efficacy endpoint excluding patients who withdraw consent from the survival status:

- Age group (<65, 65-75 and >75 years)

- Gender (Male and Female)
- BMI (<25, 25-<30, 30-<35, and ≥35 kg/m2)
- Charlson comorbidity index (<3 and ≥3)
- Diagnosis type (Bacteremia, HABP, VABP, and VP)
- Severity of illness (APACHE II [10-19]/SOFA [7-9]/qSOFA [2] and APACHE II [20-30]/SOFA [≥10]/qSOFA [3])
- Creatinine clearance group (<30 mL/min, 30-<60 mL/min, 60-<90 mL/min, and ≥90 mL/min)
- Duration of ICU stay (no ICU stay, <5, 5-14, >14 days)
- HABP/VABP/VP who are identified as positive for ABC by BPP molecular methodology
- Monomicrobial ABC infection vs polymicrobial infection
- Bacteremia patients with negative blood cultures for ABC at randomization or first dose date with a positive blood culture for ABC previously at baseline vs. Rest of bacteremia patients
- Received prior antibiotics within 24 hours prior to the first dose of study drug vs. Not Received
- Received prior antibiotics vs. Not Received
- Septic Shock status at baseline (Yes vs. No)
- Mechanical Ventilation status at baseline (Yes vs. No)
- By region (North America, Europe, Latin America, Asia-Pacific, China; North America/Europe vs. Latin America/Asia-Pacific/China; China vs. rest of the world)
- By COVID-19 status (Positive vs. Negative)

A forest plot will be presented for subgroup analyses.

9.4. Safety Analyses

All safety summaries and analyses will be performed on the Safety Population. All patients will be summarized based on the actual treatment received. Safety endpoints include the assessment of adverse events and the evaluation of changes from baseline in safety laboratory test results, ECGs, vital signs, and physical examinations.

For each safety endpoint, unless otherwise stated, the last assessment made prior to the first administration of study drug will be used as the baseline value for all analyses.

The safety analyses will be analyzed for Part A and Part B separately. For the patients who were randomized into Part A but then transferred into Part B, safety will be summarized/analyzed until the date of transfer for Part A; safety reported on or after the date of transfer will be summarized/analyzed for Part B. Baseline is the last measurement or assessment prior to the first dose of study drug of Part A for both Part A and Part B safety analysis.

9.4.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event occurring on or after the administration of the first dose of study drug. An overview of adverse events will be provided which summarizes the incidence of the following categories:

- All AEs,
- All TEAEs,
- Drug-related TEAEs,
- TEAEs by severity,
- SAEs,
- Drug-related SAEs,
- SAE leading to death,
- TEAE leading to discontinuation of study drug, and
- SAE leading to discontinuation of study drug.

Patients with multiple events will be counted only once within each category. Severity grade and relationship will be counted using the maximum severity and the strongest relationship respectively for a patient with multiple TEAEs.

The number and percentage of patients reporting a TEAE in each treatment group will be tabulated by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship (related or unrelated to study drug and imipenem/cilastatin). Summary tables will be presented alphabetically by SOC and decreasing frequency of PT in the EXT2514SUL group within SOC. For all analyses of TEAEs, if the same AE (based on PT) is reported for the same patient more than once, the AE is counted only once for that PT and at the highest severity and strongest relationship to study drug.

The number and percentage of patients reporting a drug-related TEAE, a SAE, a treatment emergent SAE, a drug-related treatment-emergent serious adverse event (TESAE), and a TEAE leading to discontinuation of study drug in each treatment group will be summarized by SOC and PT.

A list of patients who have SAEs, a list of patients who discontinue from study drug, and a list of death will be provided. All adverse events will be listed.

<u>Adverse Events of Special Interest</u>

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 2)1, 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).
- Clostridiodes difficile infection

Table 2. 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.

The number and percentage of patients reporting adverse events of special interest will be summarized by each category and treatment group in Part A in the Safety and CE Populations. In addition, proportion of patients with nephrotoxicity will be compared between the investigational and control groups using Chi-square test. The Chronic hemodialysis patients will not be included in the nephrotoxicity analysis.

9.4.2. Clinical Laboratory Evaluations

Laboratory test results (hematology, serum chemistry, and urinalysis) at each scheduled visit and change from baseline will be summarized by treatment group for Part A and Part B for Mainland Chinese patients or other patients separately.

Shift tables from baseline to each scheduled post-baseline visit will be provided for selected chemistry parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, creatinine, creatine kinase, alkaline phosphatase [ALP], potassium) and hematology parameters (hematocrit, hemoglobin, platelets, white blood cell count and differential). For chemistry parameters, the following categories will be used: < the lower limit of normal (LLN), normal, > the upper limit of normal (ULN) to ≤3×ULN, >3×ULN to ≤5×ULN, >5×ULN, and missing. For hematology parameters, the following categories will be used: low, normal, high, and missing.

The number and percentage (based on the number of patients with a normal level at baseline) of patients in each treatment group with an ALT (>3×ULN, >5×ULN, and >10×ULN), an AST (>3×ULN, >5×ULN, and >10×ULN), an ALT or AST >3×ULN, and a total bilirubin (>1.5×ULN and >2×ULN) will be presented by study visit. A listing of patients who meet the laboratory criteria for Hy's law will also be provided. The laboratory criteria for Hy's law is defined as concurrent ALT or AST>3×ULN, ALP ≤2.0×ULN, and total bilirubin >2×ULN. A listing will also be provided for the potentially clinically significant (PCS) values for the above parameters.

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

9.4.3. Vital Signs

Descriptive statistics will be provided for vital sign data (systolic and diastolic blood pressure, heart rate, and respiratory rate) presented as both actual values and changes from baseline over time by treatment group for Part A and Part B.

A listing of all vital signs will be provided by patient.

9.4.4. Electrocardiograms (ECG)

Descriptive statistics will be provided for 12-lead ECG findings (heart rate, QRS, PR, RR, QT, and QTcF) and changes from baseline for each scheduled visit for Part A and Part B. QTcF will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

The number and percentage of patients with notable ECG changes in maximum QTcF (>450 msec, >480 msec, and >500 msec) over all post-baseline evaluations, as well as in QTcF maximum changes from baseline (>30 msec and >60 msec) over all post-baseline evaluations will be summarized by treatment group.

All ECG measurements and the overall interpretation will be listed by patient.

9.4.5. Physical Examination

Physical examination findings will be listed by patient.

9.5. Pharmacokinetic Analyses

The pharmacokinetic analyses will be performed by another vendor and reported separately.

10. REFERENCES

1. Hartzell JD, Neff R, Ake J, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin Infect Dis*. 2009;48(12):1724-1728.