Protocol C3591026

A SINGLE ARM, OPEN-LABEL, MULTI-CENTER, INTERVENTIONAL STUDY EVALUATING THE EFFICACY AND SAFETY OF CEFTAZIDIME-AVIBACTAM (CAZ-AVI) IN CHINESE ADULTS WITH HAP (INCLUDING VAP)

Statistical Analysis Plan (SAP)

Version: 2

Date: 22 May 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 06 Nov 2020	Original 08 Sep 2020	N/A	N/A
2 22 May 2023	Amendment 1 07 Feb 2022	Add impact assessment of COVID-19 and remote TOC visits and related sensitivity analysis. Add COVID-19 related analyses. CCI [redacted]. Made some clarifications on MITT analysis set, baseline definitions and compliance calculation.	• Section 3.2.1: added definitions of baseline pathogens. • Section 3.4.1: deleted the baseline variables that cannot be derived in this study due to data limitations. • Section 4: made clarifications on the minimum disease requirements for MITT 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. CCI [redacted]. • Section 6.6.5: made clarifications on the treatment compliance calculation. • Section 6.7: added COVID-19 related analysis. • Appendix 4: added example SAS code.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data to be collected in Study C3591026. 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 clinical response to CAZ-AVI in HAP patients.	• Using a composite estimand strategy to estimate the clinical response rate at the test of cure (TOC) visit in participants who meet minimum disease requirements. Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before TOC visit where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering treatment with further antibiotics will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and TOC visit inclusive, development of infectious complications	• The proportion of participants with clinical cure at the TOC visit in the clinically modified intent-to-treat (cMITT) population.

Objectives	Estimands	Endpoints
	of pneumonia after Day 2 until TOC visit triggering treatment with further antibiotics will be regarded as failure clinical response.	
Secondary:	**Secondary:**	**Secondary:**
• To estimate clinical response to CAZ-AVI in HAP patients, and HAP patients with demonstrated Gram-negative pathogens.	• Using a composite estimand strategy to estimate the clinical response rate at the end of treatment (EOT) visit in participants who meet minimum disease requirements, and at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens. Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before EOT visit (or TOC visit accordingly) where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering further antibiotics treatment will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and EOT visit (or TOC visit accordingly) inclusive, development of infectious complications of pneumonia after Day 2 triggering further antibiotics treatment will be regarded as failure clinical response.	• The proportion of participants with clinical cure at the EOT visit in cMITT population, and at the EOT, TOC visits in the microbiologically modified intent-to-treat (mMITT) population.
• To estimate the microbiologic response to CAZ-AVI.	• Using a composite estimand strategy to estimate the per-patient and per-pathogen microbiological response rate at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens. Microbiological response will be categorized as favorable (ie, eradication, or presumed eradication), unfavorable (persistence, persistence with increasing minimum inhibitory concentration [MIC], or presumed persistence), and indeterminate. Per-pathogen microbiological response will be summarized with the proportion of participants achieving favorable response by baseline pathogen type; per-patient microbiological response will be summarized with the proportion of participants achieving overall favorable response (ie, favorable for each of the baseline pathogen isolate). Intercurrent events of death or identification of an infectious complication of pneumonia triggering further antibiotics treatment such that an adequate source specimen is not available to culture will be regarded as an indeterminate microbiological response if clinical response is indeterminate, and will be regarded as a presumed eradication if a clinical cure is assessed.	• The proportion of participants with the favorable per-patient microbiologic response at the EOT and TOC visits in the mMITT population. • The proportion of favorable per-pathogen microbiologic responses at the EOT and TOC visits in the mMITT population.
• To estimate the efficacy of CAZ-AVI in patients with pathogens resistant to ceftazidime.	• Using the same composite estimand strategies as the primary estimand and aforementioned secondary estimands to estimate the proportions of participants with clinical cure and with a favorable per-patient microbiological response at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens that are resistant to ceftazidime.	• The proportion of participants with clinical cure, and proportion of participants with favorable per-patient microbiologic response at the EOT and TOC visits in participants with pathogens resistant to ceftazidime in the mMITT population.

Objectives	Estimands	Endpoints
• To estimate all-cause mortality for CAZ-AVI.	• Using a treatment-policy estimand strategy in participants who meet minimum disease requirements, and in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens to estimate the proportion of participants with death at the TOC visit and Day 28 of the study. Any death that occurred after the first dose of study intervention through the nominal analysis timepoint will be included. A participant with the last known survival status that is before the nominal analysis timepoint or missing at the nominal analysis timepoint will be reported as an unknown status.	• The proportion of participants with death due to any cause (all-cause mortality) at the TOC visit and at Day 28 in the cMITT and mMITT populations.
• To evaluate the safety and tolerability of CAZ-AVI.	• N/A.	• Assessment of treatment-emergent adverse events (TEAEs) and safety-related clinical laboratory tests and vital observations.

2.1.1. Primary Estimand (E1)

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

- Population: Patients who have hospital-acquired pneumonia (HAP);
- Variable: Clinical response per investigator's assessment at the TOC visit. Clinical response will be categorized as cure, failure, and indeterminate. Intercurrent events of death on study Day 1 or Day 2, death on or before TOC visit where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering treatment with further antibiotics will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and TOC visit inclusive, development of infectious complications of pneumonia after Day 2 until TOC visit triggering treatment with further antibiotics will be regarded as failure clinical response;
- Intercurrent event: The intercurrent events are addressed as part of the variable definition;
- Population-level summary: The proportion of participants with clinical cure at the TOC visit.

2.1.2. Secondary Estimand(s)

2.1.2.1. Estimand for Clinical Response (E1)

The primary estimand E1 will be used. The proportion of participants with clinical cure at the EOT and TOC visits will be the analysis variables.

2.1.2.2. Estimand for Microbiologic Response (E2)

The secondary estimand for microbiologic response will use the composite policy strategy to estimate the per-patient and per-pathogen microbiological response rate to CAZ-AVI accounting for both treatment adherence and response. 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 who have hospital-acquired pneumonia (HAP) and have demonstrated Gram-negative pathogens;
- Variable: The per-patient and per-pathogen 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 or identification of an infectious complication of pneumonia triggering further antibiotics treatment such that an adequate source specimen is not available to culture will be regarded as an indeterminate microbiological response if clinical response is indeterminate, a presumed persistence if a clinical failure is assessed and a presumed eradication if a clinical cure is assessed.
- Intercurrent event: The intercurrent events are addressed as part of the variable definition;
- Population-level summary: Per-pathogen microbiological response will be summarized with the proportion of participants achieving favorable response by baseline pathogen type; per-patient microbiological response will be summarized with the proportion of participants achieving overall favorable response (ie, favorable for each of the baseline pathogen isolate).

2.1.2.3. Estimand for Efficacy in Patients with Pathogens Resistant to Ceftazidime (E3)

Using the same composite estimand strategies as the primary estimand and aforementioned secondary estimands to estimate the proportion of participants with clinical cure and with a favorable per-patient microbiological response at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens that are resistant to ceftazidime.

2.1.2.4. Estimand for All-cause Mortality (E4)

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 who have hospital-acquired pneumonia (HAP);
- Variable: Death due to any cause at the TOC visit and Day 28;

- Intercurrent event: Identification of an infectious complication of pneumonia triggering further antibiotics treatment will not impact the analysis. Any death that occurred after the first dose of study intervention through the nominal analysis timepoint will be included.

- Population-level summary: The proportion of participants with death due to any cause at the TOC visit and Day 28.

CCI [redacted].

2.2. Study Design

This is a single arm, multi-center interventional study evaluating the effectiveness and safety of CAZ-AVI in Chinese adults with HAP (including VAP).

Approximately 235 participants will be enrolled. Each participant is expected to complete the study, including follow-up, within approximately 6 weeks. The study intervention will be administered IV for a minimum of 7 days and a maximum of 14 days. Participants must receive the study intervention for at least 7 days. At any time after 7 days, the investigator will have the option to continue the study intervention or discontinue the study intervention completely.

The participant is to return to the study center for the scheduled visits following discharge from the hospital. An overall clinical assessment, vital sign measurements, ventilation status and detailed pulmonary assessment will be performed at Day 1 (baseline), daily during treatment with IV therapy, and at the EOT, and TOC (21 to 25 calendar days from enrollment) visits. In addition to these visits, death and AEs will be assessed until the final protocol follow up (FPFU) visit (28 to 32 calendar days after the last dose of CAZ-AVI). The FPFU visit may be conducted either in person or by telephone contact (Figure 1).

Figure 1. Study Outline

Baseline Visit	Treatment with IV therapy (Day 1 - 14)	EOT visit within 24 hours after the last infusion	TOC visit Day 21 - 25 after enrollment	FPFU visit Day 28 - 32 after the last dose of CAZ-AVI

- The proportion of participants with clinical cure at the TOC visit in the cMITT population.

3.1.1. Clinical Response

Clinical response outcome assessments will be assigned to each participants by the investigator at the EOT and TOC visits Table 2 and Table 3 respectively). Clinical response will be classified as clinical cure, clinical failure, or indeterminate based on clinical outcome. A clinical failure occurring at an earlier time point (eg, EOT) will be carried forward to the TOC visit. If the clinical response at the TOC visit is missing, it will be considered as being indeterminate unless there was a previous clinical failure, in which case the clinical response will be considered as clinical failure at the TOC visit.

Table 2. Definitions of Clinical Response at the EOT Visit

Clinical response	Definition
Clinical Cure	Participants will be considered to be a cure for clinical response if: • The participant is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for HAP/VAP are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for HAP[a] prior to EOT.
Clinical Failure	Participants who meet any 1 of the following criteria will be considered to be a failure for clinical response: • Mortality due to HAP/VAP between Day 3 of study intervention and the EOT visit inclusive. • Incomplete clinical resolution or worsening of HAP-specific signs and symptoms that requires additional antibacterial therapy for HAP at or before EOT. • Development of infectious complications of pneumonia such as empyema or lung abscess after Day 2.
Indeterminate	Participants who meet any 1 of the following criteria will be considered to be indeterminate for clinical response: • Participant lost-to-follow-up or assessment is not undertaken, such that a determination of clinical response cannot be made. • Death on or before the date of the EOT visit where HAP is clearly non-contributory. • Death on study Day 1 or Day 2. • Identification of an infectious complication of pneumonia such as empyema or lung abscess between Day 1 and Day 2 inclusive.

a. In addition to protocol-allowed antibacterial therapy with study drug and open-label empiric linezolid and aminoglycoside, narrow-spectrum Gram-positive agents (ie, agents without Gram-negative coverage - eg, linezolid, vancomycin) and metronidazole (or any other antibiotic active solely against anaerobes) initiated after enrollment for HAP are permitted (ie, do not constitute a clinical failure), but must not continue past EOT.

Table 3. Definitions of Clinical Response at the TOC Visit

Clinical response	Definition
Clinical Cure	Participants will be considered to be a cure for clinical response if: • The participant was not a clinical failure at EOT, and the participant is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for HAP was taken between EOT and TOC inclusive.
Clinical Failure	Participants who meet any 1 of the following criteria will be considered to be a failure for clinical response: • Designated as a clinical failure at an earlier time point (eg, EOT). • Mortality due to HAP between Day 3 of study intervention and the TOC visit inclusive. • Persistence, incomplete clinical resolution, worsening or recrudescence of HAP-specific signs and symptoms that requires initiation of antibacterial therapy for HAP between EOT and TOC, inclusive. • Development of complications of HAP such as empyema or lung abscess at or before the TOC visit.
Indeterminate	Participants who meet any 1 of the following criteria will be considered to be indeterminate for clinical response: • Participant lost-to-follow-up on or before the TOC visit or the assessment is not undertaken, such that a determination of clinical response cannot be made. • Death on or before the date of TOC visit where HAP is clearly non-contributory. • Death on study Day 1or Day 2 inclusive. • Identification of an an infectious complication of pneumonia such as empyema or lung abscess between Day 1 and Day 2 inclusive.

3.2. Secondary Endpoint(s)

- The proportion of participants with clinical cure at the EOT visit in cMITT population, and at the EOT, TOC visits in the mMITT population.
- The proportion of participants with the favorable per-patient microbiologic response at the EOT and TOC visits in the mMITT population.
- The proportion of favorable per-pathogen microbiologic responses at the EOT and TOC visits in the mMITT population.
- The proportion of participants with clinical cure, and proportion of participants with favorable per-patient microbiologic response at the EOT and TOC visits in participants with pathogens resistant to ceftazidime in the mMITT population.

- The proportion of participants with death due to any cause (all cause mortality) at the TOC visit and at Day 28 in the cMITT and mMITT populations.

- Assessment of TEAEs and safety-related clinical laboratory tests and vital observations.

3.2.1. Microbiological Response

Baseline respiratory cultures will be obtained within 48 hours prior to Day1 and after development of signs and symptoms of HAP (ideally before receipt of any systemic antibiotics). For cases that there are multiple respiratory cultures, the baseline respiratory culture is defined as the last respiratory culture obtained via BAL, mini BAL or PBS prior to Day 1. If BAL, mini BAL or PBS specimens are not available, the baseline respiratory culture will be defined as the last respiratory culture obtained via endotracheal aspirate prior to Day 1. If none of these are available, the baseline culture is defined as the last sputum culture obtained prior to Day 1.

Baseline blood cultures will be defined as all the cultures ontained within 24 hours prior to Day 1.

All the pathogens identified from the baseline respiratory cultures and the baseline blood cultures will be treated as baseline pathogens.

Baseline microbiology susceptibility for each baseline pathogen is defined as the result with the highest MIC value or the worst susceptibility if no MIC value available.

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. Data from local lab will be used only if the microbiology tests were not done in the central lab.

Microbiological response at the EOT and TOC visits will be assessed based on the pathogens isolated at baseline and during the course of treatment or the post-treatment period in the mMITT population. Microbiological response will be assessed per-pathogen and per-patient (overall) according to the definitions as provided below.

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”. “Super infection” and “new infection” will be considered separately.

3.2.1.1. Per-Pathogen Microbiological Response

The per-pathogen microbiological response will be categorized according to the following definitions presented in Table 4 for each baseline pathogen . Per-pathogen response will be derived for the pathogens seen in either respiratory sample or blood samples, and will also be derived separately for pathogens seen only in the blood sample. Appendix 2 contains a

clarification of the definitions in these 2 ways, based upon example scenarios following a particular pathogen "X" appearing in either the respiratory sputum sample or the blood sample.

Table 4. Microbiological Response Categories

Microbiological response[a]	Definition
Eradication	An adequate source specimen[b] demonstrates absence of the original baseline pathogen.
Presumed eradication	An adequate source specimen[b] was not available to culture and the participant was assessed as a clinical cure.
Persistence - Persistence with increasing MIC[c]	Adequate source specimen[b] demonstrates continued presence of the original baseline pathogen. Continued presence of the causative organism in a culture of the respiratory infection obtained during or upon completion of treatment with IV study intervention, and the pathogen that was susceptible to IV study intervention pre-treatment displays a ≥4-fold higher MIC to IV study intervention after treatment with IV study intervention.
Presumed persistence	An adequate source specimen[b] was not available to culture and the participant was assessed as a clinical failure.
Indeterminate	An adequate source specimen[b] was not available to culture and the participant's clinical response was assessed as indeterminate.

a. The microbiological outcome will be determined from cultures obtained at the EOT and TOC visit window respectively.
b. When assessing a respiratory sputum sample, an adequate source specimen is required - any sample that may yield the growth of pathogen eg, blood, respiratory specimens, or pleural fluid.
c. 'Persistence with increasing MIC' is a subset of 'persistence'.

- For the per-pathogen response in respiratory site or blood, the pathogens observed in respiratory or blood samples are "pooled", so that a follow-up pathogen observed in either culture source would count as persistence.

- Once persistence, persistence with increasing MIC, or presumed persistence is experienced for a pathogen (at or beyond EOT) it will be carried forward to any later visits with a favorable or indeterminate response.

- Once eradication is observed for a blood pathogen, no further blood samples would be expected, and therefore the eradication will be carried forward to later visits with no blood sample collected.

An adequate sputum sample is defined as follows:

- From expectorated or induced sputum, an adequate sample is one with <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per low-power field upon a Gram stain; throat secretions are considered to be inadequate; all other specimens (endotracheal aspirate, BAL, mini-BAL, PBS) are considered to be adequate.

3.2.1.2. Per-Patient Microbiological Response

Per-patient (overall) microbiological response at the EOT and TOC visits will be determined based on individual outcomes for each baseline pathogen, including those from respiratory and blood samples.

For participants from whom only 1 causative pathogen is isolated, the overall microbiological response will be based on the microbiological response assessment for that pathogen. For participants from whom more than 1 baseline pathogen is isolated, the overall microbiological response (patient-level) will be favorable only if the microbiological response for each of the baseline pathogens isolated is favorable. The overall microbiological response will be unfavorable if any one of the baseline pathogens is unfavorable. The overall microbiological response will be indeterminate in all other situations.

3.2.1.3. MIC Among Pathogens

The CAZ-AVI MIC categories that will be used are: ≤0.008, 0.015, 0.03, 0.06, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256 and >256 µg/mL. For ceftazidime MIC categories that will be used are: ≤0.03, 0.06, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and >128 µg/mL. All categories above 32 µg/mL will be grouped as ">32" in summary tables. For the purposes of this study, MICs reported as 0.06 and 0.12 µg/ml are equivalent to 0.0625 and 0.125 µg/ml respectively. If a patient has more than 1 isolates tested for the same pathogen species, the highest MIC value to CAZ-AVI for that pathogen will be selected.

3.2.2. Emergent Infections

Pathogens first appearing after baseline in participants with a baseline pathogen are categorized in Table 5 and will be summarized separately.

Table 5. Emergent infections

Emergent infection	Definition
Super-infection	Emergence of new pathogen from any specimen[a] during treatment with study therapy associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics.
New infection	Emergence of new pathogen from any specimen[a] after completion of study therapy associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics.

a. When assessing a respiratory sputum sample, an adequate source specimen is required.

3.2.3. All-cause Mortality

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

Mortality at TOC

For each analysis set, the number of participants who died up to the TOC visit will be calculated as the number of participants with a date of death on or before the end of the TOC visit window (Day 25). Participants who have died after Day 25 will be excluded from the death count at the TOC visit and will be assumed to be alive at the TOC visit. If there is no record of a patient's death and they attended the TOC visit, or if the patient is known to be alive after Day 25, then they will be considered to be alive at the TOC visit. Participants who withdrew from the study before attending the TOC visit will be considered to have "unknown" mortality status, unless further information is available (eg, date of death).

Mortality at Day 28

For each analysis set, the number of participants who died up to the Day 28 will be calculated as the number of participants with a date of death on or before Day 28. Participants who have died after Day 28 will be excluded from the death count at the Day 28 and will be assumed to be alive at Day 28. If there is no record of a patient's death and they attended the FPFU visit, or if the patient is known to be alive after Day 28, then they will be considered to be alive at Day 28. Participants who withdraw from the study before attending the FPFU visit will be considered to have "unknown" mortality status, unless further information is available (eg, date of death).

CCI [redacted]

3.4. Baseline Variables

Baseline varaibes are defined as the last non-missing values observed before treatment begins unless otherwise specified.

3.4.1. Subgroup Analysis Variables

The following baseline variables will be used in the subgroup analyses for primary efficacy endpoint of clinical cure rate in the cMITT population.

- Type of infection (Non-VAP and VAP).
- Baseline severity of disease (via APACHE II score) (10-19, 20-30).
- Ventilated or non-ventilated at baseline.

  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.

- Type of infection will be further considered by assessment of early- and late-VAP (among the VAP participants; VAP development on day 3 or 4 of hospitalisation defines 'early'; and VAP development on or after day 5 of hospitalisation defines 'late').
- Prior systemic antibiotic use (yes/no)

  Note: 'yes' if the patient is considered to be 'exposed' to prior antibiotic therapy within 2 days before randomization.

- Monomicrobial or polymicrobial infection (or no pathogen).

  Note: Mostly, type of microbial infection will be derived from the baseline sputum culture result. If more than one pathogen is isolated from the baseline sputum culture result, then the microbial type would be considered as polymicrobial. Otherwise, the microbial type would be considered as monomicrobial. However, if other (ie, blood) culture results occur to show additional pathogen(s) different from sputum culture results by which participants are considered monomicrobial, then these participants will be overridden as polymicrobial.

- Bacteremic at baseline (yes/no).

  Note: If a bacterial pathogen is reported from the baseline blood culture results, regardless of whether the same pathogen is found in the baseline sputum culture or not, the patient would be designated as "bacteremic at baseline". Otherwise, the patient would be considered as "not bacteremic at baseline".

- Age (18-45; 46-64; 65-74; 75-90).
- Gender (male, female).
- Renal function category at baseline (CrCl 16-50 mL/min, CrCl 51-150 mL/min, CrCl 151+ mL/min).

3.4.2. Other Baseline Variables

Demographic and baseline characteristics include the following (besides above variables that will be used for subgroup analysis):

- Age (years);
- Medical history;
- Height (cm);
- Weight (kg);
- Body mass index (BMI) [kg/m^2];
- BMI category (<18.5, 18.5 - <25, 25 - <30, ≥30);
- APACHE II score;
- Number of prior systemic antibiotic use (1 antibiotic, 2 antibiotics, 3 or more antibiotics);
- Baseline pathogens;
- Estimated creatinine clearance (CrCl) [mL/min];
- Gram stain (G+ alone, G- alone, or G-mixed (ie, both + and -)).

3.5. Safety Endpoints

The safety endpoints of this study are:

- Incidence of adverse events by study period: treatment period [from first dose to EOT] and for the full study period [from first dose to FPFU];
- 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.

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 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 unblinding and releasing the database and classifications will be documented per standard operating procedures.

Participant/Defined 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.
Modified Intent-to-Treat (MITT) Analysis Set	It will consist of all enrolled participants who have minimum disease criteria[a] and receive any amount of study intervention.
clinical Modified Intent-to-Treat (cMITT) Analysis Set	This is a subset of the MITT analysis set, and will include participants: • whose (properly obtained) baseline respiratory or blood cultures demonstrate Gram-negative pathogens with or without concomitant Gram-positive pathogens (excluding participants with Gram-negative pathogens not expected to respond to either study intervention [ie, participants with only the following monomicrobial Gram negative infections: any of the *Acinetobacter* species; or any *Legionella* species; or *Stenotrophomonas maltophilia*; or *Elizabethkingia meningoseptica*]); OR • participants in whom no etiologic pathogens are identified from respiratory or blood cultures at baseline.
microbiological Modified Intent-to-Treat (mMITT) Analysis Set	It is a subset of the MITT analysis set, and will include participants: who have a properly obtained respiratory culture demonstrating Gram-negative pathogens, excluding participants not expected to respond to CAZ-AVI (ie, participants with only the following monomicrobial Gram-negative infections: any of the *Acinetobacter* species; or any *Legionella* species; or *Stenotrophomonas maltophilia*; or *Elizabethkingia meningoseptica*). If baseline respiratory cultures are not available or do not identify a respiratory pathogen, but a Gram-negative organism known to cause pneumonia is identified from baseline blood cultures, the participant will qualify for the mMITT population.
Safety Analysis Set (SAS)	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

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

a. Minimum disease criteria for HAP will be determined based on the following inclusion criteria.

Inclusion Criteria 3:

Onset of signs and symptoms (including Inclusion Criteria 4, 6, and 7) ⩾48 hours after admission or <7 days after discharge from an inpatient acute or chronic care facility.

Inclusion Criteria 4:

New or worsening infiltrate on chest X-ray or CT scan obtained within 48 hours prior to screening.

Inclusion Criteria 6:

At least 1 of the following systemic signs:

- Fever (temperature >38°C) or hypothermia (rectal/core temperature <35°C)
- White blood cell (WBC) count >10,000 cells/mm3, or WBC count <4500 cells/mm3, or >15% band forms.

Inclusion Criteria 7:

At least 2 of the following respiratory signs or symptoms:

- A new onset of cough (or worsening of cough).
- Production of purulent sputum or endotracheal secretions.
- Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds, dullness to percussion, egophony).
- Dyspnea, tachypnea or hypoxemia (O2 saturation <90% or PaO2 <60 mmHg while breathing room air).
- A need for mechanical ventilation or, for already ventilated participants, acute changes made in the ventilator support system to enhance oxygenation, as determined by, for example arterial blood gas or worsening PaO2/FiO2.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This is an estimation study. No formal hypothesis testing will be performed for this study.

5.2. General Methods

All data will be presented for the single CAZ-AVI treatment arm. 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 corresponding 95% CIs for the response rates will be calculated using Jeffrey's method (Brown et al. 2001; Cai 2005).[1,2] Listings of individual participat data will also be produced.

Categorical and qualitative variable summaries for safety will include the frequency and percentage of subjects who are in the particular category. In general, the denominator for the

percentage calculation will be based upon the total number of participants in the cooresponding analysis population.

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

Per protocol, the investigors must continue to collect AEs and perform safety reporting responsibilities per protocol via telephone contact or other methods as appropriate if on-site vists interrupted by the COVID-19 pandemic. 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 categorized as "Visit was done remotely", 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 efficacy data, 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 the TOC visit in the cMITT population

- Estimand strategy: Composite policy strategy estimand E1 (Section 2.1.1).
- Analysis set: cMITT population (Section 4).
- Analysis methodology: Jeffrey's method (Brown et al. 2001; Cai 2005)[1,2] will be used to calculate the 95% CIs for the response rate (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 cMITT analysis population will be summarized. Clincial cure rate and the corresponding 2-sided 95% CI will be provided.
- Results will be listed together with the Phase 3 clinical study REPROVE to observe the consistency trend.

6.1.2. Sensitivity Analyses

A sensitivity analysis of clinical response at TOC visit 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 of clinical response at TOC visit will be performed by removing participants with remote TOC visits 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 the EOT Visit in cMITT Population, and at EOT, TOC Visits in the mMITT Population

- Estimand strategy: Composite policy strategy estimand E1 (Section 2.1.2.1).
- Analysis set: cMITT population and the mMITT population (Section 4).
- Analysis methodology: Jeffrey's method (Brown et al. 2001; Cai 2005)[1,2] will be used to calculate the 95% CIs for the response rate (Section 5.2).
- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.2.1), 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 EOT visit in the cMITT analysis population and at EOT and TOC visits in the mMITT population will be summarized. Clincial cure rate and the corresponding 2-sided 95% CI will be provided.

6.2.2. Microbiologic Response at the EOT and TOC visit

- Estimand strategy: Composite policy strategy estimand E2 (Section 2.1.2.2).
- Analysis set: mMITT population (Section 4).
- Analysis methodology: Jeffrey's method (Brown et al. 2001; Cai 2005)[1,2] will be used to calculate the 95% CIs for the per-patient and per-pathogen microbiological response rate (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 microbiological response at the EOT and TOC visits will be summarized. Per-pathogen microbiological response will be summarized with the proportion of participants achieving favorable response by baseline pathogen; per-patient microbiological response will be summarized with the proportion of participants achieving overall favorable response (ie, favorable for each of the baseline pathogen isolate). Per-patient and per-pathogen (if numbers permit) favorable microbiological response rate and the corresponding 2-sided 95% CI will be provided.

6.2.3. Clinical and Microbiologic Response in Participants with Pathogens Resistant to Ceftazidime

- Estimand strategy: Composite policy strategy estimand E3 (Section 2.1.2.3).
- Analysis set: the subpopulation of participants with pathogens resistant to ceftazidime in the mMITT population (Section 4).
- Analysis methodology: Jeffrey's method (Brown et al. 2001; Cai 2005)[1,2] will be used to calculate the 95% CIs for the clinical cure rate and the favorable per-patient microbiologic reponse rate (Section 5.2).
- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.2.3), the definition of clinical and microbiological response (Section 3.1.1 and Section 3.2.1) and methods to handle missing data (Section 5.4).
- The number and percent of participants having clinical cure, failure, and indeterminate and having favorable, unfavorable, and indeterminate microbiological response at the EOT and TOC visits will be summarized. Clincial cure rate and the per-patient favorable microbiological response rate and the corresponding 2-sided 95% CI will be provided.

6.2.4. 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.

6.2.5. All-Cause Mortality

- Estimand strategy: Treatment policy strategy estimand E4 (Section 2.1.2.4).
- Analysis set: Same analyses will be done in the cMITT and mMITT populations respectively (Section 4).
- Analysis methodology: Jeffrey's method (Brown et al. 2001; Cai 2005)[1,2] will be used to calculate the 95% CIs for the all-cause mortality (Section 5.2).
- Intercurrent events and missing data: These have been accounted for in the estimand (Section 2.1.2.4).
- The number and percent of participants with death due to any cause at the TOC visit and at Day 28 will be summarized. And the corresponding 2-sided 95% CI for all cause mortality will be provided.

6.2.6. Safey Endpoints

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

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6.4. Subset Analyses

Subset analyses will be performed for primary endpoint (clinical cure rate at TOC vist) for the subgroups as defined in Section 0 in the cMITT population.

The analysis described for the clinical cure rate at TOC visit in Section 6.1.1 will be done for each subgroup. A forest plot presenting all the subgroups may be presented for point estimate of the clinical cure rate and the corresponding 2-sided 95% CI.

The subgroup results will be compared with same subgroups in the REPROVE study. Due to different study times, operations, drug resistance, etc, the comparisons of results between this study and REPROVE study will not be subject to statistical comparison.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline patient and disease characteristics included in Section 3.4 will be summarized for the single CAZ-AVI treatment group in the cMITT and safety analysis set. Baseline disease characteristics will also be summarized for the mMITT analysis set.

Baseline microbiology will be summarized. The susceptibility profile and MIC frequency distributions to CAZ-AVI and ceftazidime 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 enrolled but are never treated, who complete the study up to the TOC visit, who complete the study up to the FPFU visit, who are withdrawn from the study treatment (CAZ-AVI) and who are withdrawn from the study, including reason for withdrawal, will be summarized for all participants.

The number of participants in each of the analysis sets (ie, MITT, cMITT, mMITT, safety) will be summarized.

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

All safety analyses will be performed 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, lab parameters (hematology, blood chemistry, and urinalysis), vital signs, discontinuations from study, discontinuations from treatment and treatment duration.

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

All TEAEs will be summarized separately for the study periods (treatment period [from first dose to the EOT visit] and for the full study period [from first dose to the end of study). TEAEs will be summarized by number and percent by system organ class (SOC) and preferred term (PT).

The following summaries for the CAZ-AVI treatment 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 for the CAZ-AVI treatment as following:

- Summary of TEAEs by system organ class and preferred term;
- Summary of TEAEs by system organ class and preferred term, split 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,

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 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 Appendix 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.

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 FPFU 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 ≥3xULN for ALT or AST or a value of ≥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 patient 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 for the single CAZ-AVI treatment group.

Vital signs for all participants will be listed.

6.6.4. Extent of Exposure and Compliance

Exposure to study drug during the treatment period will be summarized for the safety analysis set.

Exposure (in days) to study therapy will be summarized. In addition, the number of IV infusions and the number of each individual component of study therapy will be summarized by baseline renal status (categories based on CrCl as outlined in Section 0).

Descriptive statistics (number of patients, mean, SD, minimum, median and maximum value) of treatment compliance will be presented for CAZ-AVI treatment group using the cMITT and safety analysis sets.

Compliance over the whole treatment period 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 subject 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. Medication compliance will be summarized (n, mean, standard deviation, median, minimum and maximum). The compliance will also be summarized in the following categories: <80%, ≥ 80% to 120%, and >120% by the number and percentage of subjects.

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

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

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.

APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint/Variable	Analysis Set	Statistical Method	Timepoint	Objective	Estimand
Clinical Cure	cMITT	Summary of Proportion 95% CI for Response Rate	TOC	Primary Endpoint	E1
Clinical Cure	cMITT	Summary of Proportion 95% CI for Response Rate	EOT	Secondary Endpoint	E1
Clinical Cure	mMITT	Summary of Proportion 95% CI for Response Rate	EOT and TOC	Secondary Endpoint	E1
Microbiologic Response	mMITT	Summary of Proportion 95% CI for Response Rate	EOT and TOC	Secondary Endpoint	E2
Clinical Cure and Favorable Per-patient Microbiologic Response	participants with pathogens resistant to ceftazidime in the mMITT population	Summary of Proportion 95% CI for Response Rate	EOT and TOC	Secondary Endpoint	E3
Death	cMITT and mMITT	Summary of Proportion 95% CI for mortality	TOC and Day 28	Secondary Endpoint	E4

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Appendix 3. Criteria for Potentially Clinically Significant Lab Results

Table 8. 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 9. 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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Appendix 5. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	llkaline phosphatase
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
BAL	bronchalveoloar lavage
BMI	Body mass index
BUN	blood urea nitrogen
CAZ-AVI	ceftazidime-avibactam
CDARS	Clinical Data Analysis and Reporting System
CFB	change from baseline
CI	confidence interval
cMITT	clinical modified intent-to-treat
CrCL	creatinine clearance
EOT	end of treatment
FPFU	final protocol follow up
HAP	hospital-acquired pneumonia
HLGT	High-Level Group Terms
HLT	High-Level Terms
IV	intravenously
LLN	lower limit of normal range
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
PBS	Protected Brush Specimen
PCS	Potentially clinically significant
PT	Preferred Term
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	Standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TOC	test of cure
ULN	upper limit of normal range
VAP	ventilator-associated pneumonia
WBC	white blood cell