Non-Interventional Study Protocol
C3591037

Real-World Study of Ceftazidime-Avibactam to Characterize the Usage in Clinical Practice

Statistical Analysis Plan
(SAP)

Version: 1.0

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable.

2 INTRODUCTION

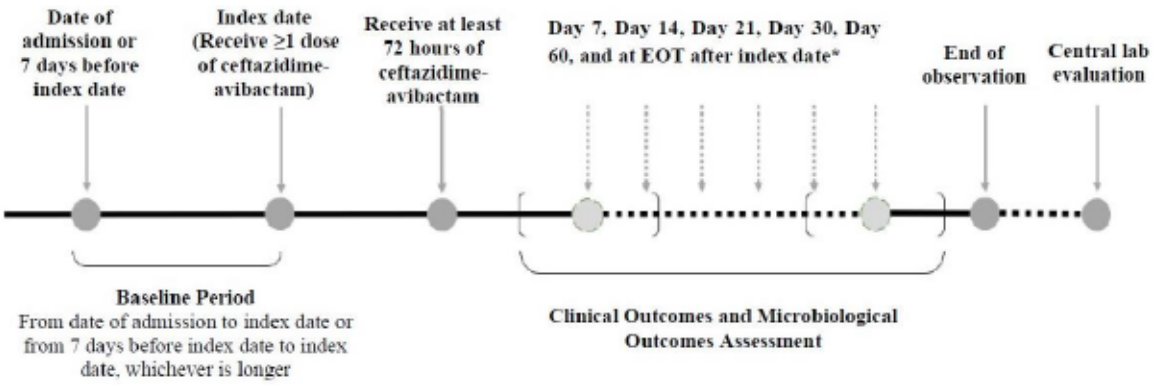
Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

Infections caused by multidrug-resistant gram-negative bacilli (MDR-GNB) and extensively drug-resistant gram-negative bacilli (XDR-GNB) can be difficult to treat and are associated with high morbidity, mortality, and increased medical burden. This constitutes a serious threat to public health that there is an urgent need of new antibiotic agents with activity against MDR-GNB. Considering the limited cases studied in the clinical trials and the increasing post-approval use of ceftazidime-avibactam in clinical settings, it is necessary to understand the real-world use of ceftazidime-avibactam focusing on treatment of XDR-GNB infection, with carbapenem-resistant Klebsiella pneumoniae (CRKP) as the most frequently reported pathogen.

2.1 STUDY DESIGN

This is a multicenter, observational study aiming to examine the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice at approximately 20 clinical research centers in China. Approximately 450 hospitalized patients receiving ≥1 dose of ceftazidime-avibactam from 01 July 2022 to 31 December 2022 will be enrolled. The recruitment will last for approximately 6 months or until recruitment target is met. Eligible patients are adult patients who have been treated with ≥1 dose of ceftazidime-avibactam during hospitalization. Each patient will be only included in the study once.

Medical information will be collected from the patients' medical records. Patients will be followed from the first dose of ceftazidime-avibactam until death, withdraw of the study, 60 days following hospital discharge, whichever comes first. The clinical outcomes and microbiological outcomes will be evaluated at: 7 days, 14 days, 21 days, 30 days, 60 days, and EOT after the first dose of ceftazidime-avibactam, if patients are not discharged prior to the next upcoming timepoint. The clinical and microbiological outcomes will be assessed by the investigator and recorded in case report form (CRF). The study data collection and assessment schedule are described in Figure 1. All assessments described in this non-interventional protocol are part of China clinical practice or treatment guidelines.



* Outcomes will be evaluated at each timepoint if patients are not discharged prior to the next upcoming timepoint. Three days identification window will be applied before and after each time points.

Figure 1 Study design

Study population:
Hospitalized patients treated with ≥1 dose of ceftazidime-avibactam at approximately 20 China clinical research centers. Patients will be followed from the first dose of ceftazidime-avibactam until death, withdraw of the study,60 days following hospital discharge, whichever comes first. The study will enroll approximately 450 in-patients treated with ceftazidime-avibactam.

Data source:
The study data source will be medical records from the clinical research centres and microbiological result from the central lab.
Pre-treatment microbiology sample and result, and post-treatment microbiology sample and result will be collected from laboratory records when available, and microbiological outcome and the failure reason.
The microbiological outcome and the failure reason will be obtained from central lab investigator assessment.

Treatment/cohort labels:
This is single arm study. The treatment label is "ceftazidime-avibactam".

2.2 STUDY OBJECTIVES

The main objective of this observational study is to describe the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice in China.
The primary objectives of this study are to:

- *Describe the clinical outcomes of patients (i.e., treatment success, failure, or indeterminate) at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at end of treatment (EOT) (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.*

- *Describe the microbiological outcomes of patients at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.*
- *Describe the real-world usage of ceftazidime-avibactam at clinical practice, including patient baseline characteristics, type of infection, source of infection, etc.*
- *Describe the microbiological features of isolated strains at baseline, including pathogen identification, distribution, susceptibility of ceftazidime-avibactam and other common antibiotic drugs including carbapenem-resistant organisms, and genotype characteristics of carbapenem-resistant organisms.*

The secondary objectives of this study are to:

- *Describe the antibiotic treatment administered to the enrolled patients, including the dosage, frequency, duration (start and end dates) of ceftazidime-avibactam, and combination medications with ceftazidime-avibactam.*
- *Describe the in-hospital length of stay (LOS), LOS in intensive care unit (ICU) and healthcare resource utilization in patients treated with ceftazidime-avibactam.*
- *Describe the readmission rate due to the recurrence of infection happened in the same location 30 and 60 days after discharge.*
- *Determine the in-hospital all-cause mortality.*

3 INTERIM ANALYSES

One interim analysis will take place for this study *once the clinical outcomes at end of treatment (EOT) are collected for 200 patients in the case report form (CRF).*
Derivations and definitions for the interim analysis will be based on those required for the final analysis contained in this analysis plan. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim analysis.

4 STUDY SAMPLE SIZE

Sample size for this study was calculated with the goal of maximizing precision (confidence interval [CI]) when estimating clinical and microbiological treatment success. 450 eligible patients will be enrolled.

Clinical Success Assumptions:

- *Considering all data lost due to all kinds of reasons, 62.5% of eligible patients are assessable for clinical outcome (success or failure).*
- *65% of the assessable patients experience clinical treatment success.*

Microbiological Success Assumptions:

- *Considering all data lost due to all kinds of reasons, 50% of eligible patients are assessable for microbiological outcome.*
- *75% of the assessable patients experience microbiological success.*

*Table 1 displays the precision of each estimate (*Wald *95% CI), for different rate of clinical and microbiological success and sample sizes ranging from 200 to 350 evaluable patients. Assuming clinical success rate is 65% and 280 patients (about 62.5% of 450 patients) are evaluable after enrolling 450 eligible patients, the precision of clinical success rate is 59.4% and 70.6%, i.e., the width of 95% CI is 11.2%. Assuming microbiological success rate is 75% and 220 patients (about 50% of 450 patients) are evaluable after enrolling 450 eligible patients, the precision of microbiological success rate is 69.3% and 80.7%, i.e., the width of 95% CI is 11.4%.*

Table 1. Precision of the estimate (*Wald *95% CI) for different clinical and microbiological success rates and number of evaluable patients

Number of Evaluable Patients	*Clinical and Microbiological Success Rate (%)*				
	60	*65*	*70*	*75*	*80*
200	*(53.2, 66.8)*	*(58.4, 71.6)*	*(63.6, 76.4)*	*(69.0, 81.0)*	*(74.5, 85.5)*
220	*(53.5, 66.5)*	*(58.7, 71.3)*	*(63.9, 76.1)*	***(69.3, 80.7)***	*(74.7, 85.3)*
240	*(53.8, 66.2)*	*(59.0, 71.0)*	*(64.2, 75.8)*	*(69.5, 80.5)*	*(74.9, 85.1)*
260	*(54.0, 66.0)*	*(59.2, 70.8)*	*(64.4, 75.6)*	*(69.7, 80.3)*	*(75.1, 84.9)*
280	*(54.3, 65.7)*	***(59.4, 70.6)***	*(64.6, 75.4)*	*(69.9, 80.1)*	*(75.3, 84.7)*
300	*(54.5, 65.5)*	*(59.6, 70.4)*	*(64.8, 75.2)*	*(70.1, 79.9)*	*(75.5, 84.5)*
320	*(54.6, 65.4)*	*(59.8, 70.2)*	*(65.0, 75.0)*	*(70.3, 79.4)*	*(75.6, 84.4)*
350	*(54.9, 65.1)*	*(60.0, 70.0)*	*(65.2, 74.8)*	*(70.5, 79.5)*	*(75.8, 84.2)*

5 HYPOTHESES AND DECISION RULES

Not Applicable.

5.1 STATISTICAL HYPOTHESES

Not Applicable.

5.2 STATISTICAL DECISION RULES

Not Applicable.

6 ANALYSIS SETS

6.1 FULL ANALYSIS SET (FAS)

The FAS will include all enrolled patients. The enrolled patients must meet the inclusion criteria, and must not meet the exclusion criteria.

6.2 CLINICALLY EVALUABLE (CE) ANALYSIS SET

The CE analysis set will include all patients from the FAS with at least 72 hours use of ceftazidime-avibactam and at least 1 non-missing clinical evaluation outcome.

6.3 MICROBIOLOGICALLY EVALUABLE (ME) ANALYSIS SET

The ME analysis set will include all patients from the FAS with at least 72 hours use of ceftazidime-avibactam and at least 1 non-missing microbiological evaluation outcome.

6.4 SUBGROUPS

Not Applicable.

7 ENDPOINTS, ESTIMANDS, AND COVARIATES

Table 2. Objectives, endpoints, and estimands

Objectives	*Endpoints*	*Estimands*
Primary:	***Primary:***	***Primary:***
Describe the clinical outcomes of patients (i.e., treatment success, failure, or indeterminate) at Day 7 (± 3 days), Day 14 (± 3 days), Day 21(± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.	*Clinical outcome*	*The clinical success rate at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.*
Describe the microbiological outcomes of patients at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.	*Microbiological outcome*	*The microbiological success rate at Day 7 (± 3 days), Day 14 (± 3 days), Day 21(± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam initiation, if patients are not discharged prior to the next upcoming timepoint.*
Describe the real-world usage of ceftazidime-avibactam at clinical practice, including patient baseline characteristics, type of infection, source of infection, etc.	• *Baseline characteristics* • *Indication* • *Source of infection*	*The number and percentage of patients by demographic characteristics, indication, type and source of infection.*
Describe the microbiological features of isolated strains, including pathogen identification, distribution, susceptibility of ceftazidime-avibactam and other common antibiotic drugs including carbapenem-	*At baseline:* • *Pathogen identification* • *Drug susceptibility* • *Genotype and type of enzyme*	• *The number and percentage of isolated strains.* • *Susceptibility and resistance rate of ceftazidime-avibactam and other common antibiotic drugs* • *The number and percentage of carbapenem-resistant organisms*

Objectives	*Endpoints*	*Estimands*
resistant organisms, and genotype characteristics of carbapenem-resistant organisms.		
Secondary:	***Secondary:***	***Secondary:***
Describe the antibiotic treatment administrated to the enrolled patients: including the dosage, frequency, duration of ceftazidime-avibactam, and combination medications with ceftazidime-avibactam	• *Dose* • *Frequency* • *Duration of expose (start and end dates)* • *Combination therapy*	• *The number and percentage of patients treated in different dose and frequency of ceftazidime-avibactam.* • *The descriptive statistics on the duration of exposure to ceftazidime-avibactam.* • *The number and percentage of patients receiving combination therapy with ceftazidime-avibactam.* • *The number and percentage of patients in each combination therapy with ceftazidime-avibactam.*
Describe the in-hospital LOS, LOS in ICU and healthcare resource utilization in patients treated with ceftazidime-avibactam.	• *LOS* • *LOS in ICU* • *Admission diagnosis* • *Discharge diagnosis* • *Concomitant procedures* • *Mechanical ventilation*	• *Descriptive statistics of LOS and ICU LOS.* • *The number and percentage of patients by different admission and discharge diagnosis.* • *The number and percentage of patients with invasive procedures, source of infection management, dialysis, surgery, etc* • *Length of mechanical ventilation*
Describe the readmission rate due to the recurrence of infection happened in the same location 30 and 60 days after discharge.	*Readmission*	*The percentage of patients with any readmission due to recurrence of infection happened in the same location within 30 and 60 days after discharge.*
Determine the in-hospital all-cause mortality.	*Death*	*The percentage of patients treated by ceftazidime-avibactam died during hospitalization.*

7.1 ENDPOINTS

Primary endpoint:

- *The clinical outcome will be summarized in CE analysis set.*
- *The microbiological outcome and its subcategory will be summarized overall and by pathogen in ME analysis set. The microbiological outcome will also be summarized based on the evaluation by site investigator and the central lab, respectively.*
- *The microbiological failure reason will be summarized in ME analysis set.*

- *Indication, type of infection, site of infection and source of infection for the initial ceftazidime-avibactam will be summarized in the FAS.*
- *The identified pathogen, susceptibility, genotype and type of enzyme at baseline will be summarized in FAS.*

Secondary endpoint (*summarized in both FAS and CE analysis set)*

- *Summarize the dose and frequency, of ceftazidime-avibactam. Summarize the combination therapy with ceftazidime-avibactam by therapy name.*
- *The LOS and ICU LOS will be summarized using descriptive statistics.*
- *The admission diagnosis, discharge diagnosis and baseline diagnosis at initiating ceftazidime-avibactam will be summarized.*
- *The concomitant procedures will be summarized by preferred term defined by Medical Dictionary for Regulatory Activities (MedDRA).*
- *The length of mechanical ventilation will be summarized using descriptive statistics.*
- *The rate of readmission due to recurrence of infection happened in the same location 30 and 60 days after discharge will be summarized.*
- *The mortality in hospital will be summarized.*

Table 3. List of variables and definitions

Variable	*Role*	*Operational Definition*
Informed consent	*Required for participation*	*Signed informed consent form submitted to study personnel.*
Age	*Baseline characteristic*	*As recorded in medical record. Age at ICF sign-off.*
Sex	*Baseline characteristic*	*As recorded in medical record.*
Ward of admission	*Baseline characteristic*	*As recorded in medical record.*
Employment	*Baseline characteristic*	*As recorded in medical record.*
Height, weight	*Baseline characteristic*	*Height and weight as recorded in medical record.*
Alcohol consumption	*Baseline characteristic*	*Alcohol consumption as recorded in medical record.*
Smoking	*Baseline characteristic*	*Smoking frequency as recorded in medical record.*
Comorbidity	*Baseline characteristic*	*Assessed the baseline by investigator. See protocol section 9.3.1.*
Recent hospitalization	*Baseline characteristic*	*Within 90 days prior to date of admission for the current hospitalization, date of admission and discharge, reason for hospitalization.*
History of antibiotic exposure	*Baseline characteristic*	*Antibiotic(s) used within 90 days prior to date of admission for the current hospitalization.*
Recent healthcare procedure	*Baseline characteristic*	*Within the 30 days before ceftazidime-avibactam initiation.*

Variable	*Role*	*Operational Definition*
Pre-treatment disease severity (APACHE II, SOFA, Pitt Bacteremia Score, or other prognostic assessment)	*Baseline characteristic*	*Measured at time of receiving 1st dose of ceftazidime-avibactam treatment. For ICU patients, record the APACHE II and SOFA score; for patients admitted to other wards, APCHE II and SOFA are recorded as available. See protocol section 9.3.2 for APACHE II and SOFA score. See protocol section 9.3.3 for Pitt Bacteremia Score. See protocol ANNEX 6 for SOFA score.*
Admission diagnosis	*Baseline characteristic*	*Diagnosis at the start of the hospitalization as recorded in medical record.*
Source of infection	*Baseline characteristic / sub-group identifier*	*As recorded in medical record. See protocol section 9.3.4.*
Indication for ceftazidime-avibactam	*Baseline characteristic / sub-group identifier*	*Site of infection (organ) and type of infection; date of diagnosis. See protocol section 9.3.5.*
Pre-treatment microbiology sample	*Baseline characteristic*	*Microbiological culture(s) of current infection before ceftazidime-avibactam initiation (sample date(s), sample site(s)).*
Pre-treatment microbiology results	*Baseline characteristic / sub-group identifier*	*Results from microbiological culture (method of testing, identified pathogen(s), susceptibility, MDR) before ceftazidime-avibactam. See protocol section 9.3.6.*
Prior antibiotic therapy	*Baseline characteristic*	*Antibiotic(s) used for current infection before ceftazidime-avibactam initiation. Dates of administration, dose(s), frequency, duration, route of administration, empiric or definitive therapy (See protocol section 9.3.7).*
Ceftazidime-avibactam	*Exposure*	*Dates of administration, dose(s), frequency, duration, reason of treatment discontinuation, empiric or definitive therapy (See protocol section 9.3.7).*
Combination antibiotic therapy	*Exposure / sub-group identifier*	*Name(s) of antibiotic(s) used concurrently with ceftazidime-avibactam, dates of administration, dose(s), frequency, duration, route of administration, empiric or definitive therapy (See protocol section 9.3.7).*
Microbiology sample after treatment initiation	*Outcome*	*Microbiological culture(s) after ceftazidime-avibactam initiation (sample date, sample site).*
Microbiology results after treatment initiation	*Outcome*	*Results from microbiological culture after treatment initiation (method of testing, identified pathogen(s), susceptibility, MDR).*
Discharge diagnosis	*Outcome*	*Diagnosis when discharge.*
Clinical outcome	*Outcome*	*Success, failure, and indeterminate. See protocol section 9.3.8.*
Microbiological outcome	*Outcome*	*Success, failure, emergent infections and unevaluable. See protocol section 9.3.8*
Death (all-cause mortality) during hospitalization	*Outcome*	*Death during hospitalization after start of ceftazidime-avibactam treatment. Date and all-cause death will be collected.*
Length of hospital stay	*Outcome*	*Date(s) of hospital admission, date(s) of hospital discharge.*

Variable	*Role*	*Operational Definition*
Admission date	*Outcome*	*As recorded in medical record.*
Discharge date	*Outcome*	*As recorded in medical record.*
Length of ICU stay	*Outcome*	*Date(s) of ICU admission, date(s) of ICU discharge.*
ICU admission date	*Outcome*	*As recorded in medical record.*
ICU discharge date	*Outcome*	*As recorded in medical record.*
Hospital readmission	*Outcome*	*Hospital readmission for the recurrence of infection happened in the same location 30 and 60 days after discharge, reason for readmission, date of readmission.*
Healthcare resource utilization	*Outcome*	*Detailed list of therapeutic and diagnostic procedures (mechanical ventilation, dialysis, computed tomography [CT], magnetic resonance imaging [MRI], invasive procedures, other) and dates of procedures.*
Hospital ward	*Outcome*	*All wards attended, ward of admission, ward of diagnosis (surgical, medical, oncology, hematology, infectious disease, ICU, other).*
Physician specialty	*Site characteristic*	*Medical specialty of the treating physician (e.g., infectious disease, surgical).*

7.2 COVARIATES

Covariates and corresponding levels are shown below, and set up in the CRF.

Patient demographics – Sex:

- Female
- Male

Patient demographics – Employment:

- Civil servant
- Technician
- Office worker
- Business manager
- Workman
- Farmer
- Student
- Soldier
- Freelancer
- Self-employed
- Unemployed
- Retired

Patient demographics – Alcohol concumption:

- Never
- Current
- Former

Patient demographics – Smoking:

- Never

- Current
- Former

Source of infection:

- Hospital-acquired infection (HAI)
- Community-acquired infection (CAI)

Indication for ceftazidime-avibactam:

- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP) / ventilator-associated pneumonia (VAP)
- Limited treatment options (LTO)

Pre-treatment microbiology results – Identified pathogen:

- Escherichia coli
- Klebsiella pneumoniae
- Proteus mirabilis
- Enterobacter cloacae
- Klebsiella oxytoca
- Citrobacter freundii
- Pseudomonas aeruginosa
- Serratia marcescens
- Haemophilus influenzae
- Other

Pre-treatment microbiology results – Carbapenem-resistant organisms genotype:

- *bla*$_{KPC}$
- *bla*$_{NDM}$
- *bla*$_{IPM}$
- *bla*$_{VIM}$
- *bla*$_{OXA-48}$
- Other

History of antibiotic(s) exposure:

- Anotomical Therapeutic Chemical 3 terms coded using World Health Organization Drug Global 2022 Sep. or higher (English version).

8 GENERAL CONSIDERATIONS

8.1 INDEX HOSPITALIZATION AND INDEX DATE

- *The index hospitalization is defined as patients' first hospitalization met the eligible criteria.*
- *The index date will be defined as the date of patients initiated ≥1 dose of ceftazidime-avibactam treatment during the index hospitalization.*

8.2 BASELINE

- Baseline assessment: Unless otherwise specified, the baseline assessment of this study is the last non-missing assessment before the start of ceftazidime-avibactam treatment (including unscheduled assessments). In the case where the last non-

missing assessment and the index date coincide, that assessment will be considered pre-baseline.

- Baseline period: The baseline period is defined as from date of admission to index date or from 7 days before index date to index date, whichever is longer. When patients have multiple records for variables of interest during the baseline period, the one closest to the index date will be selected.

Baseline assessment will be performed in baseline period.

8.3 COMMON CALCULATIONS

Study day will be calculated as:

- Study day = Target (clinical outcome assessment, readmission, death, etc.) date – first ceftazidime-avibactam administration date + 1, if target date >= first ceftazidime-avibactam administration date.
- Study day = Target (pre-treatment microbiological assessment, etc.) date – first ceftazidime-avibactam administration date, if target date < first ceftazidime-avibactam administration date.

8.4 SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

9 HANDLING OF MISSING VALUES

Missing administration date, mechanical ventilation date and admission/discharge date will be imputed per the worst case scenario. See APPENDIX 1 Partial/Missing Date Conventions for more details.

10 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

10.1 STATISTICAL METHODS

This study aims to describe the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice in China. The results will mainly be presented descriptively.

No statistical testing will be performed in this study.

For interval estimate of proportion, a two-sided Clopper-Pearson exact CI and a two-sided Wald CI will be used. Unless otherwise specified in the description of the analyses, 95% CI will be considered as a default (alpha= 5%).

10.2 STATISTICAL ANALYSES

10.2.1 Disposition and Withdrawals

Patient disposition and withdrawals data is from eCRF (case report form) "Non-English text", i.e., "End of Observation" form. Inclusion and exclusion criteria data is from eCRF "Non-English text", i.e., "Inclusion/Exclusion Criteria" form.

Patient disposition and withdrawals, including inclusion and exclusion criteria will be descriptively presented in number and percentage based on the number of all enrolled patients.
Analysis sets will be derived programmatically per definitions in section 6 Analysis Sets and presented in number and percentage based on the number of all enrolled patients.
Patient disposition, withdrawals, and analysis sets will be listed based on all enrolled patients.

10.2.2 Demographics and Other Baseline Characteristics

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – relative to date of consent, from eCRF "Non-English text", i.e., "Demographics" form
- Sex - from eCRF "Non-English text", i.e., "Demographics" form
- Ward of admission at current hospitalization and recent hospitalization – from eCRF "Non-English text form and from eCRF "Non-English text" form, i.e., "Index Hospitalization" and "Recent Hospitalization" form
- Employment – from eCRF Non-English text", i.e., "Employment Information" form
- Weight (kg) – from eCRF "Non-English text", i.e., "Height and Weight" form
- Height (cm) – from eCRF "Non-English text", i.e., "Height and Weight" form
- Body mass index (BMI) (kg/m^2)
- Alcohol consumption – from eCRF "Non-English text", i.e., "Smoking and Alcohol Consumption" form
- Smoking – from eCRF "Non-English text", i.e., "Smoking and Alcohol Consumption" form
- Deyo-Charlson Comorbidity Index – from eCRF "Non-English text", i.e., "Comorbidity" form
- Recent hospitalization – from eCRF "Non-English text", i.e., "Recent Hospitalization" form
- History of antibiotic exposure – from eCRF Non-English text", i.e., "History of Antibiotic Exposure" form
- Risk factors for infection– from eCRF "Non-English text, i.e., "Risk factors for infection" form
- Recent healthcare procedure – from eCRF Non-English text", i.e., "Risk factors for infection (invasive procedures)" form
- Pre-treatment disease severity – from eCRF Non-English text", i.e., "Assessment of Pre-treatment Disease Severity" form
- Source of infection – from eCRF "Non-English text form at Non-English text", and at Non-English text (Non-English text) " visit, i.e., "Source of infection" form at "Baseline" and "Index Date" visit.

- Indication for ceftazidime-avibactam – from eCRF "Non-English text" form, at "Non-English text", and at "Non-English text") " visit, i.e., "Indication for Ceftazidime-Avibactam" form at "Baseline" and "Index Date" visit.
- Type of infection – from eCRF "Non-English text" form including the LTO-specific infection, at "Non-English text", and at "Non-English text (Non-English text 1 Non-English text)" visit, i.e., "Indication for Ceftazidime-Avibactam" form at "Baseline" and "Index Date" visit.

Demographics data and other baseline characteristics will be descriptively presented and listed based on the FAS.

Antibiotics used within 90 days prior to current admission, and prior antibiotics used on or after admission but before initiating ceftazidime-avibactam, will be coded using World Health Organization Drug Global 2022 Sep. or higher (English version).

The number and percentage of patients in each antibiotics used within 90 days prior to current admission (in Anatomical Therapeutic Chemical (ATC) level 4 and Preferred Name), will be summarized based on the FAS.

The number and percentage of patients in each prior antibiotics used on or after admission but before initiating ceftazidime-avibactam (in ATC level 4 and Preferred Name), will be summarized based on the FAS.

Recent health procedures and LTO-specific infection will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or higher (English version).

The number and percentage of patients with LTO-specific infection (in Preferred Terms) will be summarized based on the FAS.

10.2.3 Microbiological Results at Baseline

10.2.3.1 Pathogen Identification

The pathogen data are from eCRF "Non-English text" form at "Non-English text" and "Non-English text 1 Non-English text)", i.e., "Microbiological Results" form at "Baseline" and "Index Date" visit. Baseline assessment will be derived based on section 8.2 Baseline.

The number and percentage of identified pathogen at baseline will be summarized based on the FAS.

The identified pathogen at baseline will be listed based on the FAS.

10.2.3.2 Pathogen Susceptibility

The susceptibility data are from eCRF "Non-English text" form at "Non-English text" and "Non-English text (Non-English text 1 Non-English text)", i.e., "Microbiological Results" form at "Baseline" and "Index Date" visit. Baseline assessment will be derived based on section 8.2 Baseline.

The susceptibility of ceftazidime-avibactam and other common antibiotic drugs including carbapenem-resistant organisms at baseline will be summarized and listed based on the FAS.

10.2.3.3 Carbapenemase genes

The carbapenemase genes data are from eCRF "Non-English text" form at "Non-English text" and "Non-English text", i.e., "Microbiological Results (strain gene test)" form at "Baseline" and "Index Date" visit. Baseline assessment will be derived based on section 8.2 Baseline.

The number and percentage of carbapenemase genes will be summarized based on the FAS.

The carbapenemase genes will be listed based on the FAS.

10.2.3.4 Type of Enzyme

The type of enzyme data are from eCRF "Non-English text" form at "Non-English text", and Non-English text Non-English text", i.e., "Microbiological Results" form at "Baseline" and "Index Date" visit. Baseline assessment will be derived based on section 8.2 Baseline.

The number and percentage of carbapenemase enzyme positive result at baseline will be summarized and listed based on the FAS.

10.2.3.5 Combination Susceptibility

The combination susceptibility data are from eCRF Non-English text" form at "Non-English text", and Non-English text", i.e., "Microbiological Results" form at "Baseline" and "Index Date" visit. Baseline assessment will be derived based on section 8.2 Baseline.

The number and percentage of combination susceptibility result at baseline will be summarized and listed based on the FAS.

10.2.4 Concomitant Procedures

Concomitant procedures data are from eCRF "Non-English text" of Non-English text" form, and "Non-English text of "Non-English text" form, i.e., "Therapeutic/Diagnostic Procedures" of "Healthcare Resource Utilization" form and "Healthcare Procedures" of "Risk factors for infection (invasive procedures)" form. Data will be used from this form if the procedure is still ongoing after the initiation of ceftazidime-avibactam, and will be coded using MedDRA version 25.1 or higher (English version).

The number and percentage of patients with concomitant procedures (in preferred terms) will be summarized based on the FAS and the CE analysis set.

Concomitant procedures, including mechanical ventilation, will be listed based on the FAS and the CE analysis set.

10.2.5 Length of Mechanical Ventilation

Mechanical ventilation data is from eCRF "Non-English text" of Non-English text form, i.e., "Therapeutic/Diagnostic Procedures" of "Healthcare Resource Utilization" form.

Length of mechanical ventilation will be summarized based on the FAS and the CE analysis set.
For i^{th} patient, given that multiple mechanical ventilations may occur, firstly each period (say, n^{th}) of mechanical ventilation (days) M_{in} is calculated as:
n^{th} mechanical ventilation end date – n^{th} mechanical ventilation start date + 1.
Then secondly, length of mechanical ventilation (days) of i^{th} patient M_i is calculated as:

$$M_i = \sum_{j=1}^{N_i} M_{ij} ,$$

where N_i is the number of mechanical ventilation of a patient.
Refer to APPENDIX 1 Partial/Missing Date Conventions for imputation algorithm of mechanical ventilation start/end date.

10.2.6 Study Medication Exposure

Exposure to ceftazidime-avibactam data is from the eCRF "Non-English text", i.e., "Medication Exposure" form. Exposure, including duration of exposure, will be summarized based on the FAS and the CE analysis set.
For i^{th} patient, given that multiple ceftazidime-avibactam administrations may occur, firstly each period (say, n^{th}) of ceftazidime-avibactam exposure (days) E_{in} is calculated as:
n^{th} ceftazidime-avibactam administration end date – n^{th} ceftazidime-avibactam administration start date + 1.
Then secondly, duration of exposure (days) of i^{th} patient E_i is calculated as:

$$E_i = \sum_{j=1}^{N_i} E_{ij} ,$$

where N_i is the number of ceftazidime-avibactam administration period of a patient.
Refer to APPENDIX 1 Partial/Missing Date Conventions for imputation algorithm of ceftazidime-avibactam administration start/end date.
Exposure will be listed based on the FAS and the CE analysis set.

10.2.7 Combination Therapy with Ceftazidime-Avibactam

Combination therapy with ceftazidime-avibactam data is from eCRF "Non-English text", "Non-English text" forms (i.e., "History of Antibiotic Exposure" and "Prior Antibiotics Therapy" forms, data will be used from these two forms if the prior antibiotics are still used after the initiation of ceftazidime-avibactam), and "Non-English text" form (i.e., "Combination Antibiotic Therapy" form), and will be coded using World Health Organization Drug Global 2022 Sep. or higher (English version).
The number and percentage of patients in each combination therapy with ceftazidime-avibactam (in ATC level 4 and Preferred Name) will be summarized based on the FAS and the CE analysis set.
Combination therapy with ceftazidime-avibactam will be listed based on the FAS and the CE analysis set.

10.2.8 Clinical Success Rate

Clinical outcome data is from eCRF "Non-English text" form, i.e., "Clinical Outcome" form at Day 7, Day 14, Day 21, Day 30, Day 60, end of treatment and unscheduled visit if any.
The clinical success rate will be summarized by visit (not including unscheduled visit), based on the CE analysis set.
The clinical success rate for a specific visit is a proportion, and is defined as:
number of patients with clinical outcome "success" in a specific visit / number of patients with clinical outcome assessed in a specific visit.
Clinical outcome will be listed based on the CE analysis set (including unscheduled visit).

10.2.9 Microbiological Success Rate

Microbiological outcome data is from eCRF "Non-English text" form, i.e., "Microbiological Outcome" form at Day 7, Day 14, Day 21, Day 30, Day 60, end of treatment and unscheduled visit if any.
The microbiological success rate, microbiological outcome, its subcategory, and microbiological failure reason, will be summarized by visit (not including unscheduled visit), last pathogen detected at baseline period and index date, and by evaluation (site investigaotor or central laboratory), based on the ME analysis set.
The microbiological success rate for a specific visit is a proportion, and is defined as:
number of patients with microbiological outcome "success" in a specific visit / number of patients with microbiological outcome assessed in a specific visit.
Microbiological outcome, including failure reason, will be listed based on the ME analysis set (including unscheduled visit).

10.2.10Length of Stay in Hospital

Hospitalization data is from eCRF "Non-English text" form and "Non-English text" form, i.e., "Index Hospitalization" form and "Information of Discharge" form.
The length of stay in hospital (readmission not included) will be summarized based on the FAS and the CE analysis set.
The length of stay in hospital is defined as:
Discharge date – admission date + 1.
The length of stay in hospital (readmission not included) in ICU will be summarized based on the FAS and the CE analysis set.
The length of stay in hospital in ICU is defined as:
ICU discharge date – ICU admission date + 1.
The hospitalization details, including admission/infection/discharge date, admission/infection/discharge diagnosis date, admission/infection/discharge diagnosis, will be listed based on the FAS and the CE analysis set.

10.2.11Admission, Infection, and Discharge Diagnosis

Admission diagnosis data is from eCRF "Non-English text" form, i.e., "Index Hospitalization" form; infection diagnosis data are from eCRF "Non-English text" form

and "Non-English text " form, i.e., "Index Hospitalization" and "Updated Diagnosis of Infection"; discharge diagnosis data is from eCRF "Non-English text " form, i.e., "Information of Discharge" form.
Admission diagnosis, infection diagnosis, and discharge diagnosis will be coded using MedDRA version 25.1 or higher (English version).
The number and percentage of patients will be summarized by different admission, infection diagnosis, and discharge diagnosis, based on the FAS and the CE analysis set.

10.2.12Readmission

Readmission data is from eCRF Non-English text form, i.e., "Information of Readmission" form.
The number and percentage of patients with any readmission due to recurrence of infection happened in the same location within 30 and 60 days after discharge, will be summarized based on the FAS and the CE analysis set. (use eCRF question "Non-English text " in "Non-English text form and "Non-English text " form, i.e., "Site of Infection" in "Indication for Ceftazidime-Avibactam" form and "Information of Readmission" form to cross-check if the infection happened in same location).
Readmission details will be listed based on the FAS and the CE analysis set.

10.2.13In-Hospital All-Cause Mortality

Mortality data are from eCRF "Non-English text " form and "Non-English text " form, i.e., "End of Observation" form and "Adverse Event" form.
The number and percentage of patients died during hospitalization will be summarized based on the FAS and the CE analysis set (death during hospitalization means the death date lies between admission date and discharge date).
Death data will be listed based on the FAS and the CE analysis set.

10.2.14Summary of Analyses

Statistical Analysis	Analysis Set	Protocol Objective	Statistical Method	Covariates/Strata
Disposition and withdrawals	All enrolled patients	Not applicable	Descriptive statistics	Not applicable
Analysis sets	All enrolled patients	Not applicable	Descriptive statistics	Not applicable
Demographics and other baseline characteristics	FAS	Primary	Descriptive statistics	Not applicable
Microbiological results at baseline	FAS	Primary	Descriptive statistics	Not applicable
Concomitant procedures	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Length of mechanical ventilation	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Study medication exposure	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Combination therapy with ceftazidime-avibactam	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Clinical success rate	CE analysis set	Primary	1. Point estimation 2. Interval estimation: Wald CI Clopper-Pearson exact CI	Not applicable
Microbiological success rate	ME analysis set	Primary	1. Point estimation 2. Interval estimation: Wald CI Clopper-Pearson exact CI	Not applicable
Microbiological success rate by pathogen	ME analysis set	Primary	1. Point estimation 2. Interval estimation: Wald CI Clopper-Pearson exact CI	Pathogen

Statistical Analysis	Analysis Set	Protocol Objective	Statistical Method	Covariates/Strata
Length of stay in hospital	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Length of stay in ICU	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Admission and discharge diagnosis	FAS CE analysis set	Secondary	Descriptive statistics	Not applicable
Readmission	FAS CE analysis set	Secondary	1. Point estimation 2. Interval estimation: Wald CI Clopper-Pearson exact CI	Not applicable
In-hospital all-cause mortality	FAS CE analysis set	Secondary	1. Point estimation 2. Interval estimation: Wald CI Clopper-Pearson exact CI	Not applicable

11 REFERENCES

C3591037 non-interventional study protocol amendment 3, dated 12 Apr. 2022.

APPENDICES

APPENDIX 1 PARTIAL/MISSING DATE CONVENTIONS

Imputed dates will not be presented in the listings.

Algorithm for admission/discharge date (including ICU)

Admission date	Partial	Impute admission date as maximum of 1. Informed consent date 2. Earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown)
	Missing	Impute admission date as informed consent date
Discharge date	Partial	Impute discharge date as minimum of 1. Latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown) 2. End of observation date
	Missing	Impute discharge date as end of observation date

Algorithm for ceftazidime-avibactam administration date

Given that a patient may be with multiple ceftazidime-avibactam administrations, imputation of each ceftazidime-avibactam administration start/end date is considered.

Start date (Note: could be index date if it is first ceftazidime-avibactam administration)	Partial	Impute start date as maximum of 1. Latest admission date before the next ceftazidime-avibactam administration (for this comparison purpose only: if null or partially missing, then set to 0) 2. Check if therapy is empiric or definitive 2.1. Latest microbiological sampling date if empiric therapy (for this comparison purpose only: if null or partially missing , then set to 0) 2.2. Latest microbiological assessment date if definitive therapy (for this comparison purpose only: if null or partially missing , then set to 0) 3. Latest previous ceftazidime-avibactam administration end date +1 (for this comparison purpose only: if null or partially missing, then set to 0) If obtaining null from above, then impute start date using the latest possible date (e.g. last day of ith ceftazidime-avibactam

		administration if i^{th} ceftazidime-avibactam administration start day unknown; last day of month if day unknown or 31st December if day and month are unknown)
	Missing	Impute start date as maximum of 1. Latest admission date before the next ceftazidime-avibactam administration (for this comparison purpose only: if null or partially missing, then set to 0) 2. Check if therapy is empiric or definitive 2.1. Latest microbiological sampling date if empiric therapy (for this comparison purpose only: if null or partially missing, then set to 0) 2.2. Latest microbiological assessment date if definitive therapy (for this comparison purpose only: if null or partially missing, then set to 0) 3. Latest previous ceftazidime-avibactam administration end date +1 (for this comparison purpose only: if null or partially missing, then set to 0)
End date	Partial	Impute end date as minimum of 1. Discharge date (for this comparison purpose only: if null or partially missing, then set to infinity) 2. End of observation date 3. Next nearest microbiological assessment date (for this comparison purpose only: if null or partially missing, then set to infinity) 4. Next ceftazidime-avibactam administration start date -1 (for this comparison purpose only: if null or partially missing, then set to infinity) If obtaining null from above, then impute end date using the earliest possible date (e.g. first day of i^{th} ceftazidime-avibactam administration if i^{th} ceftazidime-avibactam administration end day unknown; first day of month if day unknown or 1st January if day and month are unknown)
	Missing	Impute end date as minimum of 1. Discharge date (for this comparison purpose only: if null or partially missing, then set to infinity) 2. End of observation date

		3. Last microbiological assessment date (for this comparison purpose only: if null or partially missing, then set to infinity) 4. Next ceftazidime-avibactam administration start date -1 (for this comparison purpose only: if null or partially missing, then set to infinity)

Algorithm for mechanical ventilation date

Given that a patient may be with multiple mechanical ventilations, imputation of each mechanical ventilation start/end date is considered.

Start date	Partial	Impute start date as maximum of 1. Earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) 2. Latest admission date (for this comparison purpose only: if null or partially missing, then set to 0) 3. Latest previous mechanical ventilation end date + 1 (for this comparison purpose only: if null or partially missing, then set to 0)
	Missing	Impute start date as maximum of 1. Latest admission date (for this comparison purpose only: if null or partially missing, then set to 0) 2. Latest previous mechanical ventilation end date + 1 (for this comparison purpose only: if null or partially missing, then set to 0)
End date	Partial	Impute end date as minimum of 1. Latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown) 2. Discharge date (for this comparison purpose only: if null or partially missing, then set to infinity) 3. End of observation date 4. Next mechanical ventilation start date – 1 (for this comparison purpose only: if null or partially missing, then set to infinity)
	Missing	Impute end date as minimum of 1. Discharge date (for this comparison purpose only: if null or partially missing, then set to infinity) 2. End of observation date

		3. Next mechanical ventilation start date – 1 (for this comparison purpose only: if null or partially missing, then set to infinity)

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