Protocol C3591033

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

Statistical Analysis Plan
(SAP)

Version: 2

Date: 29 Jan 2023

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 19 Feb 2021	Original 22 Dec 2020	N/A	N/A
2 29 Jan 2023	Amendment 1 02 Jun 2022	Add impact assessment of COVID-19 and remote TOC visits and related sensitivity analysis. Add specifications on interim analysis. Add COVID-19 related analyses. Made some clarifications on mMITT analysis set, baseline definitions and compliance calculation.	• Section 2.3, added descriptions of independent team for the interim analysis. • Section 3.2.1: added definitions of baseline pathogens. • Section 4: made clarifications on the minimum disease requirements for mMITT analysis set. • Section 5.3: added a section on the impact assessment of COVID-19 and remote TOC visits per DMB02-GSOP-SD-GL01. • Section 5.4: made clarifications for missing data. • Section 6.1.2: added sensitivity analysis on primary endpoint to reflect the impact of remote TOC visits. • Section 6.6.5: made clarifications on the treatment compliance calculation. • Section 6.7: added COVID-19 related analysis. • Section 7.2: added some specifications on interim analysis. • Section 9.4: added example SAS code.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3591033. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

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 (CR) 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 Test of Cure (TOC) visit
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 (EOT).	• 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	• Microbiological response (defined by favorable, unfavorable, or indeterminate) at EOT and TOC visits

Objectives	Estimands	Endpoints
	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.	
• 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.

2.1.1. Primary Estimand (E1)

The primary estimand of this study will use the composite strategy to estimate the treatment effect of CAZ-AVI relative to BAT accounting for both treatment adherence and response. The estimand is defined according to the primary objective and in alignment with the primary endpoint. It includes the following 4 attributes:

- Population: Patients with infections due to Carbapenem-resistant Gram negative pathogens;
- Variable: Clinical response per investigator's assessment and adjudicated by independent adjudication committee at the TOC visit. Clinical response will be categorized as cure, failure, and indeterminate. 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;
- Intercurrent event: The intercurrent events are captured through the variable definition;
- Population-level summary: Difference of the clinical cure rate between CAZ-AVI and BAT.

2.1.2. Secondary Estimand(s)

2.1.2.1. Estimand for Clinical Response (E1)

For the secondary objectives related to clinical response, same estimand (E1) as the primary estimand will be used.

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

  The primary estimand E1 will be used.

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

  The primary estimand E1 will be used. Clinical response per investigator's assessment and adjudicated by independent adjudication committee at the EOT visit will be the analysis variables.

2.1.2.2. Estimand for Microbiological Response (E2)

The secondary estimand for microbiologic response will use the composite strategy to estimate the microbiological response of CAZ-AVI relative to BAT accounting for both treatment adherence and response. The estimand is defined according to the secondary objective and in alignment with the secondary endpoint. It includes the following 4 attributes:

- Population: Patients with infections due to Carbapenem-resistant Gram negative pathogens;

- Variable: The per-participant microbiological response at the EOT visit and TOC visit. 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 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;

- Intercurrent event: The intercurrent events are captured through the variable definition;

- Population-level summary: Difference in the proportion of participants with favorable microbiological response between CAZ-AVI and BAT.

2.1.2.3. Estimand for All-cause Mortality (E3)

The secondary estimand for all-cause mortality will use the treatment policy strategy to estimate the all-cause death rate regardless of whether an intercurrent event occurs. The estimand is defined according to the secondary objective and is in alignment with the secondary endpoints. It includes the following 4 attributes:

- Population: Patients with infections due to Carbapenem-resistant Gram negative pathogens;
- Variable: Death due to any cause at Day 28;
- Intercurrent event: 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.
- Population-level summary: Difference of the mortality rate between CAZ-AVI and BAT.

2.1.3. Additional Estimand(s)

There is no defined estimand for other endpoints.

2.2. Study Design

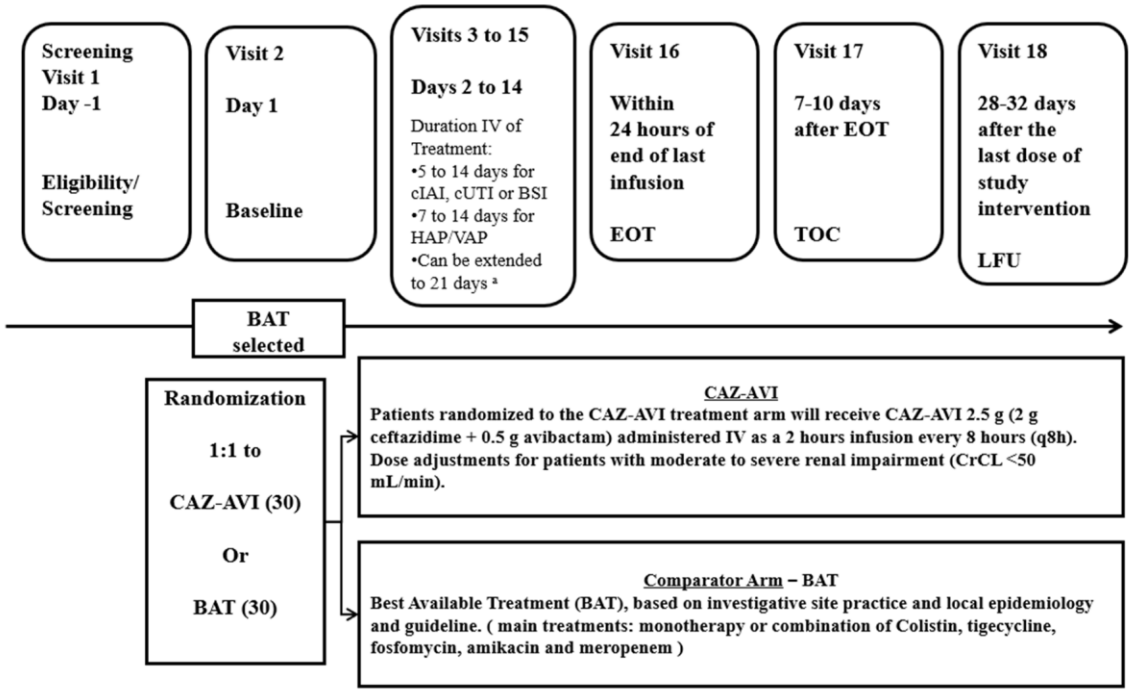
This is an open-label, randomized, multi-center, interventional, active-controlled Phase 4 study to evaluate the efficacy and safety of CAZ-AVI versus BAT in the treatment of infected participants with selected infection types (Hospital Acquired Pneumonia [HAP] (including Ventilator-Associated Pneumonia [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 randomize approximately 60 participants in a 1:1 ratio into 2 treatment groups (CAZ-AVI or BAT). Randomization will be stratified by infection site: HAP (including VAP); cUTI; cIAI; BSI (including primary BSI, catheter related BSI [CR BSI], and BSI related to HAP [including VAP], cUTI, and cIAI) that is identified prior to conducting treatment randomization. Among the 4 strata, the first 3 infection sites will not include participants with BSI.

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)(**Figure 1**).

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 requires.

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

2.3. Methods for Ensuring Blinding

The study is open-label. 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. Programmer(s) and statistician personnel who are unblinded will be responsible for producing the unblinded data outputs for the IRC review and for interim analysis prior to the CAZ-AVI license renewal application in China to help limit the access to individual participant treatment assignment until database lock has occurred.

An independent adjudication committee will be blinded with the aim of unbiased adjudication of the primary objective measure. 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.

An Internal Review Committee (IRC) will be established with an IRC charter for this study and will independently review the safety data in an unblinded fashion approximately at least

every 6 months or as needed to ensure that the safety of participants is not compromised. In addition, the committee will receive SAE reports approximately every 3 months. Details about IRC review process and frequencies are described in IRC charter.

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's safety. The IRC will also review the interim analysis outputs.

An independent team will be identified for the interim analysis (IA) and interim CSR development to maintain the study team as blinded to the summary report when study is ongoing. Anyone who will work on the IA related work and unblind to the summary report will be added to an independent team roster which mainly includes members from applicable functional lines, IRC committee members, IA CSR reviewers and IA CSR approvers. Anyone who is added to the independent team will not be involved in the routine study team work. The operation process for IA is included in the IRC charter.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Clinical response (defined by cure, failure, or indeterminate) at the TOC visit;

3.1.1. Clinical response

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 which is blinded to study treatment. In case of a discrepancy with the investigator's assignment of clinical response, the adjudication committee's assessment will prevail for the analysis.

The clinical response categories will be indicated according to the clinical response definitions as follows (Table 2):

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

Table 2. 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.
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.

3.2. Secondary Endpoint(s)

- Clinical response (defined by cure, failure, or indeterminate) at TOC visit in the microbiologically evaluable (ME) analysis set as defined in Section 4;
- Clinical response (defined by cure, failure, or indeterminate) at EOT visit;
- Microbiological response (defined by favorable, unfavorable, or indeterminate) at EOT and TOC visits;

- All-cause mortality at Day 28;
- Assessment of TEAEs, discontinuation due to AEs, safety-related clinical laboratory tests.

3.2.1. Microbiological Response

For each pathogen identified at baseline, microbiological outcome at EOT and TOC will be determined as shown in Table 3. Baseline pathogens are defined as all the pathogens identified in both screening and Day 1 visits prior to the first dose. Unplanned assessments prior to the first dose will be considered as baseline only if microbiology tests were not done in screening and Day 1 visits.

Identification of pathogens and susceptibility results will be recorded by both the local microbiology laboratory and the central reference laboratory. The identification and susceptibility results of the central reference laboratory will be regarded as definitive if there are inconsistencies between local and central lab. Data from local lab will be used only if the microbiology tests were not done in the central lab.

Baseline microbiology susceptibility is defined as the most recent data prior to first dose.

Table 3. 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).

Table 3. 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
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. 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.

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 3. 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.”

Per-participant microbiological response will be assessed as “favorable”, “unfavorable” or “indeterminate” 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. Participants will be assessed as a indeterminate microbiological

response if all baseline pathogens for that participant have a indeterminate outcome at the appropriate time point (EOT, TOC).

New pathogens that appear after Baseline are categorized in Table 4 and will be summarized separately.

Table 4. 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.

3.2.2. All-cause Mortality at Day 28

The proportion of participants who have died due to any reason up to and including 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).

CCI [redacted]

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3.4. Baseline Variables

3.4.1. Baseline Clinical Laboratory and Vital Signs

Baseline clinical laboratory (Hematology, Chemistry, etc.) and vital signs values will be defined as the last non-missing value observed before treatment begins.

3.4.2. Baseline Microbiology

Study qualifying microbiological isolate is a CR Gram negative bacteria and culture-confirmed susceptibility to CAZ-AVI that was isolated from an appropriate specimen obtained within 5 days prior to screening. Culture, identification, and in vitro susceptibility testing, isolated from adequate specimens, is performed at the local laboratory. And the isolate (including all pathogens that may or may not be carbapenem resistant) must be sent to the central microbiology laboratory vendor for confirmation.

For cIAI, adequate abdominal specimen (such as tissue or aspirate suitable for isolation) 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. Details about the specimen collection is included in the study microbiology manual.

3.4.3. Stratification Variables

Randomization will be stratified based on infectious site (HAP (including VAP), cUTI, cIAI and BSI). BSI will include primary BSI, catheter related BSI [CR BSI], and BSI related to HAP [including VAP], cUTI, and cIAI that is identified prior to conducting treatment randomization. Among the 4 strata, the first 3 infection sites will not include participants with BSI.

3.4.4. Other Baseline Variables

Demographic and baseline characteristics include the following:

- Age (years);
- Gender (male, female)
- Height (cm);
- Weight (kg);

- Medical history;
- APACHE II score;
- Prior systemic antibiotic use (yes [subcategories of ≤24h / >24h] / No);
- Failure of prior antibiotics use (Yes / No);

  Note: Based on protocol inclusion criteria #3, a participant is allowed to enter this study if one of the following 3 items is met：

  a) No - or no more than 24 hours of appropriate antibacterial therapy was administered for the current infection [this defines failure of prior antibiotic use as 'no'].
  The following two items will define failure of prior antibiotics use as 'yes':
  b) Worsening of objective symptoms or signs of infection after at least 48 hours of appropriate antibacterial therapy. OR
  c) No change of objective symptoms or signs of infection 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)

  If a patient incorrectly enter the study and do not meet the above criteria, then the patient will be assigned as 'Other'. (In other words, "failure of prior antibiotic = yes" indicates participants who failed therapy that had no potential activity against the baseline pathogens.)

- Estimated creatinine clearance (CrCl) [mL/min];
- Primary diagnosis, complicating factors for cUTI, mechanical ventilation status (for HAP/VAP);

  Note: A patient is considered to be 'ventilated' if (i) the patient is VAP, or (ii) the patient is Non-VAP and is on a ventilator on the day of enrollment.

3.5. Safety Endpoints

The safety endpoints of this study are:

- Incidence of treatment-emergent adverse events and discontinuation due to adverse events;
- Incidence of clincal laboratory abnormalities (defined as Potentially Clinically Significant [PCS] results) and summary of values and change from baseline in clinical laboratory measures by scheduled visit;

- Measurements and change from baseline in vital sign measures by scheduled visit.
- Incidence of abnormalities in the complete physical examination by scheduled visit.

3.5.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started after the study medication infusion start date and time.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) to determine System Organ Class and Preferred Term.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to the database lock and classifications will be documented per standard operating procedures.

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[a] and received any amount of study therapy. • have at least 1 carbapenem-resistant Gram-negative pathogen 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.

Participant Analysis Set	Description
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 first dose and the time of TOC. This does not include those participants who have failed study therapy and require additional antibiotics to treat their infection. • 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.

See Section 9.1 Appendix 1 for a detailed list of analysis sets used for different estimand, endpoint and timepoint.

a. Minimum disease requirements for each infection site are defined based on the following inclusion criteria as below:

Inclusion Criteria 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).

Additional minimum disease criteria for HAP/VAP (See Protocol Table 2 for details):

Additional Inclusion Criteria 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).

Additional Inclusion Criteria 2:

New or worsening infiltrate on chest X-ray (or computed tomography [CT] scan) obtained within 48 hours prior to randomization.

Additional Inclusion Criteria 3:

At least 1 of the following:

- Documented fever (temperature ≥38° C) or hypothermia (rectal/core temperature ≤ 35° C);
- WBC ≥10,000 cells/mm3, leukopenia with total WBC ≤4500 cells/mm3, 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 (O2 saturation <90% or partial pressure of O2 [pO2]<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 pO2 in arterial blood [PaO2]/fraction of inspired O2 [FiO2]) or needed changes in the amount of positive end-expiratory pressure.

Additional minimum disease criteria for cUTI:

Additional Inclusion Criteria 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/mm3 in unspun urine.

Additional Inclusion Criteria 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

Additional Inclusion Criteria 4:

Complicating factors: participant must have at least 1 of the following complicating factors:

- Documented history of urinary retention (male participants);
- 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.

Additional minimum disease criteria for cIAI:

Additional Inclusion Criteria 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)

Additional 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.

Additional minimum disease criteria for BSI:

Additional Inclusion Criteria 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/mm3) or left shift (>15% immature polymorphonuclear leukocytes [PMNs]).
- Hypotension, systolic <90 mmHg

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

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

5.2. General Methods

All data will be presented by treatment arm (CAZ-AVI, BAT, and Total). Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. The confidence interval (CI) for the response rates for each treatment group will be calculated using Jeffrey's method (Brown et al. 2001; Cai 2005)[1,2]. The CI for response rate difference between treatment arms will be derived using Miettinen & Nurminen (1985)[3] method stratified by infection site. If the number of participants in a particular stratum is small (less than 3 participants per each treatment group), then the unstratified Miettinen & Nurminen method will be used. Listings of individual participant data will also be produced.

Categorical and qualitative variable summaries for safety will include n and percentage of participants who are in the particular category and have evaluable data collected. In general, the denominator for the percentage calculation will be based upon the total number of participants with evaluable data collected in the corresponding analysis population.

5.3. Impact Assessment of COVID-19 and Remote TOC Visits

For reducing risk to participants, alternative measures were allowed in protocol amendment 1 (dated 02 Jun 2022) about participant remote safety monitoring due to COVID-19 impact. 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. 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.

As TOC visit is the primary endpoint visit, attention to the compliance of TOC visit should be paid, and mitigations to reduce the non-compliance rate during the study ongoing are applied. Although there are still some cases that the onsite TOC visit failed to be accomplished, of which some are due to COVID-19 related issues and the others are due to the participants' personal issue such as body health status. For these cases, remote TOC visit assessment will be done, which may be based on the local hospital laboratory test or through telephone contact with the participants. PDs will be reported with consistent wording starting with "Remote TOC visit…", and these PDs will be used to flag the participants during the data analysis and reporting stage.

To closely monitor the rate of remote TOC visit and limit its impact on the final results of this study, especially on the primary endpoint of clincal response at TOC visit, a threshold for TOC non-compliance was setup.

The TOC non-compliance rate of 15% was set as the monitoring threshold by study team per below considerations:

- The remote TOC visit will increase the rate of "Indeterminate" clinical response due to lack of on site assessment information for the efficacy assessment. And these will impact the final results of clincal response rate. Referring to other CAZ-AVI studies, the rate of Indeterminate is about 9.0% in cMITT analysis set.

- The TOC non-compliance will include cases for subjects who were not evaluated as clinical failure at EOT but didn't complete the TOC visit on site, including: a. Remote visit via telephone only; b. Remote visit via telephone and local hospital visit. Also the rate of indeterminate will be accumulated in the rate of non-compliance.

- To monitor the TOC non-compliance, we use the 10% which is close to the expected indeterminate rate as a reference. Meanwhile, considering the non-compliance may include some cases which are assessed as cure or failure per remote assessment, we extend the threshold to 15% to be the threshold for monitoring.

Data collected via remote assessments will be treated the same as data collected via on-site visits including the primary endpoint of clinical response at TOC visit, which will be included in the primary analysis (Section 6.1.1) regardless of the events of COVID-19 pandemic or remote TOC visits. Besides the primary analysis, sensitivity analyses will be performed to show the impact of these events (Section 6.1.2).

5.4. Methods to Manage Missing Data

For clinical response and microbiological response, missing data due to intercurrent events, loss to follow up, early discontinuation will be handled following the details stated in Section 3.1.1 and Section 3.2.1. For clinical response assessments that are not done or missing at TOC visit due to individual reasons other than the intercurrent events captured in the endpoints' definitions, the clinical response of failure at the EOT visit will be carried forward to the TOC visit, otherwise it will be handled the same as an event of loss to follow up as stated in Section 3.1.1. For microbiological response assessments that are not done or missing at TOC visit, 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. Oherwise it will be handled per Section 3.2.1.

For safety data, missing dates will be programmatically handled according to Pfizer standards.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Clinical Response at TOC visit

- Estimand strategy: Composite strategy estimand E1 (Section 2.1.1).
- Analysis set: mMITT population (Section 4).
- Analysis methodology: Jeffrey's method will be used to calculate the 95% CIs for the response rate for each treatment arm and Miettinen & Nurminen method will be used to calculate the 95% CI for the response rate difference between CAZ-AVI and BAT treatment arms (Section 5.2).
- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.1), the definition of clinical response (Section 3.1.1), and methods to handle missing data (Section 5.4).
- 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. 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.
- Subgroup analyses will be performed for infection site (cIAI, HAP including VAP, cUTI, and BSI) that is identified prior to conducting treatment randomization (see Section 3.4.3) and whether participants having BSI (Yes/No) if data permit.

6.1.2. Sensitivity Analyses

A sensitivity analysis based on the Investigator's assessment of clinical response in the mMITT analysis set at the TOC visit will be performed using the same methodology specified in Section 6.1.1.

A second sensitivity analysis based on the adjudication assessment of clinical response will be performed by removing the participants with remote TOC visits recorded as protocol deviations. Same method for the primary analysis in Section 6.1.1 will be applied.

Another sensitivity analysis for the adjudication assessment of clinical response will be performed by removing participants with remote TOC visit who didn't have any signs or symptom information collected at the TOC visit. Same method for the primary analysis in Section 6.1.1 will be applied.

6.2. Secondary Endpoint(s)

6.2.1. Clinical Response at TOC and EOT visit

- Estimand strategy: Composite strategy estimand E1 (Section 2.1.1, Section 2.1.2.1).
- Analysis set: mMITT population and the ME population (Section 4).
- Analysis methodology: Jeffrey's method will be used to calculate the 95% CIs for the response rate for each treatment arm and Miettinen & Nurminen method will be used to calculate the 95% CI for the response rate difference between CAZ-AVI and BAT treatment arms (Section 5.2).
- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.1), the definition of clinical response (Section 3.1.1), and methods to handle missing data (Section 5.4).
- The number and percent of participants having clinical cure, failure, and indeterminate at TOC visit in the ME analysis population and at EOT visit in the mMITT and ME analysis population will be summarized by treatment group. 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.

6.2.2. Microbiological Response at EOT and TOC visits

- Estimand strategy: Composite strategy estimand E2 (Section 2.1.2.2).
- Analysis set: mMITT population and the ME population (Section 4).
- Analysis methodology: Jeffrey's method will be used to calculate the 95% CIs for the per-participant microbiological response rate for each treatment arm and Miettinen & Nurminen method will be used to calculate the 95% CI for the response rate difference between CAZ-AVI and BAT treatment arms (Section 5.2).

- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.2.2), the definition of microbiological response (Section 3.2.1), and methods to handle missing data (Section 5.4).

- The number and percent of participants having favorable, unfavorable, and indeterminate per-participant microbiological response at TOC visit in the mMITT and ME analysis population will be summarized by treatment group. 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 per-participant favorable microbiological response rate.

6.2.3. Emergent Infections

The number and percentage of patients who reported at least 1 superinfection or new infection will be summarized for the mMITT analysis sets.

6.2.4. All-cause Mortality at Day 28

- Estimand strategy: Treatment policy strategy estimand E3 (Section 2.1.2.3).

- Analysis set: ITT population (Section 4).

- Analysis methodology: Jeffrey's method will be used to calculate the 95% CIs for the all-cause mortality for each treatment arm and Miettinen & Nurminen method will be used to calculate the 95% CI for the mortality difference between CAZ-AVI and BAT treatment arms (Section 5.2).

- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.2.3).

- The number and percent of participants defined as died, alive and unknown will be summarized by treatment group. 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 all cause mortality.

- 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.

6.2.5. Safey Endpoints

The details of safety analyses are described in the Section 6.6.

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6.4. Subset Analyses

Subgroup analyses will be performed for infection site (cIAI, HAP including VAP, cUTI, and BSI) that is identified prior to conducting treatment randomization (Section 3.4.3), and whether participants having BSI (Yes/No) if data permit.

The analysis described for the primary efficacy endpoint clinical response at TOC visit in Section 6.1.1 will be done for each infection site (or combined infection sites). The summaries broken down by infection site (or combined infection sites) will only present counts and percentages for individual treatment arm and difference between treatment arms due to small sample size.

Similarly, the analyses for secondary and other efficacy endpoints will be presented for each infection site (or combined infection sites).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline variables are defined as outlined in Section 3.4.

Demographic and baseline characteristics will be summarized by treatment arm and infection site in the safety analysis set. Baseline disease characteristics will also be summarized for the mMITT analysis set.

Baseline microbiology will be summarized by treatment arm and infection site (or combined infection sites). Pathogens at baseline will be summarized overall and by infection site. Pathogens will be summarized by individual baseline pathogen and by pathogen type (Gram-negative/positive pathogens, carbapenem-resistant/or not resistant).The susceptibility profile and MIC frequency distributions of study treatment for all baseline pathogens will also be summarized. Microbiological culture results will be listed.

6.5.2. Study Conduct and Participant Disposition

The number of participants who are enrolled, who are randomized, who are randomized but are never treated, who complete the study up to the EOT visit, TOC visit, who complete the study up to the LFU visit, who are withdrawn from the study treatment, and who are withdrawn from the study, including reason for withdrawal, will be summarized by treatment arm for all participants.

The number of participants in each of the analysis sets (ie, ITT, mMITT, SAS) will be summarized by treatment arm and infection site (or combined infection sites).

6.5.3. Concomitant Medications

All prior and concomitant medications will be summarized. Systemic antibiotic medications will be summarized and listed separately.

6.6. Safety Summaries and Analyses

In general, safety analyses will be performed by treatment group and infection site (or combined infection sites) on the safety population. Standard summary tables and listings will be generated using Pfizer's Clinical Data Analysis and Reporting System (CDARS) for the following parameters: adverse events, serious adverse events, death, SAEs with an outcome of death, lab parameters (hematology, blood chemistry etc.), vital signs, discontinuations from study, discontinuations from treatment, and treatment duration. Safety analyses will be primarily presented by treatment group with all infection sites combined; high-level summary of TEAE, summaries of discontinuations from study and treatment, summary of discontinuation from treatment due to treatment, summaries of death and SAE, and summary of potentially clinically significant laboratory results will be presented by treatment group and infection site (or combined infection sites).

Unless otherwise noted, AEs will be sorted by MedDRA hierarchy (alphabetically by SOC, then HLGT, HLT and PT, however only SOC and PT will be displayed in the summary tables).

6.6.1. Adverse Events

TEAEs will be summarized by number and percent by system organ class (SOC) and preferred term (PT).

The following high-level TEAE summaries will be presented:

- Any TEAE
- Any SAE
- TEAEs leading to death
- TEAEs leading to discontinuation
- Severe TEAEs

The number and percentage of participants experiencing the AEs will be summarized by as following:

- Summary of TEAEs by system organ class and preferred term
- Summary of TEAEs by system organ class and preferred term, categorised by highest reported intensity
- Summary of drug-related TEAEs by system organ class and preferred term
- Summary of TEAEs leading to discontinuation by system organ class and preferred term

- Summary of SAEs by system organ class and preferred term
- Summary of SAEs with an outcome of death
- Summary of all cause death

Appropriate listings of SAEs, AEs, AEs that led to discontinuation and AEs leading to death will be presented. Non-TEAEs will be included in the listing. Listings of the details of all deaths will also be presented.

6.6.2. Laboratory Data

Laboratory data for hematology and clinical chemistry and other satefy laboratory tests will be summarized as described in Section 5.2 by study visit for observed values and for the corresponding change from baseline (CFB) values. Frequencies of potentially clinically significant values occurring during the clinical study will also be presented (hematology and clinical chemistry). Potentially clinically significant criteria are outlined in Section 9.3.

Shifts from low, normal, and high relative to the normal range between baseline and each post-baseline time point will be evaluated for hematology and clinical chemistry laboratory parameters. For urinalysis, shifts from negative (or normal), trace and positive will be tabulated. Arterial Blood Gas (ABG) results, where available, will be summarized and listed.

In addition, a summary table will be presented which will indicate the number of subjects who separately meet the laboratory criteria for potential Hy's Law after the start of study treatment at any time up to the EOT visit and up to the LFU visit: The AST, ALT, total bilirubin and ALP elevations can occur at any time in the specific review period and do not need to occur simultaneously.

A listing of participants with elevations in any one of the AST, ALT, Total bilirubin parameters will be also presented. ie, Participants with a value of $\geqslant$3xULN (upper limit of normal range) for ALT or AST or a value of $\geqslant$2xULN for Total bilirubin. This listing will contain all the ALT, AST, Total bilirubin and ALP study data for such participants.

Listings of values for each participant will be presented with abnormal or out-of-range values flagged. Local laboratory test values will be listed for each patient.

6.6.3. Vital Signs

Vital signs will be summarized for the observed values and for the corresponding CFB values at each applicable visit by treatment group.

Vital signs for all participants will be listed.

6.6.4. Physical Examination

The numbers and percentage of subjects with an abnormal complete physical exam assessment for each body system will be displayed by scheduled visit. All the physical examination data will be listed.

6.6.5. Extent of Exposure and Compliance

Exposure (in days) to study drug during the treatment period will be summarized by treatment group for the safety analysis set.

Compliance over the whole treatment period for each drug will be calculated as follows:

$$\text{Compliance} = \frac{\text{Actual Number of Doses Received}}{\text{Planned Number of Doses}} * 100$$

The planned number of doses can be counted based on the total number of planned doses recorded in the CRF.

A participant is considered compliant if between 80% and 120% of the planned number of doses is received. Interruption in therapy is considered non-compliance only if the compliance criteria described above is not met. For the BAT treatment, the compliance can be calculated for each drug separately using above method. In the combination therapy of BAT treatment, any of the drug in the combination that meet <80% or >120% criteria will be considered non-compliance of that participant.

Considering there are multiple drugs in BAT, the compliance of each participant will be categorized as 4 categories, <80%, ≥ 80% to 120%, >120% and "both <80% and >120%". Each drug from a combination therapy meeting <80%, ≥ 80% to 120%, or >120% will be categorized first for a participant. If one drug of the combination therapy has compliance <80%, in the meantime, another drug has compliance >120%, then the participant will be categorized to "both <80% and >120%". Only when compliance for all drugs of the combination therapy meet "≥ 80% to 120%", a participant will be categorized into this category.

The compliance will be summarized in the following four categories by the number and percentage of participants in each treatment group:

- <80% (i.e. <80% in CAZ-AVI group, <80% for any drug of the combination therapy in BAT group)
- ≥ 80% to 120% (i.e. ≥ 80% to 120% in CAZ-AVI group, ≥ 80% to 120% for all drugs of the combination therapy in BAT group)
- >120% (i.e. >120% in CAZ-AVI group, >120% for any drug of the combination therapy in BAT group)

- both <80% and >120% (i.e. both <80% and >120% non-compliant issues occurred for different drugs of the combination therapy in BAT group)

6.7. COVID-19 related analyses

In addtion to the above planned sensitivity analyses in Section 6.1.2 regarding COVID-19 impact to the primary endpoint, the analyses specified below will also be provided to reflect the impact of COVID-19 pandemic.

Protocol deviations related to COVID-19 will be listed. The discontinuations from study or study drug due to COVID-19 will be summarized. And the treatment emergent COVID-19 related adverse events will be summarized by SOC and PT.

7. INTERIM ANALYSES

7.1. Introduction

The study is anticipated to have a long recruitment duration, and therefore an interim analysis will be performed prior to the CAZ-AVI license renewal application in China. 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.

7.2. Interim Analyses and Summaries

For development of the interim analysis report, the study database will be cleaned and a snapshot of the database will be created. Final unblinded tables, figures and listings (TFLs), and interim report will be produced using snapshot data by unblinded statistician and programmer(s).

Considering the small number of participants included in the interim analysis, in addition to the general analyses planned in above sections, more specifications are described below.

For the subgroup efficacy summaries by infection site, the response rate will be presented by treatment and the difference between the treatments, but the corresponding CIs will not be included due to the small number of participants in each infection site.

The efficacy summaries that will be generated based on the ME analysis set will only be displayed for the overall participants without broken down by infection site since the ME analysis set will contain fewer participants than the primary mMITT analysis set.

Considering the data for per-pathogen microbiological response will be very sparse, the interim analysis for per-pathogen microbiological response will only be summarized with overall participants using the mMITT analysis set.

8. REFERENCES

1. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical Science 2001, 16 (2):101-117.

2. Cai TT. One-sided confidence intervals in discrete distributions. J Stat Plan Inference 2005;131(1):63-68.

3. Miettinen OS, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213-226.

9. APPENDICES

9.1. Appendix 1. Summary of Efficacy Analyses

Endpoint/Variable	Analysis Set	Statistical Method	Timepoint	Objective	Estimand
Clinical Cure (adjudicated)	mMITT	Summary of Proportion 95% CI for Response Rate Difference and 95% CI between Treatment Arms	TOC	Primary Endpoint	E1
Clinical Cure (per investigator's assessment)	mMITT	Summary of Proportion 95% CI for Response Rate Difference and 95% CI between Treatment Arms	TOC	Sensitivity Analysis to Primary Endpoint	E1
Clinical Cure (adjudicated)	ME	Summary of Proportion 95% CI for Response Rate Difference and 95% CI between Treatment Arms	TOC	Secondary Endpoint	E1
Clinical Cure (adjudicated)	mMITT and ME	Summary of Proportion 95% CI for Response Rate Difference and 95% CI between Treatment Arms	EOT	Secondary Endpoint	E1
Per-participant Microbiologic Response	mMITT and ME	Summary of Proportion 95% CI for Response Rate Difference and 95% CI between Treatment Arms	EOT and TOC	Secondary Endpoint	E2
All-cause mortality	ITT	Summary of Proportion 95% CI for mortality Difference and 95% CI between Treatment Arms	TOC and Day 28	Secondary Endpoint	E3

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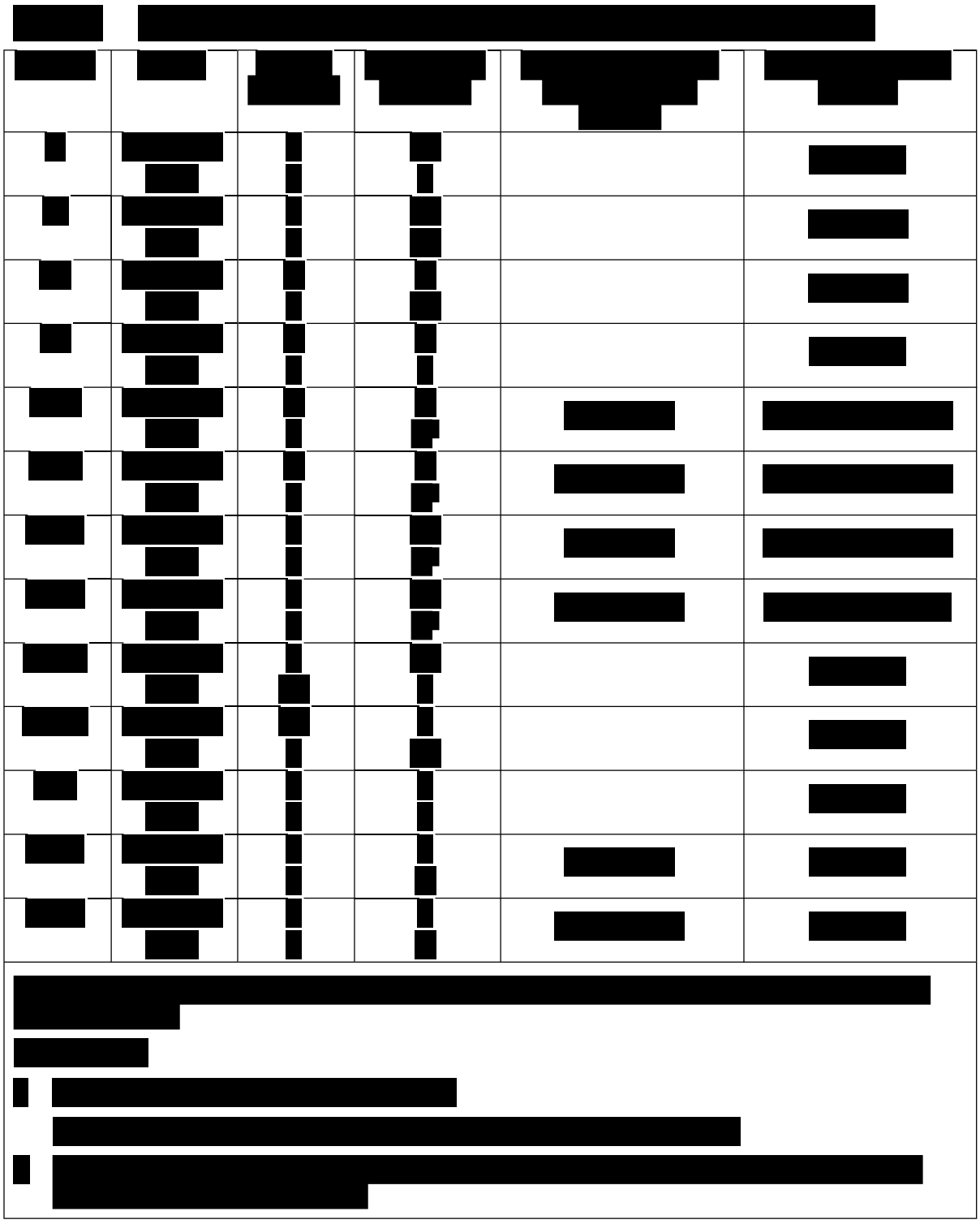

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9.3. Appendix 3. Criteria for Potentially Clinically Significant Lab Results

Table 7. HEMATOLOGY

	PCS Low Decrease; if both Below LLN and % Decrease from Baseline		PCS High Increase: if both Above ULN and % Increase from Baseline	
Parameter	**Lower Limit**	**% decrease from baseline**	**Upper Limit**	**% increase from baseline**
Hemoglobin	< 0.8 × LLN	> 20%	> 1.3 × ULN	> 30%
Hematocrit	< 0.8 × LLN	> 20%	> 1.3 × ULN	> 30%
Erythrocyte count (RBC)	< 0.8 × LLN	> 20%	> 1.3 × ULN	> 30%
Leukocytes (WBC)	< 0.65 × LLN	> 60%	> 1.6 × ULN	> 100%
Neutrophils	< 0.65 × LLN	> 75%	> 1.6 × ULN	> 100%
Lymphocytes	< 0.25 × LLN	> 75%	> 1.5 × ULN	> 100%
Eosinophils	N/A	N/A	> 4.0 × ULN	> 300%
Monocytes	N/A	N/A	> 4.0 × ULN	> 300%
Basophils	N/A	N/A	> 4.0 × ULN	> 300%
Platelets count	< 0.65 × LLN	> 50%	> 1.5 × ULN	> 100%

LLN = lower limit of normal range provided by the local laboratory; ULN = upper limit of normal range provided by the local laboratory; RBC = red blood cell; WBC = white blood cell; N/A = not applicable.

Table 8. CHEMISTRY

	PCS Low Decrease; if both Below LLN and % Decrease from Baseline		PCS High Increase: if both Above ULN and % Increase from Baseline	
Parameter	**Lower Limit**	**% decrease from baseline**	**Upper Limit**	**% increase from baseline**
Bicarbonate	< 0.7 × LLN	> 40%	> 1.3 × ULN	> 40%
Sodium	< 0.85 × LLN	> 10%	> 1.1 × ULN	> 10%
Potassium	< 0.8 × LLN	> 20%	> 1.2 × ULN	> 20%
Phosphorus	< 0.5 × LLN	> 50%	> 3.0 × ULN	> 200%
Chloride	< 0.8 × LLN	> 20%	> 1.2 × ULN	> 20%
Calcium	< 0.7 × LLN	> 30%	> 1.3 × ULN	> 30%
Alkaline phosphatase	< 0.5 × LLN	> 80%	> 2.0 × ULN	> 100%
ALT	N/A	N/A	> 3.0 × ULN	> 200%
AST	N/A	N/A	> 3.0 × ULN	> 200%
Gamma-glutamyl transferase	N/A	N/A	> 3.0 × ULN	> 200%
Total bilirubin	N/A	N/A	> 2.0 × ULN	> 150%
Direct bilirubin	N/A	N/A	> 2.5 × ULN	> 150%
Glucose, fasting	< 0.6 × LLN	> 40%	> 3.0 × ULN	> 200%
Glucose, nonfasting	< 0.6 × LLN	> 40%	> 3.0 × ULN	> 200%
Total protein	< 0.5 × LLN	> 50%	> 1.5 × ULN	> 50%
Albumin	< 0.5 × LLN	> 50%	> 1.5 × ULN	> 50%
Creatinine	N/A	N/A	> 2.0 × ULN	> 100%
Urea nitrogen (BUN)	< 0.2 × LLN > 200%	> 100%	> 3.0 × ULN	> 200%

LLN = lower limit of normal range provided by the local laboratory; ULN = upper limit of normal range provided by the local laboratory; N/A = not applicable; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.

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9.5. Appendix 5. List of Abbreviations

Abbreviation	Term
ABG	arterial blood gas
AE	adverse event
ALP	llkaline phosphatase
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
BAL	bronchalveoloar lavage
BAT	best available treatment
BSI	bloodstream infection
BUN	blood urea nitrogen
CAZ-AVI	ceftazidime-avibactam
CDARS	Clinical Data Analysis and Reporting System
CFB	change from baseline
CFU	colony-forming unit
CI	confidence interval
cIAI	complicated intra-abdominal infection
CR	carbapenem-resistant
CR BSI	catheter related BSI
CrCl	creatinine clearance
cUTI	complicated urinary-tract infection
EOT	end of treatment
HAP	hospital-acquired pneumonia
HLGT	High-Level Group Terms
HLT	High-Level Terms
IRC	internal review committee
ITT	intent-to-treat
IV	intravenously
LFU	late follow up
LLN	lower limit of normal range
LPF	low power field
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimun inhibitory cocentration
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to treat
N/A	not applicable
NG	no growth
PCS	Potentially clinically significant
PSB	protected-specimen brush
PT	Preferred Term
RBC	red blood cell
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SAS	safety analysis set
SD	Standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, listings
TOC	test of cure
ULN	upper limit of normal range
VAP	ventilator-associated pneumonia
WBC	white blood cell