AN OPEN-LABEL, RANDOMIZED, MULTI-CENTER, ACTIVE-CONTROLLED STUDY TO ESTIMATE THE EFFICACY AND SAFETY OF CEFTAZIDIME-AVIBACTAM (CAZ-AVI) VERSUS BEST AVAILABLE TREATMENT (BAT) IN THE TREATMENT OF INFECTIONS DUE TO CARBAPENEM-RESISTANT GRAM-NEGATIVE PATHOGENS IN CHINESE ADULTS

Study Intervention Number:	PF-06947386
Study Intervention Name:	Ceftazidime-Avibactam
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Short Title: The Efficacy and Safety of Ceftazidime-Avibactam (CAZ-AVI) Versus Best Available Treatment (BAT) in the Treatment of Infections due to Carbapenem-resistant Gram-negative Pathogens in Chinese Adults

Protocol Amendment Summary of Changes Table

Document History			
Document	**Version Date**	**Summary and Rationale for Changes**	**Substantial or Nonsubstantial**
Amendment 1	02 June 2022	• Based on real clinical practice and the definition of best available treatment, added investigator's standard of care in line with local guidelines as the dose and frequency selection criteria of BAT administration on the basis of the LPD in section 4.1, section 4.2 and section 6.1.1.2. • During the COVID-19 pandemic, for reducing risk to participants, the following changes have been incorporated in section 1.3 and section 6.1:	Substantial
		1. If participants are unable to visit study sites due to COVID-19 pandemic or local policies, the investigators must continue to collect AEs and perform safety reporting responsibilities per protocol via telephone contact or other methods as appropriate (Section 1.3 note "v").	Non-substantial
		2. Protocol-specified safety laboratory tests may be performed at a local hospital if the study participant is unable to visit the study site, where allowable by law or local guidance. Local laboratory reference ranges need to be documented (Section 1.3 note "i").	Non-substantial
		3. If the sponsor cannot provide study drugs centrally due to COVID-19 pandemic, and the investigator assesses that the participant should receive study drugs continuously,	Substantial

Document History			
Document	**Version Date**	**Summary and Rationale for Changes**	**Substantial or Nonsubstantial**
		the study drugs can be provided with local sourcing (Section 6.1).	
		• Updated CAZ-AVI information to align with new version of LPD in section 5.3.2.	Non-substantial
		• Typographical errors were corrected in section 1.3 and section 5.1.1 per PACL dated 22 Jul 2021 and 22 Dec 2021.	Non-substantial
		• Based on the guideline and local clinical practice, white blood cell count is an objective criterion for infectious disease diagnosis and efficacy assessment. Added "white blood cell count in hematology or urine test" as objective symptoms or signs in section 5.1 inclusion criterion 3 per PACL dated 22 Jul 2021.	Non-substantial
		• It is understood that the additional unstained sputum smears cannot be obtained for specimens from the screening visit which have been completed based on the standard of care at site. Clarification added that the additional unstained gram stain slide is not required in screening visit in section 10.8 per PACL dated 22 Jul 2021.	Non-substantial
		• Changed the end of reviewing concomitant therapy from "TOC" to "LFU" in section 6.5 to keep consistency with section 1.3 per PACL dated 22 Dec 2021.	Non-substantial

Document History			
Document	**Version Date**	**Summary and Rationale for Changes**	**Substantial or Nonsubstantial**
		• Modified the format of Table 11 in section 10.2 to keep the format consistent and ensure clarity per PACL dated 22 Dec 2021.	Non-substantial
Original protocol	02 Dec 2020	N/A	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: The Efficacy and Safety of Ceftazidime-Avibactam (CAZ-AVI) Versus Best Available Treatment (BAT) in the Treatment of Infections due to Carbapenem-resistant Gram-negative Pathogens in Chinese Adults

Rationale

In China, the prevalence of carbapenem-resistant (CR) pathogens has been showing an increasing trend in many national surveillance studies and observational studies. Infections due to CR pathogens are associated with high risk of death.

CAZ-AVI was approved by the National Medical Products Administration (NMPA) on 21 May 2019 for the indications of complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), and infection due to aerobic Gram-negative organisms with limited treatment options (LTO) in adults.

This study is designed to address the request from the Centre of Drug Evaluation (CDE) regarding further evaluation of effectiveness and safety of CAZ-AVI in Chinese patients with infections due to carbapenem resistant Gram-negative pathogens, which can represent the population with limited treatment options.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To estimate the efficacy of CAZ-AVI and best available treatment (BAT) in patients with infections due to Carbapenem-resistant Gram-negative pathogens.	• Estimand E1: The trial will estimate the treatment effect of CAZ-AVI relative to BAT in terms of the difference in clinical response of cure in patients with infections due to carbapenem-resistant Gram-negative pathogens. A composite estimand strategy will be used to account for intercurrent events that are part of the definition of clinical response. Intercurrent events of death after receiving <48 hours of study treatment, or inadequate infection source control at time of initial surgical procedure (for cIAI participants) will be regarded as indeterminate clinical response. Intercurrent events of death after receiving at least 48 hours of study treatment, or receiving treatment with further antibiotics for the index infection will be regarded as a failure clinical response.	• Clinical response (defined by cure, failure, or indeterminate) at TOC visit
Secondary:	**Secondary:**	**Secondary:**
• To estimate the efficacy of CAZ-AVI and BAT in patients with infections due to CR	• Estimand E1 will be the esimand for this objective.	• Clinical response (defined by cure, failure, or indeterminate) at TOC visit

Objectives	Estimands	Endpoints
gram-negative pathogens and who are microbiologically evaluable.		
• To estimate the clinical response to CAZ-AVI and BAT at the end of treatment.	• Estimand E1 will be the esimand for this objective.	• Clinical response (defined by cure, failure, or indeterminate) at EOT visit
• To estimate the microbiological response to CAZ-AVI and BAT.	• Estimand E2: The trail will estimate the treatment effect of CAZ-AVI relative to BAT in terms of the difference of favorable microbiological response in patients with infections due to carbapenem-resistant Gram-negative pathogens. A composite estimand strategy will be used to account for intercurrent events that are part of the definition of microbiological response. Intercurrent events of death after receiving <48 hours of study treatment, or inadequate infection source control at time of initial surgical procedure (for cIAI participants) will be regarded as indeterminate microbiological response. Intercurrent events that result in repeat culture of specimen not performed/clinically indicated (specific to cIAI and HAP/VAP participants) will be regarded as a presumed eradication if a clinical cure is assessed, and a presumed persistence microbiological response if a clinical failure is assessed.	• Microbiological response (defined by favorable, unfavorable, or indeterminate) at EOT and TOC visits
• To estimate the all-cause mortality for CAZ-AVI and BAT.	• Estimand E3: Using a treatment-policy estimand strategy in patients with infections due to carbapenem-resistant Gram-negative pathogens to estimate the treatment effect of CAZ-AVI relative to BAT in terms of the difference of all-cause mortality at Day 28 of the study. Any death that occurred after first dose of study drug through Day 28 will be included. A participant with the last known survival status is before Day 28 or missing will be reported as an unknown status.	• All-cause mortality at Day 28
• To evaluate the safety and tolerability of CAZ-AVI.	• N/A	• Assessment of TEAEs, discontinuation due to AEs, safety-related clinical laboratory tests.

Overall Design

This is an open-label, randomized, multi-center, interventional, active-controlled Phase 4 study to evaluate the efficacy and safety of CAZ-AVI versus BAT in the treatment of infected participants with selected infection types (Hospital Acquired Pneumonia [HAP] (including Ventilator-Associated Pneumonia [VAP]); Complicated Urinary-Tract Infection [cUTI]; Complicated Intra-Abdominal Infection [cIAI]; and Bloodstream Infection [(BSI]) due to carbapenem-resistant Gram-negative pathogens in China. Carbapenem-resistant is defined as resistant to carbapenems (imipenem, meropenem), including resistant and intermediate.

The study will consist of a Screening visit, a Baseline visit on Day 1 of the study treatment, ongoing treatment visits (Days 2-14), an End of Treatment visit within 24 hours after the last infusion, a Test of Cure (TOC) visit (7-10 days after EOT visit), and a Late Follow-Up (LFU) visit (28-32 days after the last dose of study intervention).

The study is open-label due to the complicated dosing regimens and choice of appropriate best available treatment. The investigators, site personnel, and participants will not be blinded in this open-label study. An independent adjudication committee will be blinded with the aim of unbiased adjudication of the primary objective measure.

Number of Participants

The study will randomize approximately 60 participants in a 1:1 ratio into 2 treatment groups (CAZ-AVI or BAT). Randomization will be stratified by the infection sites: HAP (including VAP); cUTI; cIAI; BSI (including primary BSI, catheter related BSI [CR BSI], and BSI related to HAP [including VAP], cUTI, and cIAI). Among the 4 strata, the first 3 infection sites will not include participants with BSI complications.

Intervention Groups and Duration

Treatment arms in the study:

- Study intervention: CAZ-AVI, participants randomized to the CAZ-AVI treatment arm will receive CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered IV as a 2-hour infusion every 8 hours (q8h). Dose adjustments are available for participants with CrCL ≤50 mL/min.

- Best Available Treatment (BAT), based on investigative site practice and local epidemiology and guideline (main treatment expected to be used as either monotherapy or in combination are colistin, tigecycline, fosfomycin, amikacin, and meropenem).

The duration of treatment is 5 days up to 14 days for cUTI, cIAI and BSI, and 7 days up to 14 days for HAP/VAP, which can be extended to 21 days depending on the participant's condition and investigator's judgement as clinical practice required.

Independent Adjudication Committee:

This is an open-label study. An independent adjudication committee consisting of at least 3 clinical experts will be convened at regular intervals during the study.

A charter will be in place for the adjudication committee. The adjudication committee will be blinded to study treatment and investigator's assessment of clinical response. The committee will review the clinical data points, reports and results of the diagnostic tests used to classify the clinical response. In case of a discrepancy with the investigator's assignment of clinical response, the adjudication committee's assessment will prevail for the analysis.

Internal Review Committee

An Internal Review Committee (IRC) will be established with an IRC charter for this study and will independently review the data in an unblinded fashion approximately every 6 months to ensure that the safety of participants is not compromised.

The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter and may propose changes to the protocol as needed to ensure participant safety. The IRC will also review results of any interim analysis as planned in the study.

Statistical Methods

This study will be an estimation study. The statistical inference will be based on point estimate and confidence interval.

Efficacy analyses:

In general, for continuous variables, N, mean, standard deviation, median, minimum, and maximum will be provided, and for categorical variables, numbers and percentages of participants from each category will be provided. In particular, the point estimate and 95% confidence interval will be calculated for each individual treatment group, as well as the difference between treatment groups in clinical cure rate and per-participant favorable microbiological response (if data permit). Individual treatment group confidence interval will be computed using Jeffrey's method. Confidence interval for difference between treatment group will be computed using Miettinen & Nurminen method stratified by infection site. If number of participants in a particular stratum is small, then the unstratified Miettinen & Nurminen method will be used. Subgroup analyses will be performed for infection type if data permit.

Safety analyses:

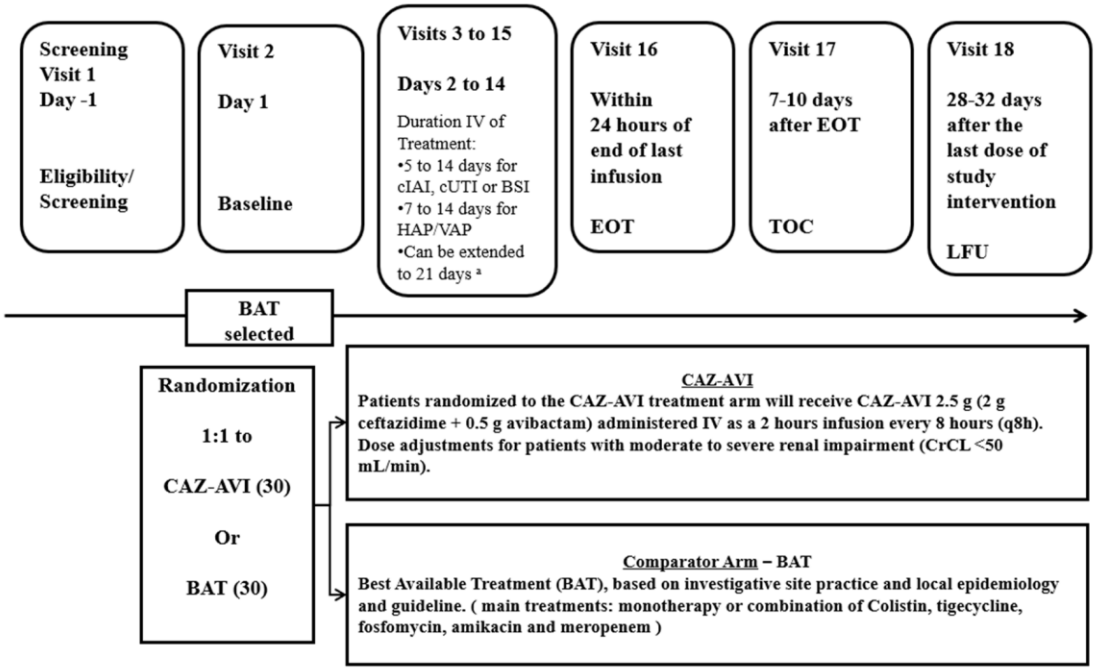
Safety data will be presented in tabular and/or graphical format and summarized descriptively. All treatment-emergent AEs, relationship with treatment, discontinuations due to AEs, and laboratory data abnormalities will be summarized using percentages. Change

from baseline for selected laboratory tests and vital signs will be summarized with descriptive statistics.

A Statistical Analysis Plan (SAP) will be developed that defines all analysis populations, and methods to summarize the efficacy and safety data.

1.2. Schema

Figure 1. Study Outline



a. Treatment duration can be extended to 21 days depending on the patient's condition an investigator's judgement as clinical practice required

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Activity Abbreviations used in this table may be found in Appendix 9	**Prescreening**	**Eligibility/ Screening**[a]	**Treatment duration**		**EOT**	**TOC**	**LFU**
Visit Window/ Study Day	**Within 5 days prior to Screening**	**Screening Visit 1 Day -1**	**Visit 2 Day 1 (Baseline)**[b]	**Visits 3-15 Days 2-14**[c]	**Visit 16 within 24 hours of end of last infusion**	**Visit 17 Day 21 to Day 24**	**Visit 18 28-32 days after the last dose of study intervention**
Study Procedure							
Abbreviated informed consent to CAZ-AVI sensitivity test of isolates[d]	X						
Informed consent		X					
Inclusion and exclusion criteria		X	X				
Demographics		X					
Medical history		X					
APACHE II score (see Appendix 6)[e]		X					
Review prior and concomitant medications (including prior antibiotic treatment)		X	X	Daily	X	X	X
Randomization			X				
Medical Procedures							
Complete physical examination		X			X	X	
Weight and height		X					

Activity Abbreviations used in this table may be found in Appendix 9	**Prescreening**	**Eligibility/ Screening**[a]	**Treatment duration**		**EOT**	**TOC**	**LFU**
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Perform focused physical examination		X	X	Daily	X	X	X[f]
Vital sign measurements[g]		X	X	Daily	X	X	
Ventilator status (HAP/VAP only)		X	X	Daily	X	X	
Urinary device status (cUTI participants only)		X	X	Daily	X	X	
Chest X ray or computed tomography scan (for HAP/VAP participants only)		X[h]	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Collection of imaging and surgical report (for cIAI participants only)		X	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Laboratory assessments[i]							
Hematology		X	X	Day 2. Then every 3 days	X	X	
Blood chemistry		X	X	Day 2. Then every 3 days[j]	X	X	
Coagulation		X	X	Day 2. Then every 3 days	X	X	
Pregnancy test[k]		X	X			X	
Estimate CrCL[l]		X	X	Day 2. Then every 3 days[j]	As clinically indicated		
Contraception check		X	X		X	X	X
Urine sample for microscopic WBC (cUTI participants only)[m]		X	X	As clinically indicated	X	X	
Collection of arterial blood gases		X[n]	As clinically indicated	As clinically indicated	As clinically indicated		

Activity Abbreviations used in this table may be found in Appendix 9	**Prescreening**	**Eligibility/ Screening**[a]	**Treatment duration**		**EOT**	**TOC**	**LFU**
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Identify isolate from study qualifying culture[o] and send to central laboratory[p]		X					
Quantitative urine culture (cUTI participants only)[q]			X	As clinically indicated	X	X	
Blood cultures			X[r]	If blood cultures are positive, repeat at least every 3 days until negative or EOT. Blood cultures should also be performed as clinically indicated.			
Culture of abdominal site infection (for cIAI participants only)[s]			As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Appropriate respiratory specimen for Gram stain/culture (for HAP/VAP participants only)			X[t]	As clinically indicated	X[u]	X	
Study intervention							
Determination and documentation of Best Available Treatment prior to randomization			X				
Study intervention administration			X	Daily			
Control treatment administration			X	Daily			
Clinical assessment							
Assess infection related signs and symptoms		X	X	Daily	X	X	
Clinical Response					X	X	
Safety assessment[v]							

Activity Abbreviations used in this table may be found in Appendix 9	**Prescreening**	**Eligibility/ Screening[a]**	**Treatment duration**		**EOT**	**TOC**	**LFU**
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Mortality[w]			X	→	→	→	X
Serious and nonserious adverse event monitoring		X	→	→	→	→	→
Concomitant treatment(s)[x]		X	X	→	→	→	X

a. Study treatment should be started as soon as possible (within 24 hours) after a participant's eligibility has been confirmed and the participant has been randomized. Consequently, Day -1 and Day 1 may be the same calendar day, ie, all procedures scheduled for Day -1 and Day 1 could happen on the same day.
b. All procedures at Visit 2 are to be done before first dose of study intervention. Repeat safety lab samples (including local lab for eligibility criteria confirmation) and CrCL assessment are only required if Visit 1 and Visit 2 are separated by surgery OR are >24 hours apart. Administration of the first dose of IV study treatment marks the beginning of study treatment Day 1 (Visit 2).
c. Treatment duration can be extended to 21 days depending on the participant's condition and investigator's judgement as clinical practice required. The investigator should continue to perform the assessments for visit 3-visit 15.
d. The abbreviated informed consent to sensitivity test of CR pathogen is only needed if the test is not the standard of care at the sites.
e. Calculate APACHE using most recent local laboratory results available within the previous 24 hours prior to Screening. Arterial blood gases are required for ventilated and recommended for non-ventilated HAP/VAP participants, and for cIAI, cUTI and BSI participants as clinically indicated. If an arterial blood gas is not clinically indicated, the APACHE score will be calculated using serum bicarbonate instead of arterial pH and assuming normal oxygenation (Variable score = 0).
f. If the participant has been discharged from hospital and is unable to return, the physical examination will not be conducted at the LFU visit since the visit will be conducted by telephone.
g. Vital signs should be measured and documented at least once daily, preferably at a similar time each day. However, if any significant excursions occur during the study day, those measurements should also be captured. The participant's body temperature will be evaluated at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature collection will be recorded. Fever will be defined as a body temperature ≥38°C. For each individual participant, the method of temperature measurement ideally should be consistent for the duration of the study. At the TOC visit only a single body temperature measurement is required. The actual time of body temperature collection will be recorded. For participants with HAP/VAP, respiratory rate (breath per minute) and peripheral O_2 saturation will be collected at Visit 2, at Visit 3, daily while the participant is receiving IV study treatment, at EOT and TOC visits.
h. Chest X-ray or CT scan, only if test has not already been performed with available results within 48 hours prior to randomization.
i. At Screening, the laboratory assessments will be performed in the local laboratory for eligibility determination as defined in Section 5. During treatment period, if ALT or AST are >3 × ULN and the participant has not met the liver discontinuation criteria (see Appendix 5), the frequency of liver laboratory

Activity Abbreviations used in this table may be found in Appendix 9	Prescreening	Eligibility/ Screening[a]	Treatment duration		EOT	TOC	LFU
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testing collection, and INR, should be increased to daily monitoring (using local laboratory data and recorded as unscheduled visits) until the liver function tests recover to ≤3 × ULN. Refer to Appendix 2 for details on collection of the required laboratory variables. Protocol-specified safety laboratory tests may be performed at a local hospital if the study participant is unable to visit the study site due to COVID-19 pandemic, where allowable by law or local guidance. Local laboratory reference ranges need to be documented.

j. In CAZ-AVI arm, for participants with changing renal function, monitor CrCL at least daily and adjust the dosage of CAZ-AVI accordingly. In BAT arm, when colistin is administered, the CrCL should be measured daily and dose adjusted appropriately. The blood chemistry test should be performed also as clinically indicated.

k. Serum or urine β-hCG for pregnancy test in female participants of childbearing potential will performed in local laboratory for eligibility determination. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study.

l. Participants must be frequently and closely monitored for rapidly changing CrCL through local laboratory measurement of serum creatinine (See Appendix 7). In case that renal function recovers or deteriorates during the treatment period, the dose of study treatment should be adjusted by the investigator to meet the appropriate dose regimen, based on the latest CrCL value and in line with Section 6.1.1.1.

m. Obtain a urine sample for microscopic WBC count to assess for presence of persisting pyuria (cUTI participants only).

n. For HAP/VAP participants – obtaining arterial blood sample for ABG (required for ventilated participants, recommended for non-ventilated participants); for cIAI, cUTI and BSI participants obtaining arterial blood sample for ABG as clinically indicated.

o. The appropriate culture for study qualifying microbiological isolate obtained within 5 days prior to screening will be detailed in the study microbiology manual (see Appendix 8). For cIAI, adequate abdominal specimen (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) must be obtained for culture at the initial qualifying procedure. For HAP/VAP, appropriate respiratory specimen including endotracheal aspirate, expectorated or induced sputum bronchoalveolar lavage (BAL), mini-BAL or protected-specimen brush (PSB) sampling should be collected for culture. For cUTI participants, a quantitative culture of urine is required. For BSI, 2 sets of blood cultures (1 anaerobic and 1 aerobic bottle in each set) should be collected.

p. Study qualifying microbiological isolate is a CR Gram-negative bacteria and culture-confirmed susceptibility to CAZ-AVI (see Inclusion Criteria in Section 5.1) that was isolated from an appropriate specimen obtained within 5 days prior to screening. And the isolate must be sent to the central microbiology laboratory vendor for confirmation.

q. A culture from urine must be obtained at Baseline and prior to the first dose of study therapy and/or change of the antibacterial therapy for participants with cUTI only.

r. All participants must have had 2 sets of blood cultures obtained prior to randomization. Repeat samples for blood cultures are not required at baseline if available within 48 hours prior to randomization. Blood should be taken prior to the first dose of study treatment if not available within 48 hours prior to randomization. When obtaining samples for blood culture, blood should be collected from 2 sites (see Appendix 8). All participants require 2 sets of blood

Activity Abbreviations used in this table may be found in Appendix 9	Prescreening	Eligibility/ Screening[a]	Treatment duration		EOT	TOC	LFU
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cultures (1 anaerobic and 1 aerobic bottle from each site, ie, 4 bottles in total). For participants who are found to be bacteremic any time during the study, repeat blood cultures should be taken at least every 3 days, until clearance of bacteremia is documented or EOT visit. Blood cultures should also be obtained as clinically indicated. See Appendix 8 for details of sample collection.

s. For cIAI participants with surgical specimens collected on or after the Baseline visit, both aerobic and anaerobic cultures should be performed on specimens collected from the site of abdominal infection and on specimens collected from other clinically relevant intra-abdominal sites (see Appendix 8).
t. Repeat respiratory specimen cultures are not required, unless a study-qualifying sample prior to screening was obtained from a non-ventilated participant and the participant is subsequently ventilated (or the participant had a bronchoscopy). In this case, an appropriate respiratory specimen should be obtained prior to the first dose of study treatment (see Appendix 8).
u. If treatment is discontinued early because the participant is failing therapy or other reasons, an appropriate respiratory specimen for Gram stain/culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered.
v. If participants are unable to visit study sites due to COVID-19 pandemic or local policies, the investigators must continue to collect AEs and perform safety reporting responsibilities per protocol via telephone contact or other methods as appropriate.
w. Investigator should also follow the participants who have died due to any reason up to Day 28 after randomization.
x. Collection of concomitant treatments will include blood and other blood product transfusions.

2. INTRODUCTION

Ceftazidime is the bactericidal β-lactam component of CAZ-AVI. It is a third-generation cephalosporin that is approved for the treatment of several bacterial infections. Its efficacy and tolerability profile is well characterized through many years of experience of use in clinical practice in numerous countries worldwide. Avibactam is a first-in-class non-β-lactam β-lactamase inhibitor of serine β-lactamases with a spectrum of inhibition that includes class A extended-spectrum beta-lactamases (ESBLs) and carbapenemases (eg, *Klebsiella pneumoniae* carbapenemase [KPC]), class C β lactamases, and some class D oxacillinases and carbapenemases. However, it is not active against class B metallo-β-lactamases, and it is not active against *Acinetobacter baumannii*.[1] The addition of avibactam to ceftazidime extends the β-lactam's antibacterial activity against pathogens producing β-lactamases that are susceptible to inhibition by avibactam, while retaining ceftazidime's bactericidal activity.[2] Avibactam therefore has the potential to restore the utility of ceftazidime in the clinical setting.

CAZ-AVI has been developed as an IV administered compound for treatment of patients with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime (CAZ-resistant).

2.1. Study Rationale

Carbapenems are the drugs of choice for serious infections caused by ESBL-producing organisms. Carbapenems are the only reliable β-lactam drugs for the treatment of severe *Enterobacter* spp. infections. Resistance to carbapenems is rare but occurs in strains that produce serine-carbapenemases (KPC enzymes) and Metallo-β-lactamases (MBLs). Over the past decade, a group of serine carbapenemases termed "KPC" has been increasingly reported from around the world.[3]

Data from China multicenter bacterial resistance networks (ie, China surveillance network for bacterial resistance [CHINET], 2004-2015[4] and Chinese antimicrobial resistance surveillance of nosocomial infection [CARES], 2016[5]) showed that the isolation rate for various organisms among various specimens (blood, urine, sputum, etc.) was:

1. Carbapenem-resistant *A baumannii* (CRAB) up to 60%-70%

2. Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) was 20% ~ 40%

3. ESBL-producing *K pneumoniae* was 25% ~ 35%

4. ESBL-producing *Escherichia coli* was 45% ~ 60%

5. CRE among various specimens (blood, urine, sputum) was 5% ~ 18%

In 2016, CHINET reported the resistance rates of *P aeruginosa* to imipenem and meropenem were 28. 7% and 25. 3%, respectively.[6]

The INFORM Global Surveillance Project tested 4411 isolates of nosocomial infections from a total of 10 medical centers in China from 2014-2016. The resistance rates of *K pneumoniae* to imipenem and meropenem were 12.2% and 12.1%, respectively and the resistance rates of *P aeruginosa* to imipenem and meropenem were 38.3% and 25.8%, respectively.

Currently the options for the treatment of Gram-negative infections, especially multidrug resistant strains including ESBL- and carbapenemase- producers, are extremely limited.

CAZ-AVI was approved by the National Medical Products Administration (NMPA) on 21 May 2019. Indications for adults approved include complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

This study is designed to address the request from the Centre of Drug Evaluation (CDE) to further evaluate the effectiveness and safety of CAZ-AVI in Chinese adult patients with infections caused by carbapenem resistant Gram-negative pathogens.

2.2. Background

2.2.1. Clinical Urgent clinical needs /Treatment status

In the light of rising resistance to carbapenems, clinicians are increasingly forced to turn to drugs that had previously fallen out of favor due to associated toxicity or lack of supportive data to guide dosing.[7] Thus, therapy options are limited for patients with infections caused by β-lactam resistant pathogens, particularly those that are resistant to carbapenems, and there are significant limitations to the few existing alternatives to carbapenems.

According to the surveillance results of China Antimicrobial Surveillance Network (CHINET), the resistance rate of *K pneumoniae* to imipenem and meropenem has increased at an alarming rate from 3.0% and 2.9% in 2005 to 20.9% and 24.0% in 2017, respectively.[8,9] Studies have found that the risk of death in patients infected with carbapenem antibiotic-resistant isolates is more than doubled compared with patients infected with non-carbapenem-resistant isolates (RR: 2.05, 95% CI: 1.56-2.69).[10] In China, the report from CRE network have shown that the mortality rate of bloodstream infections caused by carbapenem-resistant Enterobacteriales (CRE) is 43.1% (22/51), the highest among all types of CRE infection (33.5%, 222/662), followed by lower respiratory tract infection, the mortality rate is 34.8% (148/425), the mortality of urinary tract infection and intra-abdominal infection are 30.3% and 26%, respectively.[11]

There is no single treatment option for all patients with infections caused by a carbapenem-resistant (CR) pathogen, as there are limited efficacy data available for many of these therapies in the treatment of CR pathogen infections. Therapies for use in the multidrug resistant (MDR) setting (which could include CRE) include colistin, tigecycline, and fosfomycin.[12] In the case of colistin (or polymyxin B), a lack of proof of efficacy from prospective trials, coupled with the potential for nephrotoxicity are significant issues, as are increasing resistance and uncertainty over the optimum dosing regimen in critically ill

patients.[13] For tigecycline, low blood levels and failures in cases of bacteremia and HAP, poor penetration into the urinary tract for cUTIs, and a connection with increased rates of mortality are major concerns.

Infections due to CRE are associated with high risk of death; therefore effective and safe drugs are urgently needed for treatment. Since CAZ-AVI was approved in the United States and EU, multiple studies have been published by independent authors, providing real world evidence supporting the efficacy of ceftazidime-avibactam for the treatment of a wide variety of infections caused by resistant pathogens and for which other treatment options are limited or unavailable, including bacteremia, urinary tract infections, HAP including VAP and other infections caused by carbapenem resistant and multi-drug resistant Enterobacteriales and Pseudomonas spp.

2.2.2. Clinical Overview

The global adult CAZ-AVI clinical development program has been completed. Briefly, the program comprises a package of 17 completed Phase 1 clinical pharmacology studies, 2 completed Phase 2 studies (1 in complicated urinary tract infection [cUTI] and 1 in cIAI), and the following 5 Phase 3 clinical studies:

- A randomized, double-blind Phase 3 study in participants with nosocomial pneumonia (NP) including VAP: REPROVE
- Two randomized, double-blind Phase 3 studies in participants with cIAI: RECLAIM 3 and RECLAIM
- A randomized, double-blind Phase 3 study in participants with cUTI: RECAPTURE
- A randomized, open-label Phase 3 study in participants with cIAI or cUTI infections caused by CAZ-resistant pathogens: REPRISE

Across the CAZ-AVI Phase 3 studies in participants with cIAI, cUTI and HAP, CAZ-AVI (±metronidazole [MTZ]) at the proposed dose was effective in s with both CAZ-susceptible and CAZ-resistant pathogens. The observed safety profile supports the use of CAZ-AVI in the approved indications in Chinese adults.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of CAZ-AVI may be found in the China local product document (LPD), which is the SRSD for this study. The SRSD for the comparator agent is the LPD for the selected BAT.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) CAZ-AVI		
Potential risks associated with CAZ-AVI include the following: • Encephalopathy and neurological symptoms such as tremor, coma and seizures in patients with renal impairment who do not have their dose appropriately reduced • Hepatotoxicity Development of resistance • Superinfection (bacterial or fungal)	The potential risks are based on product prescribing information for CAZ-AVI and risk management plan. This potential risk has been reported with ceftazidime when the dose has not been reduced in patients with renal impairment. There were 6 CAZ-AVI ± MTZ participants with superinfection identified in microbiological samples across the programme to date, but none of the cases found could be considered to represent clinical cases of superinfection.	The dose should be reduced according to the degree of renal impairment (see Section 6.1). In participants with renal impairment, close monitoring of estimated creatinine clearance is advised. Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). For participants with hepatic impairment, investigator will closely monitor hepatic function. The duration of treatment has been selected based on the approved LPD. Investigator will closely follow the signs and symptoms during the study. If superinfection is identified, treating the underlying cause is the best way to prevent bacterial overgrowth.
Study Procedures (Not applicable)		
Other (Not applicable)		

2.3.2. Benefit Assessment

Participants enrolled into this clinical study will have cIAIs requiring surgical intervention (including open laparotomy, percutaneous drainage of an abscess and laparoscopic surgery) HAP including VAP, cUTI, or BSI that are of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to participants in this study is that they will receive effective antibiotic treatment for their infection. And in this study, they will receive close medical monitoring including physical examinations and laboratory tests and intensive disease management. The potential benefit of the study, in general, is to further characterize the efficacy and safety of a novel antibiotic in the treatment of Chinese adult patients with CR Gram-negative bacteria infection in the face of the changing pattern of antibiotic resistance.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with CAZ-AVI are justified by the anticipated benefits that may be afforded to participants with life threatening serious infections caused by CR Gram-negative whom only limited alternative treatment options are available.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

The trial will compare CAZ-AVI with BAT in patients infected with carbapenem-resistant Gram-negative pathogens. The primary trial objective is to estimate the range of the treatment effect of CAZ-AVI compared to BAT via the proportion of participants with clinical response defined as a composite endpoint that includes the intercurrent events of death and need for additional antibiotic rescue.

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To estimate the efficacy of CAZ-AVI and best available treatment (BAT) in patients with infections due to Carbapenem-resistant Gram-negative pathogens.	• Estimand E1: The trial will estimate the treatment effect of CAZ-AVI relative to BAT in terms of the difference in clinical response of cure in patients with infections due to carbapenem-resistant Gram-negative pathogens. A composite estimand strategy will be used to account for intercurrent events that are part of the definition of clinical response. Intercurrent events of death after receiving <48 hours of study treatment, or inadequate infection source control at time of initial surgical procedure (for cIAI participants) will be regarded as indeterminate clinical response. Intercurrent events of death after receiving at least 48 hours of study treatment, or receiving treatment with further antibiotics for the index infection will be regarded as a failure clinical response.	• Clinical response (defined by cure, failure, or indeterminate) at TOC visit

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
• To estimate the efficacy of CAZ-AVI and BAT in patients with infections due to CR gram-negative pathogens and who are microbiologically evaluable.	• Estimand E1 will be the esimand for this objective.	• Clinical response (defined by cure, failure, or indeterminate) at TOC visit
• To estimate the clinical response to CAZ-AVI and BAT at the end of treatment.	• Estimand E1 will be the esimand for this objective.	• Clinical response (defined by cure, failure, or indeterminate) at EOT visit
• To estimate the microbiological response to CAZ-AVI and BAT.	• Estimand E2: The trail will estimate the treatment effect of CAZ-AVI relative to BAT in terms of the difference of favorable microbiological response in patients with infections due to carbapenem-resistant Gram-negative pathogens. A composite estimand strategy will be used to account for intercurrent events that are part of the definition of microbiological response. Intercurrent events of death after receiving <48 hours of study treatment, or inadequate infection source control at time of initial surgical procedure (for cIAI participants) will be regarded as indeterminate microbiological response. Intercurrent events that result in repeat culture of specimen not performed/clinically indicated (specific to cIAI and HAP/VAP participants) will be regarded as a presumed eradication if a clinical cure is assessed, and a presumed persistence microbiological response if a clinical failure is assessed.	• Microbiological response (defined by favorable, unfavorable, or indeterminate) at EOT and TOC visits
• To estimate the all-cause mortality for CAZ-AVI and BAT.	• Estimand E3: Using a treatment-policy estimand strategy in patients with infections due to carbapenem-resistant Gram-negative pathogens to estimate the treatment effect of CAZ-AVI relative to BAT in terms of the difference of all-cause mortality at Day 28 of the study. Any death that occurred after first dose of study drug through Day 28 will be included. A participant with the last known survival status is before Day 28 or missing will be reported as an unknown status.	• All-cause mortality at Day 28
• To evaluate the safety and tolerability of CAZ-AVI.	• N/A	• Assessment of TEAEs, discontinuation due to AEs, safety-related clinical laboratory tests.

This protocol will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a IRC will conduct unblinded reviews on a regular basis throughout the trial (see Section 9.6).

Any AE that is adjudicated by the endpoint adjudication committee NOT to meet endpoint criteria will be reported back to the investigator site of incidence. Refer to Section 8.3.7 for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, randomized, multi-center, interventional, active-controlled Phase 4 study to evaluate the efficacy and safety of CAZ-AVI versus BAT in the treatment of infected participants with selected infection types (Hospital Acquired Pneumonia [HAP] (including Ventilator-Associated Pneumonia [VAP]); Complicated Urinary-Tract Infection [cUTI]; Complicated Intra-Abdominal Infection [cIAI]; Bloodstream Infection [BSI]) due to carbapenem-resistant Gram-negative pathogens in China. Carbapenem-resistant is defined as resistant to carbapenems (imipenem or meropenem), including resistant and intermediate.

Approximately 60 participants with confirmed carbapenem-resistant Gram-negative pathogens infection (with CAZ-AVI and BAT susceptibility) will be randomized in a 1:1 ratio to the 2 groups in the study, with approximately 30 participants in CAZ-AVI group and approximately 30 participants in BAT group. Randomization will be stratified by the infection sites: HAP (including VAP); cUTI; cIAI; BSI (including primary BSI, catheter related BSI [CR BSI], and BSI related to HAP [including VAP], cUTI, and cIAI). Among the 4 strata, the first 3 infection sites will not include participants with BSI complications.

Treatment arms in the study:

- Study intervention: CAZ-AVI, participants randomized to the CAZ-AVI treatment arm will receive CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered IV as a 2-hour infusion every 8 hours (q8h). Dose adjustments for participants with CrCL ≤50 mL/min will be applied based on the LPD (Section 6.1).

- Best Available Treatment (BAT), based on investigative site practice and local epidemiology and guideline (main treatments: monotherapy or combination of colistin, tigecycline, fosfomycin, amikacin and meropenem). Details for dose and frequency of administration of BAT will be based on China LPD or standard of care according to local guideline.

Duration of treatment:

The study will consist of a Screening visit, a Baseline visit on Day 1 of the study treatment, ongoing treatment visits (Days 2-14), an End of Treatment visit within 24 hours after the last infusion, a Test of Cure (TOC) visit (7-10 days after EOT visit), and a Late Follow-Up (LFU) visit (28-32 days after the last dose of study intervention). The duration of treatment is 5 days up to 14 days for cUTI, cIAI and BSI, and 7 days up to 14 days for HAP/VAP, which can be extended to 21 days depending on the participant's condition and investigator's judgement as clinical practice required (Figure 1).

The study is open-label due to the complicated dosing regimens and choice of appropriate best available treatment. The investigators, site personnel, and participants will not be blinded in this open-label study. An independent adjudication committee will be blinded with the aim of unbiased adjudication of the primary objective measure.

4.2. Scientific Rationale for Study Design

Ceftazidime is the bactericidal β-lactam component of CAZ-AVI. It is a third generation cephalosporin that is approved for the treatment of several bacterial infections. Its efficacy and tolerability profile is well characterized through many years of experience of use in clinical practice in numerous countries worldwide. Avibactam is a first-in-class non-β-lactam β-lactamase inhibitor of serine β-lactamases with a spectrum of inhibition that includes class A extended-spectrum beta-lactamases (ESBLs) and carbapenemases (eg, KPC), class C β-lactamases, and some class D oxacillinases and carbapenemases. It is not active against class B metallo-β-lactamases, and it is not active against *A baumannii*. The addition of avibactam to ceftazidime extends the β-lactam's antibacterial activity against pathogens possessing β-lactamases that are susceptible to inhibition by avibactam, while retaining ceftazidime's bactericidal activity. Avibactam therefore has the potential to restore the utility of ceftazidime in the clinical setting.[2]

CAZ-AVI was approved by the National Medical Products Administration (NMPA) on 21 May 21 2019 for the indications of cIAI, HAP including VAP, LTO in adults. The basis of the Limited Treatment Options (LTO) indication is pharmacokinetic/pharmacodynamic (PK/PD) extrapolation and the ceftazidime existing approvals. Ceftazidime is approved for the treatment of infections in a broad range of body sites beyond the standard indications (cIAI, cUTI, HAP). The established efficacy of ceftazidime in these additional indications (eg, complicated skin and skin structure infections [cSSTIs]) indicates that ceftazidime achieves adequate tissue penetration and exposure across body sites. The key physico-chemical properties and PK characteristics (eg, protein binding, distribution, excretion) of ceftazidime and avibactam are similar and therefore both compounds will partition across body sites in a similar fashion. Since the mechanism of action of antibiotics, including CAZ-AVI, is based on direct action on the bacteria causing an infection rather than action on the human body. It supports CAZ-AVI to be used in the treatment of other infection site.

Since CAZ-AVI approved in the United States and EU, multiple studies have been published by independent authors, providing real world evidence supporting the efficacy of ceftazidime-avibactam for the treatment of a wide variety of infections caused by resistant pathogens and for which other treatment options are limited or unavailable, including

bacteremia, urinary tract infections, HAP including VAP and other infections caused by carbapenem resistant and multi-drug resistant Enterobacteriales and Pseudomonas spp.

This study is designed to address the request from the Centre of Drug Evaluation (CDE) to further evaluate the effectiveness and safety of CAZ-AVI in Chinese patients with carbapenem resistant Gram-negative pathogens infections.

There is no single treatment option for all patients with infections caused by a carbapenem-resistant (CR) pathogen, as there are limited efficacy data available for many of these therapies in the treatment of CR pathogen infections. Therapies for use in the multi-drug resistant (MDR) setting (which could include CRE) include colistin, tigecycline, and fosfomycin.[7] Therefore, the BAT is selected and will be administered per current treatment guidelines, investigative site practice and local epidemiology, and may include colistin, tigecycline, fosfomycin, amikacin and meropenem, as monotherapy or in combination. Details for dose and frequency of administration of BAT will be based on China LPD or standard of care according to local guideline.

Human reproductive safety data are limited for CAZ-AVI, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. However, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

The CAZ-AVI dose for treatment of patients with cIAI, cUTI and HAP has been confirmed by clinical efficacy demonstrated in the controlled, Phase 3 studies of participants with cIAI (RECLAIM, RECLAIM3 and REPRISE), cUTI (RECAPTURE and REPRISE), and NP, including VAP (REPROVE). These studies confirm that avibactam plasma exposures achieved with the studied dose are adequate to protect ceftazidime and result in efficacy against CAZ-resistant pathogens that is comparable to efficacy against CAZ-susceptible pathogens.

The PK samples collected from participants participating in the Phase 3 studies were used to calculate individual plasma profiles, from which exposure and PK/PD target attainment were calculated. Joint target attainment was achieved in >98% of participants across the Phase 3 studies in cIAI, cUTI and HAP; and the joint target attainment rate was 98.9% in the 262 Chinese and Taiwanese participants for whom PK samples were available from the Phase 3 studies (Table 1).

Table 1. Comparison of ceftazidime and avibactam exposure and target attainment in Phase 3 participants stratified across different races

Covariate Category: Race	n	CAZ $C_{ss,max}$ (µg/mL)	CAZ $AUC_{ss,0-24}$ (µg.h/mL)	AVI $C_{ss,max}$ (µg/mL)	AVI $AUC_{ss,0-24}$ (µg.h/mL)	Target attainment (%)
Chinese & Taiwanese	262[a]	77.6 (112.5)	884 (120.5)	14.7 (154.9)	151 (155.1)	98.9 (97.6, 100.0)
Caucasian/ Other	1209	68.6 (112.9)	848 (125.0)	12 (159.4)	135 (161.3)	98.3 (97.6, 99.1)
Asian non-Chinese/ non-Japanese	248	82.2 (118.4)	968 (121.9)	14.9 (166.5)	166 (170.8)	99.6 (98.8, 100.0)
Japanese	45	90.4 (82.6)	1021 (94.8)	16.1 (134.3)	164 (130.9)	100.0 (N/A)

a. Comprising 250 participants from mainland China and 12 participants from Taiwan.

Note: Geometric mean (%CV) are reported for $C_{ss,max}$ and $AUC_{ss,0-24}$. Target attainment rates are reported as the observed percent (95% CI) of participants who achieved the joint target of 50% fT>CAZ-AVI MIC of 8 mg/L for ceftazidime and 50% fT >1.0 mg/L for avibactam.

The population PK models for ceftazidime and avibactam (CAZ-MS-09) including Phase 3 data were used to conduct Monte Carlo simulations in order to calculate the probability of target attainment (PTA) to confirm that the dose selected for the treatment of participants with cIAI, cUTI, and NP achieved sufficient exposure to exceed the joint PK/PD target in >90% of the population (joint PK/PD target of 50% fT>CAZ AVI MIC of 8 mg/L for ceftazidime and 50% fT>CT of 1 mg/L for avibactam). The simulation settings took into account the demographic distribution for each indication from Phase 3 studies conducted. Ceftazidime and avibactam concentration time courses were simulated from 5000 theoretical participants (all races) with cIAI, cUTI, and NP (including VAP and non-VAP). From these simulated profiles, the exposure in terms of $AUC_{ss,0-24}$ and $C_{ss,max}$ were calculated and found to be comparable across each indication and in line with the exposure data that are available from each of these participant types.

The overall PTA analysis for each indication demonstrated that the proposed dosing regimen used for CAZ-AVI in Phase 3 (2000 mg ceftazidime + 500 mg avibactam given as a 120 minute IV infusion, q8h, in patients with normal renal function) is predicted to achieve sufficient exposure to exceed the joint PK/PD target (MIC of 8 mg/L) in ≥94.9% of the simulated patient population (across indications). The approved dose level in the China LPD was based on the data from competed pivotal studies and the PK study in Chinese.

For participants with changing renal function, doses of CAZ-AVI will be modified as needed in accordance with the approved LPD.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last follow-up visit. The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female >18 years of age, inclusive, at Visit 1 (Screen 1).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participant must have a diagnosis of an infection (HAP/VAP, cUTI, cIAI, BSI) due to confirmed carbapenem-resistant aerobic Gram-negative pathogens, requiring administration of IV antibacterial therapy (See additional inclusion criteria for each indication).

    Culture-confirmed susceptibility to CAZ-AVI and each components of the chosen BAT (except carbapenems) based on evidence from culture or other phenotypic or molecular testing within 5 days prior to screening for any cultured Gram-negative pathogen according to the local microbiology laboratory testing (the central laboratory testing will be as a confirmatory data).

    Note: If a participant is found to have a Gram-negative species not expected to respond to CAZ-AVI and/or BAT (eg, *A baumanii, Stenotrophomonas species*) in addition to the causative Gram-negative CR pathogen, the participant may be enrolled in the study if the investigator considers that this species is a colonizer and does not warrant specific treatment.

3. Participant who had received appropriate prior empiric antibacterial therapy for a carbapenem-resistant pathogen must meet at least 1 of the following criteria:

    a) No or no more than 24 hours of appropriate antibacterial therapy was administered for the current infection. OR

b) Worsening of objective symptoms or signs of infection (includes white blood cell count in hematology or urine test) after at least 48 hours of appropriate antibacterial therapy. OR
c) No change of objective symptoms or signs of infection (includes white blood cell count in hematology or urine test) after at least 72 hours of appropriate antibacterial therapy.

(Note: Therapy will be considered appropriate if microbiological susceptibility test results show that all carbapenem-resistant pathogens are susceptible to at least 1 of the antibacterial[s] received)

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.1.1. Additional Inclusion Criteria

Table 2. Additional Inclusion Criteria

	Inclusion Criteria
cUTI	1. Expectation, in the judgment of the Investigator, that any indwelling urinary catheter, nephrostomy tube, indwelling ureteric stent will be removed or replaced (if removal is not clinically acceptable) before or as soon as possible, but not longer than 12 hours, after randomization. 2. Participant had pyuria in the 5 days prior to study entry as determined by a midstream clean catch or catheterized urine specimen with ≥10 white blood cells (WBCs) per high-power field on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine. 3. At least two of the following signs or symptoms: Chills or rigors or warmth associated with fever (eg, oral temperature ≥38 degrees Celsius) Flank pain (pyelonephritis) or pelvic pain (cUTI) Nausea or vomiting Dysuria, urinary frequency, or urinary urgency Costo-vertebral angle tenderness on physical examination 4. Complicating factors: participant must have at least 1 of the following complicating factors: • Documented history of urinary retention (male participants);

Table 2. Additional Inclusion Criteria

	Inclusion Criteria
	• Functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a postvoid residual urine volume of at least 100 mL; • Use of intermittent bladder catheterization or presence of an indwelling bladder catheter for at least 48 hours prior to obtainment of study-qualifying culture; • Urogenital procedure (such as cystoscopy or urogenital surgery) within the 7 days before study entry prior to obtainment of study qualifying-culture
HAP/ VAP	1. Onset of symptoms >48 hours after admission or <7 days after discharge from an inpatient care facility (for which the duration of admission was >3 days). 2. New or worsening infiltrate on chest X-ray (or computed tomography [CT] scan) obtained within 48 hours prior to randomization. 3. At least 1 of the following: • Documented fever (temperature ≥38°C) or hypothermia (rectal/core temperature ≤35°C); • WBC ≥10,000 cells/mm^3, leukopenia with total WBC ≤4500 cells/mm^3, or >15% immature neutrophils (bands) noted on peripheral blood smear. At least 2 of the following: • A new cough (or worsening of cough at Baseline); • Production of purulent sputum or purulent endotracheal secretions; • Auscultatory finding consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds, dullness on percussion, egophony); • Dyspnea, tachypnea (eg, respiratory rate greater than 25 breaths per minute, or hypoxemia (O_2 saturation <90% or partial pressure of O_2 [pO_2]<60 mmHg while breathing room air); • Need for acute changes in the ventilator support status/system to enhance oxygenation, as determined by worsening oxygenation (arterial blood gas [ABG] or pO_2 in arterial blood [PaO_2]/fraction of inspired O_2 [FiO_2]) or needed changes in the amount of positive end-expiratory pressure. 4. For known carbapenem-resistant Gram-negative pathogens infections, the respiratory specimen includes a culture either of expectorated sputum or a specimen of respiratory secretions obtained by endotracheal aspiration in intubated participants, or by bronchoscopy with bronchoalveolar lavage (BAL), mini-BAL or protected-specimen brush (PSB) sampling (BAL, mini-BAL or PSB only for

Table 2. Additional Inclusion Criteria

	Inclusion Criteria
	participants undergoing bronchoscopy as part of their clinical management during the time).
BSI	1. Participant has a confirmed diagnosis of primary BSI or catheter related BSI (CR BSI) or the indication of BSI related to HAP (including VAP), cUTI, cIAI. 2. At least 1 positive blood culture within 5 days prior to study entry indicating presence of carbapenem-resistant Gram-negative pathogens. Participants with polymicrobial including CR Gram-negative pathogens blood infections may be included in the study. 3. Signs and symptoms of systemic infection are characterized by at least one of the following: • Chills, rigors, fever (temperature of ≥38.0°C or ≥100.4°F) or hypothermia(temperature <35°C [<95°F]); • Elevated white blood cell count (≥10,000/mm^3) or left shift (>15% immature polymorphonuclear leukocytes [PMNs]). • Hypotension, systolic <90 mmHg
cIAI	1. Participant must have a study-qualifying specimen obtained from an abdominal source during a surgical intervention within the 5 days prior to study entry. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. 2. The participant has at least 1 of the following diagnosed during the surgical intervention: • Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall • Diverticular disease with perforation or abscess • Appendiceal perforation or periappendiceal abscess • Acute gastric or duodenal perforations, only if operated on >24 hours after diagnosis • Traumatic perforation of the intestines, only if operated on >12 hours after diagnosis • Other secondary peritonitis (not primary/ spontaneous bacterial peritonitis associated with cirrhosis or chronic ascites) • Intra-abdominal abscess (including of liver or spleen provided that there was extension beyond the organ with evidence of intraperitoneal involvement)

Table 2. Additional Inclusion Criteria

	Inclusion Criteria
	3. One or more systemic signs or symptoms that accompany cIAI, such as fever, hypotension, abdominal pain, nausea/vomiting, abdominal mass on clinical examination, altered mental status.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Any allergy to cephalosporins regardless of seriousness of that reaction. Severe hypersensitivity to any other betalactams (eg, penicillins, monobactams or carbapenems).

3. Participant is expected to require more than 21 days of treatment per the investigator's judgment.

4. Participants who need more than 3 systemic antibiotics as part of best available treatment (BAT) for the treatment of the Gram-negative infection.

5. Participant has a concurrent bacterial infection such as endocarditis, osteomyelitis, central nervous system (CNS) infection, prosthetic joint infection, *C difficile* diarrhea OR non-bacterial infection such as active tuberculosis, or pulmonary disease such as cystic fibrosis.

6. Participants receiving hemofiltration or peritoneal dialysis.

7. Participant is pregnant or breastfeeding.

Prior/Concomitant Therapy:

8. Co-administration of CAZ-AVI with probenecid or chloramphenicol, and co-administration of any systemic antibiotic other than per protocol is not allowed.

Prior/Concurrent Clinical Study Experience:

9. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

10. Participant has an Acute Physiology and Chronic Health Evaluation (APACHE) II score >30.

Other Exclusions:

11. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.2.1. Additional Exclusion Criteria

Table 3. Additional Exclusion Criteria

	Exclusion Criteria
cUTI	1. Participants with suspected or confirmed complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, or prostatitis, or history of any illness that, in the opinion of the investigator, may confound the results of the study or pose additional risk in administering the study therapy to the participant. 2. Participants with renal transplantation. 3. Participants with a permanent urinary diversion (eg, with ileal loops, cutaneous ureterostomy or vesicoureteral reflux). 4. Participants who are likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (eg, recurrent UTIs). 5. Any recent history of trauma to the pelvis or urinary tract. 6. Participants with uncomplicated lower urinary tract infections (generally female participants with urinary frequency, urgency, or pain or discomfort without systemic symptoms or signs of infection).
HAP/ VAP	1. Pulmonary disease that precludes evaluation of therapeutic response (eg, lung cancer, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection, or recent pulmonary embolism). 2. Participants with lung abscess, pleural empyema, or post-obstructive pneumonia. 3. Participants with uncompensated heart failure.

Table 3. Additional Exclusion Criteria

	Exclusion Criteria
	4. Participant is a recipient of a lung or heart transplant. 5. Participants with myasthenia gravis.
BSI	1. Participant has a prosthetic cardiac valve or synthetic endovascular graft. 2. Participant has a suspected or documented medical condition with well-defined requirement for prolonged antibiotic treatment (eg, infectious endocarditis, osteomyelitis/septic arthritis, undrainable/undrained abscess, unremovable/unremoved prosthetic associated infection, non-removable or implantable device or line).
cIAI	1. Participant has infections limited to the hollow viscous, such as simple cholecystitis, gangrenous cholecystitis without rupture, and simple appendicitis, or has acute suppurative cholangitis, infected necrotizing pancreatitis, or pancreatic abscess. 2. Participant has abdominal wall abscess or small-bowel obstruction without perforation or ischemic bowel without perforation. 3. Participant has a cIAI managed by staged abdominal repair (STAR), or "open abdomen" technique, or marsupialization. This criterion is intended to exclude participants in whom the abdomen is left open, particularly those for whom re-operation is planned. 4. Participant who has prior liver, pancreas or small bowel transplant.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Controlled sodium diet

Each vial contains approximately 146 mg sodium, which is equivalent to 7.3% of the maximum daily sodium intake recommended by WHO. The maximum daily dose of this

product is equivalent to 22% of the maximum daily sodium intake recommended by WHO. This should be considered when administering CAZ-AVI to participants who are on a controlled sodium diet.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. The participants who are screen failures will not be re-screened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

Not applicable.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Intervention Name	**Zavicefta (ceftazidime/avibactam or CAZ-AVI)**	**Best Available Treatment (BAT)**	**Metronidazole**
ARM Name	CAZ-AVI treatment arm	BAT treatment arm	CAZ-AVI arm and optional for BAT arm
Type	Drug	Drug	Drug
Dose Formulation	Powder for injections	Vial	Solution for injections
Unit Dose Strength(s)	CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam)	N/A	500 mg / 100 ml
Dosage Level(s)	CAZ-AVI 2.5 g administered IV as a 2-hour infusion every 8 hours (q8h).	N/A	MTZ 500 mg IV q8h (by IV infusion over 60 minutes)
Route of Administration	Infusion	Infusion	Infusion
Use	Experimental	Active comparator	other
IMP or NIMP	IMP	IMP	IMP
Sourcing[a]	Provided centrally by the sponsor. Refer to the IP manual.	Provided centrally by the sponsor. Refer to the IP manual.	Provided centrally by the sponsor. Refer to the IP manual.

Intervention Name	Zavicefta (ceftazidime/avibactam or CAZ-AVI)	Best Available Treatment (BAT)	Metronidazole
Packaging and Labeling	Zavicefta will be provided in a sealed vial within a carton and is labeled in a way that is consistent with the study design and with the regulatory requirement for each country. Refer to the IP manual.	Study intervention will be provided in container. Each container will be labeled as required per country requirement. Refer to the IP manual.	Study intervention will be provided in container. Each container will be labeled as required per country requirement. Refer to the IP manual.
Current/Former Name(s) or Alias(es)	Zavicefta	N/A	Metronidazole Injection

a. If the sponsor cannot provide study drugs centrally due to COVID-19 pandemic, and the investigator assesses that the participant should receive study drugs continuously, study drugs can be provided with local sourcing.

6.1.1. Administration

The duration of treatment is 5 days up to 14 days for cUTI, cIAI and BSI, and 7 days up to 14 days for HAP/VAP, which can be extended to 21 days depending on the participant's condition and investigator's judgement as clinical practice required.

6.1.1.1. CAZ-AVI Treatment Arm

Participants randomized to the CAZ-AVI treatment arm will receive CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered IV as a 2-hour infusion every 8 hours (q8h).

No dosage adjustment is required in participants with estimated CrCL ≥ 51 - ≤ 80 mL/min.

Table 4 shows the recommended dose adjustments for participants with estimated CrCL ≤ 50 mL/min. For participants with changing renal function, monitor CrCL at least daily and adjust the dosage of Zavicefta accordingly.

Table 4. Recommended intravenous doses for participants with estimated CrCL ≤ 50 mL/min[a]

Estimated CrCL (mL/min)	Dose regimen[b]	Frequency	Infusion time
31~50	1.25 g (1 g/0.25 g)	Every 8 hours	2 hours
16~30	0.94 g (0.75 g/0.19 g)	Every 12 hours	2 hours
6~15	0.94 g (0.75 g/0.19 g)	Every 24 hours	2 hours
≤5[c]	0.94 g (0.75 g/0.19 g)	Every 48 hours	2 hours

a. CrCL estimated using the Cockcroft-Gault formula.
b. Dose recommendations are based on pharmacokinetic modelling.
c. Ceftazidime and avibactam are removed by haemodialysis. Dosing of CAZ-AVI on haemodialysis days should occur after completion of haemodialysis.

6.1.1.2. Comparator Treatment Arm- Best Available Treatment

The comparator treatments in this study are to be the best available treatment (BAT) based upon site practice and local epidemiology. The choice of BAT for each participant must be recorded prior to randomization. Acceptable BAT may include but not limit to the following (which can be used as monotherapy or in combination):

- Aminoglycoside;
- Colistin (or polymyxin B if colistin is not available or readily accessible);
- Fosfomycin;
- Meropenem;
- Tigecycline.

Participants randomized to this BAT group, may receive combination therapy for Gram-negative coverage (such as with an aminoglycoside) as per the investigator's standard of care. All components of combination therapy must be selected and documented prior to randomization. If randomized to BAT, all components must be initiated at the start of study therapy.

The BAT must not consist solely of the original failed therapy. Switching therapy within the carbapenem class should be considered carefully by investigators as this may not represent best clinical practice.

Details for dose and frequency of administration of BAT (as well as any warnings, precautions, and contraindications) will be based on China LPD or standard of care according to local guideline.[16]

The warnings, precautions, and contraindications found in the local LPD for the specific BAT antibacterial chosen by the investigator must be closely reviewed. If a participant has contraindications for a particular BAT option, that antibiotic should not be used, but other BAT options to which the participant has no contraindications may be considered.

The investigator should follow dose adjustments for participants with renal impairment as established by the China LPD and locally accepted standard of care according to local guideline.

6.1.1.3. Optional Gram positive Antibiotics

Participants may receive optional vancomycin or linezolid at the investigators discretion to provide antibiotic cover for a Gram positive infection. The need for an adjunctive Gram positive antibiotic should be reevaluated once culture and susceptibility results are available and the Gram positive agent should be discontinued if a Gram positive species is not isolated or is no longer suspected.

6.1.1.4. Optional Aminoglycosides

In CAZ-AVI arm, participants with HAP/VAP and proven or suspected coinfection with *P aeruginosa* may receive an optional IV aminoglycoside (eg, amikacin, gentamicin or tobramycin, based upon local practice and epidemiology) at the investigators discretion to allow coverage for suspected or proven *P aeruginosa* infection. The need for adjunctive aminoglycoside therapy should be re-evaluated once culture and susceptibility results are available and the aminoglycoside should be discontinued if *P aeruginosa* is not isolated or is no longer suspected. The need for continued dosing with an aminoglycoside should be reviewed at least after 72 hours to mitigate potential nephrotoxic effect.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual or other specified location.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the

IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

See the IP manual or LPD for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. The study will randomize approximately 60 participants in a 1:1 ratio into 2 treatment groups (CAZ-AVI and BAT). Randomization will be stratified by the infection type: HAP (including VAP); cUTI; cIAI; BSI.

6.3.1. Allocation to Study Intervention

This is an open label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. Potential bias will be reduced by central randomization and involving a central blinded adjudication committee to review the clinical response data.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be re-dispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

Not applicable. This is an open-label study. The investigators, site personnel, and participants will not be blinded in this open-label study; however, reasonable attempts by investigators and site personnel should be made to minimize bias wherever possible. Programming and statistical personnel separate from the Sponsor study team will be responsible for producing the data outputs and will help limit access by the study team to individual participant and group treatment assignment until database lock has occurred.

6.4. Study Intervention Compliance

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Participant compliance with dosing administration will be verified by accounting doses administered. The participant dosing compliance should be within the range of 80% and 120% of expected doses during treatment period. Participant noncompliance cases should be discussed with medical monitors.

6.5. Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

All prescription and over the counter medications, including blood and other blood product transfusions, herbal products, being taken by the participant from signed informed consent prior to registration (considered prior medications) and from registration through the LFU visit (considered concomitant medications) must be documented on the appropriate pages of the eCRF. Systemic antibiotics should be documented for the entire duration of the study (from 2 weeks prior to study entry through the LFU visit).

The use of probenecid or chloramphenicol is not permitted from informed consent to end of IV study treatment.

Concomitant medications which are allowed per protocol, restricted and prohibited are detailed in Table 5, Table 6, and Table 7, respectively:

Table 5. Allowed Concomitant Medication

Allowed Procedure/ Medication/ Class of Drug:	Participants with cIAI:	Participants with cUTI:	Participants with BSI:	Participants with HAP/VAP:
MTZ	Participants in the CAZ-AVI arm will all receive MTZ as part of study therapy (see Section 6.1.1.1). Participants in the BAT arm may receive MTZ if the chosen BAT does not provide adequate anaerobic coverage.	N/A	N/A	N/A
Vancomycin or linezolid	If a Gram-positive pathogen is suspected then vancomycin or linezolid may be added to the study regimen according to the usual practice of the investigator. If a Gram-positive pathogen is not isolated, then the Gram-positive agent should be stopped, at the investigator's discretion, and participants should continue in the study.	If a Gram-positive pathogen is suspected then vancomycin or linezolid may be added to the study regimen according to the usual practice of the investigator. If a Gram-positive pathogen is not isolated, then the Gram-positive agent should be stopped, at the investigator's discretion, and participants should continue in the study.	If a Gram-positive pathogen is suspected then vancomycin or linezolid may be added to the study regimen according to the usual practice of the investigator. If a Gram-positive pathogen is not isolated, then the Gram-positive agent should be stopped, at the investigator's discretion, and participants should continue in the study.	If a Gram-positive pathogen is suspected then vancomycin or linezolid may be added to the study regimen according to the usual practice of the investigator. If a Gram-positive pathogen is not isolated, then the Gram-positive agent should be stopped, at the investigator's discretion, and participants should continue in the study.

Table 5. Allowed Concomitant Medication

Allowed Procedure/ Medication/ Class of Drug:	Participants with cIAI:	Participants with cUTI:	Participants with BSI:	Participants with HAP/VAP:
IV aminoglycoside (eg, amikacin, gentamicin or tobramycin based upon local practice and epidemiology)	N/A	N/A	N/A	In the CAZ-AVI arm, an IV aminoglycoside may be added if *P aeruginosa* is suspected. If aminoglycoside is started, and if *P aeruginosa* is NOT subsequently isolated, then aminoglycoside should be discontinued. The need for continued dosing with an aminoglycoside should be reviewed after 72 hours to mitigate potential nephrotoxic effects.
Peritoneal lavage with saline or other non-antibacterial-containing solution.	Permitted (note that antibiotic peritoneal lavage is not allowed).	N/A	N/A	N/A
Topical antibacterial and antifungals (or any oral antibiotic that has very poor absorption systemically, eg, oral vancomycin).	Permitted except that they may not be applied to the surgical site.	Permitted	Permitted	Permitted

Table 6. Restricted Concomitant Medications

Restricted Procedure/Medication/Class of Drug:	Participants with cIAI, HAP/VAP, cUTI or BSI:
Systemic antibiotics	Concomitant systemic antibiotics are not allowed (except those specified as allowed per the protocol), unless the participant is considered to have failed study treatment and requires additional antibiotics to treat their infection. OR The participant develops a new infection at a remote site and the investigator considers addition of non-study antibiotics essential for the safety and well-being of the participant.
Systemic antifungals	Antifungal treatment to treat the cIAI, HAP/VAP, cUTI or BSI should be avoided unless clinically indicated. For other infection that are not the primary diagnosis, a systemic antifungals may be added.

Table 7. Prohibited Concomitant Medications

Prohibited Procedure/Medication/Class of drug:	Participants with cIAI, cUTI or BSI:	Participants with HAP/VAP
Probenecid or chloramphenicol	Not permitted from informed consent to end of IV study treatment	
Antibiotic peritoneal lavage	Not permitted (note that peritoneal lavage with saline or other non-antibacterial-containing solution is allowed).	N/A.
Inhaled antibiotics	N/A.	Should be avoided from the start to the end of IV study treatment for participants in either treatment arm.

The use of other systemic antimicrobials not specified by this protocol is not permitted during the study. However, if a new infection develops at a remote site (ie, outside of the abdomen for cIAI participants or outside of the urine tract for cUTI or outside of the lung for HAP/VAP participants) between the date and time of the first dose of study treatment and the LFU visit, and the investigator considers addition of non-study antibiotics essential to the safety and well being of the participant, additional antibiotics may be added. If possible, the investigator should first discuss this with the Medical Monitor and attempt to choose antibiotics (guided by local microbiology and sensitivity testing) that will not have antibacterial activity against the participant's baseline pathogens to avoid confounding the assessment of the effect of study therapy.

Information on contraindications, special warnings and precautions and interactions with other medicinal products and other forms of interaction for protocol allowed antibiotics are available in the respective LPD for these products and investigators are recommended to refer to these for further prescribing information.

Other medication, which is considered necessary for the participant's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. Should a participant require immunosuppressive agents or chemotherapy after being enrolled to IV study therapy, the investigator should contact the Pfizer physician before initiating therapy. Continued receipt of study therapy will be determined based upon assessment of the safety risk to the participant. Participants should remain in the study and complete all scheduled protocol assessments.

Any participant planning to undergo surgical treatment not compatible with the aims of the study must not be enrolled. For participants who need to undergo an unplanned surgical procedure during the study, the reason for the surgery must be documented as an AE in the eCRF.

6.6. Dose Modification

In case a dose reduction is necessary, please refer to Section 6.1.1.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants may be discontinued from study intervention in the following situations:

- Condition under investigation resolved prior to minimum treatment period;
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment;
- Occurrence of an AE or any other condition posing a risk to a participant or jeopardizing a safe continuation of the study treatment for the respective participant (as judged by the investigator, and/or the national coordinators, and/or the Medical Monitor and the Study Sponsor);
- Positive pregnancy test at any time during the treatment period.
- In the absence of any alternative explanation for the increase in the following abnormalities, individual participants should be withdrawn if the following criteria are met (see also Appendix 5):
    - ALT or AST >8 × ULN;
    - ALT or AST >3 × ULN and TBili >2 × ULN or international normalized ratio (INR) >1.5;

- ALT or AST >3 × ULN and with appearance of symptoms and signs suggestive of new or progressive liver disease (eg, new or worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [eosinophils >2 × ULN]);

- A participant meeting Hy's Law criteria (see Appendix 5).

- Treatment failure (refer to Table 8);

- In the opinion of the investigator, it is not in the best interest of the participant to continue the study treatment or at the request of the sponsor or delegates that the participant stops participation in the study;

- Severe non-compliance with the CSP.

Investigators should not discontinue a participant from study therapy on the basis of microbiologic results alone (ie, culture and susceptibility results) without evidence of failure. However, the investigator should frequently re-assess the risk/benefit ratio to the participant as additional data become available during the study.

For participants who discontinue study intervention early, all subsequent scheduled assessments should be collected. The EOT visit should occur within 24 hours of study intervention discontinuation.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment

- Adverse event (eg, risk to participant, as judged by the investigator or Pfizer)

- Severe noncompliance to study protocol, as judged by the investigator and/or Pfizer

- Treatment failure

- In the opinion of the investigator, it is not in the best interest of the participant to continue the IV study therapy or at the request of Pfizer that the participant stops participation.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, post-treatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

Refused further follow-up;

Lost to follow-up;

Death;

Study terminated by sponsor;

At the time of discontinuing from the study, if possible, an early discontinuation visit (EOT visit) should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available

information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline

purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 142 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. Clinical Response Assessment

Clinical response will be determined at the EOT and TOC visits as either cure, failure or indeterminate. The clinical response at each visit will be assessed by the investigator, and subsequently by an independent adjudication committee that will be blinded to study treatment (see Section 9.6). In case of a discrepancy with the investigator's assignment of clinical response, the adjudication committee's assessment will prevail for the analysis. Reason for failure will be indicated according to the clinical response definitions as follows (Table 8):

Table 8. Definition of Clinical Response Categories at the EOT and TOC Visits

Clinical Response	Definition
Cure	Baseline signs and symptoms have improved such that after study treatment, no further antimicrobial treatment for the index infection (ie, cIAI, cUTI, HAP/VAP or BSI) is required.[a] In addition, none of the failure criteria listed below should be met. **Additionally for cIAI participants:** No unplanned drainage or surgical intervention is necessary since the initial procedure.

Table 8. Definition of Clinical Response Categories at the EOT and TOC Visits

Clinical Response	Definition
Failure	Participants who meet any of the following criteria will be considered a treatment failure: • Death (after receiving at least 48 hours of study treatment). • Participant who received treatment with further antibiotics for the index infection.[a] This includes participants prematurely discontinued from study treatment due to an AE who require further antibiotics for the index infection. **Additionally for cIAI participants:** • Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively in situation of adequate infection source control at time of initial surgical procedure. • Postsurgical wound infections (eg, signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care).
Indeterminate	• Death (after receiving less than 48 hours of study treatment). • Participant lost to follow-up. **Additionally for cIAI participants:** • Inadequate infection source control at time of initial surgical procedure.

a. Further antibiotics for the index infection should only be initiated for ongoing or worsening signs and symptoms of the infection.

If a participant is assessed as a clinical failure at the EOT visit, this assessment will be carried forward to the TOC visit.

CCI [redacted]

8.1.2. Microbiological Response

For each pathogen identified, microbiological outcome at EOT and TOC will be determined as shown in Table 9.

Table 9. Definition of Microbiological Response Categories at the EOT and TOC Visits, for Each Pathogen Identified at Initial/Pre Study (Study Qualifying) Culture

Microbiological Response	Definition
Eradication	Absence (or urine quantification $<10^3$ CFU/mL for cUTI participants) of causative pathogen from an appropriately obtained specimen[a] at the site of infection.
Presumed eradication	Repeat culture of specimens were not performed/clinically indicated in a participant who had a clinical response of cure (specific to cIAI and HAP/VAP participants).
Persistence **-Persistence with increasing MIC**	Causative organism is still present from an appropriately obtained specimen at the site of infection (for cUTI, the urine culture taken at study intervention completion grows $\geq 10^3$ CFU/mL of the original pathogen identified at trial entry). If the causative organism displays ≥4-fold higher MIC to study therapy after treatment with IV study therapy, the response will also be categorized as "Persistence with increasing MIC".
Presumed persistence	Participant was assessed as a clinical failure and repeat culture of specimens were not performed/clinically indicated (specific to cIAI and HAP/VAP participants).
Indeterminate microbiological response	Death (after receiving less than 48 hours of study treatment). Participant lost to follow-up such that a determination of microbiological response cannot be made on the basis of clinical status. **Additionally for cIAI participants:** Inadequate infection source control at time of initial surgical procedure.

a. A definition of an appropriately obtained specimen for each infection site will be included in the study microbiology manual (see Appendix 8). For participants with cIAI, an appropriately obtained specimen for determination of microbiological response is defined as a specimen obtained using an adequate technique (eg, surgical procedure [laparotomy or laparoscopy], percutaneous drainage (where in place for less than 24 hours) or wounds where the participant has a superficial or deep surgical wound reported at any point during the follow up period). From expectorated or induced sputum, an adequate sample is one with ≤10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Low Power Field (LPF) upon a Gram stain; throat secretions are considered to be inadequate; other specimens such as endotracheal aspirate, BAL, mini BAL, and PSB are considered to be adequate. For participants with cUTI, preferred methods of collection of urine for culture include straight catheterization using sterile technique (preferred for female participants), midstream clean catch and suprapubic specimen collection using sterile technique. For blood specimens for culture, 2 sets of blood cultures should be collected (ie, 4 bottles) from 2 different sites for aerobic and anaerobic incubation. One set of blood cultures must be obtained through a venipuncture. Collect samples, ideally over a period of 2 hours at least 10 to 20 minutes apart from separate sites.

If a pathogen is assessed as persistence or persistence with increasing MIC at the EOT visit, this assessment will be carried forward to the TOC visit.

8.1.2.1 Microbiological Response Assessment

The per-participant and per-pathogen microbiological response at the EOT and TOC visits will be assessed based on the pathogen(s) isolated from the study qualifying baseline and post-baseline cultures per the definitions outlined below. It is based on outcome per-pathogen isolated from the study-qualifying culture and on the isolation of pathogens during the course of treatment or the post-treatment period.

Per-pathogen Microbiological Assessments after Completion of All Follow Up Visits

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 9. Microbiological responses other than "indeterminate" will be classified as "favorable" or "unfavorable." Favorable microbiological response assessments include "eradication" and "presumed eradication." Unfavorable microbiological response assessments include "persistence", "persistence with increasing MIC", and "presumed persistence." Participants with a microbiological response assessment of "indeterminate" will be considered to be non-evaluable for the micro-ITT and ME analysis sets. Classifications such as "superinfection" and "new infection" will be considered separately (see "emergent infections" below).

Per-participant (Overall) Microbiological Response Assessments

Overall microbiological response will also be assessed as "favorable" or "unfavorable" for each participant. Participants will be determined to have a favorable microbiological response if all baseline pathogens for that participant have a favorable outcome (eradicated or presumed eradicated) at the appropriate time point (EOT, TOC). If the outcome for any pathogen is unfavorable (persistence, persistence with increasing MIC, or presumed persistence), the participant will be considered to have an unfavorable microbiological response.

Emergent Infections

New pathogens that appear after Baseline are categorized in Table 10 and will be summarized separately.

Table 10. Definition of Emergent Infection Categories

Emergent Infection	Definition
Superinfection	**cIAI/HAP/VAP/Bacteraemia**: Emergence of a new pathogen(s) associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics during the period up to and including the EOT visit. **cUTI**: Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL from a urine culture associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics during the period up to and including the EOT visit.
New infection	**cIAI/HAP/VAP/Bacteraemia**: Emergence of new pathogen(s) associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics in the time period after the EOT visit. **cUTI:** Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL from a urine culture associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics in the time period after the EOT visit.

8.1.3. All-cause mortality at Day 28

The proportion of participants who have died due to any reason up to the TOC and up to Day 28 will be measured. The denominator for the calculation of the proportion will include all participants irrespective of the status (dead, alive and unknown).

The number of participants who died up to Day 28 of the study will be calculated as the number of participants with a date of death on or before the end of Day 28; participants who have died after Day 28 will be assumed to be alive at Day 28. If there is no record of a participant's death and the participant attended the LFU visit, or if the participant is known to be alive after Day 28, then the survival status will be considered as alive at Day 28. Participants who withdraw from the study before Day 28 will be considered to have "unknown" mortality status, unless further information is available (eg, date of death).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. If the participant's actual height and weight are not

available, the height and weight may be estimated for study use. All height and weight measurements should be recorded in the CRF as actual or estimated.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

The following infection-related focused physical examinations will be conducted:

For HAP/VAP participants, a pulmonary assessment, which includes auscultation, will be performed.

For cIAI participants, abdominal signs and symptoms will be assessed and postoperative abdominal and wound examinations will be performed. Surgical wound examination should occur daily even if inspection is limited by the presence of a negative pressure wound therapy device. A thorough wound evaluation should occur when a full dressing change is performed.

For cUTI participants, focused physical examination will include an assessment for suprapubic pain and costovertebral angle tenderness. And investigator should assess the catheter and nephrostomy tube status if present.

For BSI participants, focused physical examination will include general appearance, vital signs, and focal signs of source infection.

8.2.2. Vital Signs

Tympanic or axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 1 blood pressure measurement.

8.2.3. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with

the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.4. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant’s receiving the IP. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant or legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1 will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation, ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation, ingestion or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until a minimum of 28 calendar days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation, ingestion or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events (Not applicable)

8.3.7. Disease -Related Events and/or Disease -Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with CR pathogens infection and can be serious/life threatening:

- Death

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the corresponding CRF page in the participant's CRF within 24 hours.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Death will be adjudicated by an independent adjudication committee. Any SAE that is adjudicated by the endpoint adjudication committee NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint

criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the endpoint adjudication committee.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

This section is not applicable because lack of efficacy is captured as an efficacy outcome (Table 8).

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of CAZ-AVI greater than specified in protocol in Section 6.1.1.1 will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of CAZ-AVI (whichever is longer)
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

This study will be an estimation study. For the primary efficacy objective and the secondary efficacy objectives except for estimating all-cause mortality, composite estimand strategy will be used; for the secondary efficacy objective of estimating all-cause mortality at Day 28, a treatment-policy estimand strategy will be used.

Primary Efficacy Estimand:

Estimand E1 -- A composite estimand strategy will be used to estimate the treatment effect of CAZ-AVI relative to BAT in terms of clinical response rate in patients with infections due to carbapenem-resistant Gram-negative pathogens. Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment and adjudicated by independent adjudication committee. Intercurrent events will be part of the definition of clinical response. Intercurrent events of death after receiving <48 hours of study treatment, or inadequate infection source control at time of initial surgical procedure (for cIAI participants) will be regarded as indeterminate clinical response. Intercurrent events of death after receiving at least 48 hours of study treatment, or receiving treatment with further antibiotics for the index infection will be regarded as failure clinical response. The difference in the proportion of participants with clinical cure rate between treatment groups will be summarized.

Secondary Efficacy Estimands:

- To estimate the efficacy of CAZ-AVI and BAT in patients with infections due to CR Gram-negative pathogens and who are microbiologically evaluable:

  Estimand E1 will be the estimand for this secondary objective.

- To estimate the clinical response to CAZ-AVI and BAT at end of treatment:

  Estimand E1 will be the estimand for this secondary objective.

- To estimate the microbiological response to CAZ-AVI and BAT:

  Estimand E2 -- A composite estimand strategy will be used to estimate the treatment effect of CAZ-AVI relative to BAT in terms of the microbiological response rate in patients with infections due to carbapenem-resistant Gram-negative pathogens. Microbiological response will be categorized as favorable (ie. eradication, or presumed

eradication), unfavorable (persistence, persistence with increasing MIC, or presumed persistence), and indeterminate. Intercurrent events will be part of the definition of microbiological response. Intercurrent events of death after receiving <48 hours of study treatment, or inadequate infection source control at time of initial surgical procedure (for cIAI participants) will be regarded as indeterminate microbiological response. Intercurrent events that result in repeat culture of specimen not performed/clinically indicated (specific to cIAI and HAP/VAP participants) will be regarded as a presumed eradication if a clinical cure is assessed, and a presumed persistence microbiological response if a clinical failure is assessed. Participants with intercurrent events that result in an indeterminate assessment will be excluded from the evaluable population. The difference in the proportion of participants with favorable microbiological response between treatment groups will be summarized.

- To estimate the all-cause mortality for CAZ-AVI and BAT:

  Estimand E3 -- A treatment-policy estimand strategy will be used in patients with infections due to carbapenem-resistant Gram-negative pathogens to estimate the treatment effect of CAZ-AVI relative to BAT in terms of the all-cause mortality at Day 28 of the study. Any death that occurred after first dose of study intervention through Day 28 will be included. A participant with the last known survival status is before Day 28 or missing will be reported as an unknown status. The difference in the mortality rate between treatment groups will be summarized.

9.1.2. Hypothesis

There are no formal hypothesis tests planned for this study. Statistical inference will be based on point estimate and confidence interval.

9.2. Sample Size Determination

The study will randomize approximately 60 participants in a 1:1 ratio to CAZ-AVI and BAT treatment groups. Through literature review and meta-analysis, the clinical cure rate of CAZ-AVI in the target carbapenem-resistant population was approximately estimated to be 57%.

Due to the life-threatening nature of CRE infections, the scarcity of participants for LTO indication and the large variation associated with limited sample size, a non-inferiority study design is not feasible for the current study. The sample size is based on feasibility assessment, literature review with meta-analysis, and simulation. Approximately 30 participants per arm (60 total sample size) is considered sufficient to quantitate the clinical cure rates in each treatment group, and the difference between treatment groups. The small numbers of participants will be reflected in the precision of the estimate of individual treatment group and treatment difference.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Intent-to-Treat (ITT) Analysis Set	It will include all participants randomly assigned to study intervention and who take at least one dose of study intervention.
microbiologically Modified ITT (mMITT) Analysis Set	It is a subset of the ITT analysis set, and will include participants who: • meet minimum disease requirements and received any amount of study therapy. • have at least 1 carbapenem-resistant Gram-negative pathogens in an adequate initial/pre-study culture. Participants with inherently resistant pathogens (monomicrobial infections due to any *Acinetobacter* spp.) will be excluded from the mMITT analysis set.
Microbiologically Evaluable (ME) Analysis Set	It is a subset of the mMITT analysis set, and will include participants who: • received at least 3 days of study intervention (CAZ-AVI or BAT), or received study intervention treatment for ≥ 48 hours with ≥80% compliance, or received study intervention treatment for <48 hours before discontinuing treatment due to an AE. • did not receive concomitant antibiotic therapy with potential activity against any baseline carbapenem-resistant Gram-negative pathogens between the time of randomization and the time of TOC. This does not include those participants who have failed study therapy and require additional antibiotics to treat their infection.

Participant Analysis Set	Description
	• had the baseline entry organism(s) genetically confirmed by central microbiological testing. • did not have a clinical outcome of indeterminate for the respective analysis at EOT or TOC visits. • had no important protocol deviations that may affect the assessment of efficacy.
Safety Analysis Set (SAS)	All participants who take any study intervention. Participants will be analyzed according to the product they actually received

The above analyses sets will be used for different endpoints according to the objectives and estimands:

For the primary objective and estimand, the mMITT analysis set will be used to analyze the clinical cure rate at TOC visit.

For the secondary objectives and estimands, clinical cure rate at TOC visit will be analyzed in the ME analysis set; clinical cure rate at EOT visit will be analyzed in the mMITT and ME analysis sets; favorable microbiological response at EOT and TOC visits will be analyzed in the ME analysis set; and all-cause mortality at Day 28 will be analyzed in the ITT analysis set.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

The treatment effect will be evaluated based on the point estimate and its corresponding 95% confidence interval (CI) for CAZ-AVI and BAT treatment individually and for the difference between the 2 treatments. No adjustment for multiple comparisons will be made.

9.4.2. Primary Endpoint(s)

The number and percent of participants having clinical cure, failure, and indeterminate at TOC visit in the mMITT analysis population will be summarized by treatment group. Responses missing at the analysis visit such as due to intercurrent events, loss to follow up, early discontinuation will follow the details stated in Table 9 and Table 10 in Section 8.1. The point estimate and 95% confidence interval will be calculated for each individual

treatment group, as well as the difference between CAZ-AVI and BAT treatments in clinical cure rate. Individual teatment group confidence interval will be omputed using Jeffrey's method. The confidence interval for difference between CAZ-AVI and BAT treatments will be derived using Miettinen & Nurminen method stratified by infection site. If the number of participants in a particular stratum is small, then the unstratified Miettinen & Nurminen method will be used.

Subgroup analyses will be performed for infection type (cIAI, HAP including VAP, cUTI, and other) and whether participants having BSI (Yes/No) if data permit.

9.4.3. Secondary Endpoint(s)

Same analysis method as that for primary endpoint will be applied.

Clinical response will be tabulated showing the number and percentage of participants at the TOC visit in the ME analysis population, and at the EOT visit in the mMITT and ME analysis populations. Microbiological response will be tabulated at the EOT and TOC visits in the mMITT and ME analysis populations. The number and percentage of participants who have died due to any cause by Day 28 will be summarized for the ITT population. For summaries in the ME analysis population, participants with indeterminate clinical and microbiological responses will be excluded by definition.

For all-cause mortality at Day 28 in the ITT analysis population, the number and percentage of participants defined as died, alive and unknown will be summarized by treatment group. The analysis for the proportion of participants with death due to any cause (all-cause mortality) will be presented by providing the difference in the proportions between the treatment groups and its 95% CI. If the proportion of participants with unknown status is unbalanced between the treatment groups, then a sensitivity analysis will be considered for all-cause mortality.

9.4.4. Other Safety Analyses

All safety analyses will be performed on the safety population. These will be presented in tabular and/or graphical format and summarized descriptively and will follow Pfizer standards as appropriate.

The MedDRA coding system will be used to classify all AEs with respect to system organ class and preferred term. All treatment-emergent AEs , relationship with treatment, discontinuations due to AEs, and laboratory data abnormalities will be summarized by treatment group using percentages. Change from baseline for selected laboratory tests and vital signs will be summarized with descriptive statistics.

For continuous variables, absolute and change from baseline values in selected laboratory tests, and vital signs will be summarized with N, mean, standard deviation, median, minimum, and maximum. Number and percentages of participants from each category meeting the categorical criteria of laboratory abnormality will be presented.

9.4.5. Other Analyse(s) (Not applicable)

9.5. Interim Analyses

The study is anticipated to have a long recruitment duration, and therefore an interim analysis may be performed prior to the CAZ-AVI license renewal application in China when a complete study report is not yet accomplished. The analysis methods in the interim report will follow the methods planned for the full study and will be based on communication with China agency.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

9.6.1. Independent Adjudication Committee:

This is an open-label study. An independent adjudication committee consisting of at least 3 clinical experts will be convened at regular intervals during the study.

A charter will be in place for the adjudication committee. The adjudication committee will be blinded to study treatment and investigator's assessment of clinical response. The committee will review the clinical data points, reports and results of the diagnostic tests used to classify the clinical response. In case of a discrepancy with the investigator's assignment of clinical response, the adjudication committee's assessment will prevail for the analysis.

In addition, for cIAI participants classified as a clinical failure, and all cIAI participants classified as a cure who undergo another procedure (eg, another surgical procedure) subsequent to randomization, the adjudication committee will review the adequacy of the surgical source control. All cIAI participants assessed by the adjudication committee as having inadequate initial infection source control (ie, the cIAI procedure performed was not considered to be adequate to control the source of infection) will be reclassified as having an indeterminate clinical response and will be excluded from the Microbiologically Evaluable (ME) analysis set.

9.6.2. Internal Review Committee:

An internal review committee (IRC) will be established with a IRC charter for this study and will independently review the data in an unblinded fashion approximately every 6 months to ensure that the safety of participants is not compromised.

The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter and may propose changes to the protocol as needed to ensure participant safety. The IRC will also review results of any interim analysis as described in Section 9.5. The recommendations made by the IRC to alter the conduct of the study will be forwarded to the appropriate Pfizer management for final decision. The Pfizer management will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants or their legally authorized representative must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that his/her personal study related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant or their legally authorized representative must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant’s participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it

should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 11. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Coagulation	Arterial blood gas[a]	Urine test	Other
Hemoglobin, Hematocrit, RBC count, MCV, MCH, MCHC, Platelet count, WBC count, Total neutrophils (Abs), Eosinophils (Abs), Monocytes (Abs), Basophils (Abs), Lymphocytes (Abs)	BUN/Urea, Creatinine, Glucose (fasting), Calcium, Sodium, Potassium, Chloride, AST, ALT, Total bilirubin, Alkaline phosphatase, Uric acid, Albumin, Total protein, Bicarbonate (HCO_3)/ CO_2CP	Partial thromboplastin time, Prothrombin time, International normalized ratio (INR)	Partial pressure of oxygen (PaO_2), Partial pressure of carbon dioxide ($PaCO_2$), pH, Oxygen saturation Bicarbonate	Microscopic examination[b]: red blood cells, white blood cells, casts, crystals, bacteria, yeast cells or parasites Culture	At screening only: FSH[c], Pregnancy test (β-hCG)[d]

a. For HAP/VAP participants, arterial blood gases are required for ventilated participants, recommended for non-ventilated participants at Screening visit to calculate APACHE II score; for cIAI, cUTI and BSI participants, arterial blood gases are only collected as clinically indicated to calculate APACHE II score at Screening visit. For all participants, arterial blood gases are collected as clinically indicated at Baseline, during treatment period and at EOT.

b. For cUTI participants, a microscopic analysis is performed to confirm the presence of pyuria at Screening and Baseline, as clinically indicated during treatment period and at EOT and TOC.

c. For confirmation of postmenopausal status only.

d. Serum or urine β-hCG for female participants of childbearing potential

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse

events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as the data become available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) :

Refrain from donating sperm.

PLUS either**:**

Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

    - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
    - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   Oral;

   Intravaginal;

   Transdermal;

   Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   Oral;

   Injectable.

8. Sexual abstinence:

   Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

> Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
>
> For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
>
> - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).
>
> - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: APACHE II Classification System

APACHE II SCORE FORM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
1. Temperature (°C)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
2. Mean arterial pressure (mm Hg)	≥160	130–159	110–129		70–109		50–69		≤49
3. Heart rate (ventricular response)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
4. Respiratory rate (non-ventilated or ventilated)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
5. Oxygenation A-aDO_2 or PaO_2 (mm Hg) a) FiO_2 ≥0.5:record A-aDO_2	≥500	350–499	200–349		<200				
b) FiO_2 <0.5:record only PaO_2					>70	61–70		55–60	<55
6. Arterial pH – If no ABGs record Serum HCO_3 below	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
7. Serum Sodium (mmol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
8. Serum Potassium (mmol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
9. Serum Creatinine (mg/dL) Double points for acute renal failure	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
10. Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
11. White Blood Count (k/mm^3)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
12. Glasgow Coma Scale (Score = 15 minus actual GCS)	15 – GCS=								
A. Total Acute Physiology Score (APS)	Sum of the 12 individual points =								
Serum HCO_3 (venous-mmol/L) Not preferred, use if no ABGs	≥52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15

<table>
<tr><th>Glasgow Coma Scale</th><th>(Circle appropriate response)</th><th><u>B</u> Age</th><th>Points</th><th><u>C</u></th><th>Chronic Health Points</th><th>Apache-II Score (sum of A+B+C)</th></tr>
<tr><td>Eyes open</td><td>verbal – <u>nonintubated</u></td><td>Age</td><td>Points</td><td colspan="2" rowspan="4">If any of the 5 CHE categories is answered yes give +5 points for non-operative or emergency postoperative patient</td><td rowspan="11">A APS points
+B Age points
+C Chronic Health Points
Apache II</td></tr>
<tr><td>4 – spontaneously</td><td>5 - oriented</td><td>≤44</td><td>0</td></tr>
<tr><td>3 – to speech</td><td>4 – confused</td><td>45-54</td><td>2</td></tr>
<tr><td>2 – to pain</td><td>3 – inappropriate words</td><td>55-64</td><td>3</td></tr>
<tr><td rowspan="2">1 – no response</td><td>2 – incomprehensible sounds</td><td>65-74</td><td>5</td></tr>
<tr><td>1 – no response</td><td>≥75</td><td>6</td><td colspan="2">Liver</td></tr>
<tr><td colspan="2">Motor response</td><td colspan="2" rowspan="7">Age points =</td><td>CV</td><td>Class IV angina or at rest or with minimal self-care activities</td></tr>
<tr><td>6 – to verbal command</td><td>verbal – <u>intubated</u></td><td>Pulmonary</td><td>Chronic hypoxemia or hypercapnia or polycythemia of PHT > 40 mm Hg</td></tr>
<tr><td>5 – localizes to pain</td><td>5 – seem able to talk</td><td rowspan="2">Kidney</td><td rowspan="2">Chronic peritoneal or hemodialysis</td></tr>
<tr><td>4 – withdraw to pain</td><td>3 – questionable ability to talk</td></tr>
<tr><td>3 – flexion to pain</td><td rowspan="3">1 – generally unresponsive</td><td>Immune</td><td>Immune compromised host</td></tr>
<tr><td>2 – extension to pain</td><td colspan="2">Chronic Health Points =</td></tr>
<tr><td>1 – no response</td></tr>
</table>

10.7. Appendix 7: Calculation of Estimated Creatinine Clearance

Estimated creatinine clearance will be calculated using the following Cockcroft-Gault formula.[14] The weight obtained at Screening should be used to qualify for entry into the study. In order to determine the need to adjust the dose and/or dosing interval of IV study therapy to be administered, the participant's estimated creatinine clearance must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the participant's most recent actual (not ideal) body weight, and the Cockcroft-Gault formula.

Cockcroft-Gault formula:

Estimated creatinine clearance is calculated by Cockcroft-Gault as follows:

- For serum creatinine in mg/dL:

estimated creatinine clearance = [(140 – age) × weight in kilograms] / [72 × serum creatinine in mg/dL]

[× 0.85 if female]

- For serum creatinine in µmol/L:

estimated creatinine clearance = [(140 – age) × weight in kilograms × constant] / [serum creatinine in µmol/L]

where constant = 1.23 for males and 1.04 for females

10.8. Appendix 8: Microbiological Assessments

All microbiological assessments will be initiated at the local laboratory for specimen collection, shipment of isolates, and analysis of isolates according to the sections below and as outlined in more detail in the microbiology laboratory manual. All microbiological isolates (except anaerobic bacterial pathogens isolated from participants with respiratory infections and urine tract infections) must be shipped to the central reference laboratory for confirmation of microbiological assessments. An unstained Gram stain slide of each respiratory specimen from induced sputum and expectorated sputums must also be sent to the central reference laboratory.

All specimens should be processed according to recognized methods that culture for both aerobic and anaerobic organisms[15] following the standard operating procedures of the clinical microbiology laboratory at each study center. All cultured isolates should be kept by the local laboratory at –20°C or colder (preferably at 70°C) until the end of the study or when contacted by the central reference laboratory (except for screening visit).

Specimen collection:

a. Intra-abdominal specimens: An adequate abdominal specimen (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) should be obtained from all participants and sent to the local laboratory for culture, identification, and in vitro susceptibility testing. If treatment is discontinued early because the participant is failing therapy and the participant requires a second surgery, an appropriate specimen for culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered. The CRF should indicate whether or not a sample was obtained.

b. Respiratory specimens: An adequate and appropriate respiratory specimen should be sent to the local laboratory for Gram stain (expectorated and induced sputum only), culture, identification, and in vitro susceptibility testing.

Appropriate specimens from ventilated participants include:

- endotracheal aspirate;
- BAL;
- mini BAL;
- PSB sample.

Appropriate specimens from nonventilated participants include:

- expectorated or induced sputum;
- BAL;

- mini BAL;

- PSB sample.

Note that there may be nonventilated participants who develop HAP and subsequently require intubation and mechanical ventilation. If such participants require ventilation prior to the first dose of study treatment, a specimen appropriate for the participant should be obtained even if the participant has already provided a sputum sample. In addition, participants undergoing bronchoscopy prior to the first dose of study treatment should provide a respiratory specimen during the procedure even if a sputum sample or endotracheal aspirate has already been obtained.

To be adequate, respiratory specimen from expectorated or induced sputum must show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Low Power Field (LPF) upon a Gram stain.

When clinically indicated, pleural fluid should be sampled for Gram stain, culture identification, in vitro susceptibility testing; isolates should be sent to the central laboratory for confirmation. Additionally, (when indicated) cell counts, pH and lactate dehydrogenase (LDH) of pleural fluid as well as serum LDH should also be obtained. It is not necessary to submit a Gram stain slide of pleural fluid to the central laboratory.

If treatment is discontinued early because the participant is failing therapy or other reasons, an appropriate respiratory specimen for culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered. The CRF should indicate whether or not a sample was obtained.

c. Blood specimen: Blood cultures should be obtained prior to the first dose of study treatment (if blood cultures are not available within 48 hours prior to randomization) and thereafter as clinically indicated. When obtaining samples for blood culture, 2 sets of blood cultures should be collected (ie, 4 bottles) from 2 different sites for aerobic and anaerobic incubation. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. One set of blood cultures must be obtained through a venipuncture. Collect samples, ideally over a period of 2 hours at least 10 to 20 minutes apart from separate sites. If a participant is on antibiotics, blood cultures should ideally be taken immediately before the next dose. Organisms isolated in the blood within 48 hours prior to randomization or at Baseline will be assigned a microbiologic response similar to those given for pathogens isolated from abdominal, urine or respiratory specimens (see Table 9 for list of response categories). Details concerning the collection of blood cultures are provided in the laboratory manual.

d. Urine specimen: Urine samples specimens should not be obtained from urinary catheter bags. Preferred methods of collection of urine for culture include:

- Straight catheterization using sterile technique (preferred for female participants);

- Midstream clean catch;

- Suprapubic specimen collection using sterile technique.

Urine specimens must not be obtained from indwelling catheter bags. When necessary, urine specimens in participants with indwelling bladder catheters may be obtained by sterile aspiration through the catheter port . The urine specimen should be plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, this test may be performed within 24 hours of collection if the specimen is stored at 2°C to 8°C before processing. The specimen for microscopic evaluation (eg, evidence of persisting pyuria) and culture obtained at Baseline should be collected before randomization and administration of study therapy.

10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
%CV	% coefficient of variation
%fT	percentage of time over the dosing interval that free drug concentrations exceed the threshold concentration or minimum inhibitory concentration
A-aDO_2	alveolar-arterial oxygen difference
ABG	arterial blood gas
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
APACHE	acute physiology and chronic health evaluation
APS	acute physiology score
AST	aspartate aminotransferase
$AUC_{ss,0-24}$	steady-state total daily area under the plasma concentration-time curve
BAL	bronchoalveolar lavage
BAT	best available treatment
β-hCG	beta-human chorionic gonadotropin
BSI	bloodstream infection
BUN	blood urea nitrogen
CARES	chinese antimicrobial resistance surveillance
CAZ-AVI	ceftazidime-avibactam
CDE	Centre of Drug Evaluation
CFR	Code of Federal Regulations
CFU	colony-forming unit
CHINET	china antimicrobial surveillance network
CHP	chronic health points
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
CO_2CP	carbon dioxide combining power
CONSORT	Consolidated Standards of Reporting Trials
Covid-19	coronavirus disease of 2019
CR	carbapenem-resistant
CRAB	carbapenem-resistant Acinetobacter baumannii
CrCL	creatinine clearance
CRE	carbapenem-resistant Enterobacteriaceae

Abbreviation	Term
CRF	case report form
CRO	contract research organization
CRPA	carbapenem-resistant pseudomonas aeruginosa
CSP	clinical study protocol
CSR	clinical study report
$C_{ss,max}$	maximum steady-state drug concentration in plasma during a dosing interval
cSSTI	complicated skin and skin structure infection
CT	clinical trial; computed tomography
cUTI	complicated urinary-tract infection
CV	coefficient of variation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRE	disease-related event
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
IRC	Internal Review Committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOT	end of treatment
ESBL	extended-spectrum beta-lactamase
EU	European Union
EudraCT	European Clinical Trials Database
FiO_2	fraction of inspired O_2
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	glasgow coma scale/score
GGT	gamma-glutamyl transferase
HAP	hospital-acquired pneumonia
HCO_3	Hydrogencarbonate or bicarbonate
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log

Abbreviation	Term
IRB	Institutional Review Board
IRC	internal review committee
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous/ly
KPC	*Klebsiella pneumoniae* carbapenemase
LDH	lactate dehydrogenase
LFT	liver function test
LFU	late follow up
LPD	local product document
LPF	low power field
LTO	limited treatment options
MBL	metallo-β-lactamase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multidrug resistant
MedDRA	Medical Dictionary for Regulatory Activities
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
mMITT	microbiologically modified intent-to-treat
MTZ	metronidazole
N	number
N/A	not applicable
NIMP	noninvestigational medicinal product
NMPA	National Medical Products Administration
NP	nosocomial pneumonia
O_2	oxygen
PACL	Protocol Administrative Change Letter
PaO_2	pressure of O_2 in arterial blood
PD	pharmacodynamic(s)
pH	potential of hydrogen
PHT	pulmonary hypertension
PI	principal investigator
PK	pharmacokinetic(s)
PMN	polymorphonuclear leukocyte
pO_2	partial pressure of O_2
PSB	protected-specimen brush
PT	prothrombin time
PTA	probability of target attainment
q8h	every 8 hours
RBC	red blood cell

Abbreviation	Term
RR	resistance rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
spp	plural of species
SRSD	single reference safety document
STAR	staged abdominal repair
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TOC	test of cure
ULN	upper limit of normal
US	United States
UTI	urinary-tract infection
VAP	ventilator-associated pneumonia
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

11. REFERENCES

1. Drawz SM, Papp-Wallace KM, Bonomo RA. New β-lactamase inhibitors: a therapeutic renaissance in an MDR world. Antimicrob Agents Chemother. 2014;58(4):1835-46.

2. Keepers TR, Gomez M, Celeri C, et al. Bactericidal activity, absence of serum effect, and time-kill kinetics of ceftazidime-avibactam against β-lactamase-producing Enterobacteriaceae and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2014;58:5297-305.

3. Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumonia* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother. 2010;65(6):1119-25.

4. Hu FP, Guo Y, Zhu DM, et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. Clin Microbiol Infect. 2016;22:S9-S14.

5. National Health and Family Planning Commission. Report on Antimicrobial Stewardship and Current Status of Antimicrobial Resistance in China (2017). Peking Union Medical College Publishing House 2017. (available upon request)

6. Hu Fupin, Guo Y, Zhu DM, et al. CHINET surveillance of bacterial resistance across China: report of the results in 2016. Chin J Infect Chemother 2017; 17:481–91.

7. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:1-12.

8. Hu F, Zhu D, Wang F, et al. Current status and trends of antibacterial resistance in China. Clin Infect Dis. 2018;67(Suppl 2):S128-34.

9. Hu Fupin, Guo Y, Zhu DM, et al. Antimicrobial resistance profile of clinical isolates in hospitals across China: report from the CHINET Surveillance Program, 2017. Chin J Infect Chemother. 2018;18(3):241-9.

10. Falagas ME, Tensarli GS, Karageorgopoulos DE, et al. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerg Infect Dis. 2014;20(7)(Jul):1170-5.

11. Zhang Y, Wang Q, Yin Y, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae infections: report from the China CRE Network. Antimicrob Agents Chemother. 2018;62(2):e01882-17.

12. Karaiskos I, Giamarellou H. Multidrug-resistant and extensively drug-resistant Gram-negative pathogens: current and emerging therapeutic approaches. Exp Opin Pharmacother 2014;15(10):1351-70.

13. Rigatto MH, Behle TF, Falci DR, et al. Risk factors for acute kidney injury (AKI) in patients treated with polymyxin B and influence of AKI on mortality: a multicentre prospective cohort study. J Antimicrob Chemother. 2015; 70(5):1552-7.

14. Cockcroft DW, Gault HM. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

15. Thomson RB Jr. Specimen collection, transport, and processing: bacteriology. In: Murray PR, editor. Manual of Clinical Microbiology. 9th ed. Washington, DC: ASM Press; 2007:291-333.

16. Expert consensus writing group on the diagnosis, treatment and prevention of carbapenem-resistant Enterobacteriaceae bacterial infections in China, Professional Committee on Infectious Diseases of China Medical Education Association, and Professional Committee on Prevention and Control of Bacterial Infection and Drug Resistance of Chinese Medical Association. Expert consensus on diagnosis, treatment and prevention of carbapenem-resistant Enterobacteriaceae infections in China. Chinese Medical Journal, 2021, 101(36): 2850-2860. DOI: 10.3760/cma. j.cn112137-20210219-00438.