NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	*Retrospective analysis to characterize the real world use patterns, efficacy and safety of ceftazidime-avibactam in the management of gram negative infections.*
Protocol number	**X9001260**
Protocol version identifier	*2*
Date	21 October 2020
Active substance	Ceftazidime- Avibactam Pharmacotherapeutic group: Antibacterials for systemic use, ceftazidime, combinations, ATC code: J01DD52
Medicinal product	*Ceftazidime- Avibactam*
Research question and objectives	*What is the real world usage pattern of Ceftazidime-avibactam for the treatment of Gram negative infections?*
Author	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AEM	Adverse Event Monitoring
APACHE	Acute Physiology and Chronic Health Evaluation Score
BSI	Bloodstream Infection
CAI	Community-Acquired Infection
cIAI	Complicated Intra-Abdominal Infection
CIOMS	Council for International Organizations of Medical Sciences
CRE	Carbapenem-Resistant *Enterobacteriaceae*
cUTI	Complicated Urinary Tract Infection
DCCI	Deyo-Charlson Comorbidity Index
ECDC	European Centre for Disease Prevention and Control
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESBL	Extended-Spectrum Beta-Lactamase
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HAI	Hospital-Acquired Infection
HAP	Hospital-Acquired Pneumonia
HAUTI	Healthcare-Associated Urinary Tract Infection
HCAI	Healthcare-Associated Infection
HCAP	Healthcare-Associated Pneumonia
IAI	Intra-Abdominal Infection
ICF	Informed Consent Form

Page 6 of 58**Abbreviation**	**Definition**
ICU	Intensive Care Unit
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
KPCs	*Klebsiella pneumoniae* Carbapenemases
LOS	Length of Stay
MDR	Multidrug-Resistant
MDRGN	Multidrug-Resistant Gram-Negative Organism
MODS	Multiple Organ Dysfunction Score
NI	Non-interventional
NIS	Non-Interventional Study
NP	Nosocomial Pneumonia
ODIN	Organ Dysfunction and Infection System
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAPS	Simplified Acute Physiologic Score
SOFA	Sequential Organ Failure Assessment
SRSD	Single Reference Safety Document
SSI	Surgical Site Infection
UTI	Urinary Tract Infection
VAP	Ventilator-Associated Pneumonia
WBDC	Web-Based Data Capture
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Below are the proposed names of the investigators:

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

Retrospective analysis to characterize the real world use patterns, efficacy and safety of ceftazidime-avibactam in the management of gram negative infections.

Version 2; 21 October 2020

PPD & PPD, *Pfizer* PPD *India*

- *Rationale and background:*

Antimicrobial resistance is increasing in India with up to 12-59% of E. coli being extended spectrum beta-lactamase (ESBL) producers and up to 30% being carbapenemase producers (CP). Among the infections caused by Gram-negative bacteria (GNB), the most common drug-resistant organisms are Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae) and non-fermentors (Pseudomonas aeruginosa, Acinetobacter baumannii). ESBL rates are as high as 70% in E. coli and K. pneumoniae. Carbapenem resistance (CR) rates were found significantly varied with different organisms (10%, 40%, 25% and 70% for E. coli, K.pneumoniae, P. aeruginosa and A. baumannii, respectively).

Ceftazidime-avibactam is a combination of the third-generation cephalosporin ceftazidime and the novel, non-β-lactam β-lactamase inhibitor, avibactam. Avibactam has a broad spectrum of activity, inhibiting Ambler class A (e.g. TEM-1, CTX-M-15, KPC-2, KPC-3), class C (e.g. AmpC) and certain class D β-lactamases (e.g. OXA-10, OXA-48); it is not active against class B enzymes (metallo-β-lactamases). The clinical efficacy of intravenous ceftazidime-avibactam in the treatment of cUTI, cIAI and HAP (including VAP) in adults was demonstrated in pivotal phase III non-inferiority trials (all versus carbapenem comparators), where ceftazidime-avibactam treatment was associated with high response rates.

Though ceftazidime-avibactam has proven efficacious in non-inferiority phase III trials and real world evidence for its efficacy and safety in carbapenem resistant infections is available globally, however real-world information about of treatment characteristics, safety, and efficacy against multidrug-resistant (MDR) gram negative bacteria including carbapenem-resistant *Enterobacteriaceae* (CRE), is lacking in India.

- *Research question and objectives*

The main objective of this non-interventional (retrospective) study is to describe the general treatment patterns, effectiveness, and safety of ceftazidime-avibactam in real-world settings in India

- *Study design:*

This is a non-interventional retrospective study to examine the real world usage, effectiveness, and safety of ceftazidime-avibactam for the treatment of Gram negative infections in India. Eligible patients would be adults who have been treated with ≥ 48 hours of ceftazidime-avibactam

in routine practice from 01 June 2019 to 01 April 2020. Patient should have completed the treatment with ceftazidime -avibactam before 01 April 2020 Data will be collected through the abstraction of hospital medical records (electronic) if available or through the individual patient medical record in case electronic records are not available. Collected study data will include but will not be limited to patient characteristics, clinical and microbiologic characteristics of the infection, and treatment patterns, effectiveness, and safety of ceftazidime-avibactam.

- *Population*

All hospitalized patients who have received at least 48 hours of ceftazidime-avibactam

- *Variables – include exposures, outcomes, and key co-variates*

Exposures: ceftazidime-avibactam

- Outcomes: clinical effectiveness, microbiological outcomes, adverse events (AEs), serious adverse events (SAEs), recurrence of infection during the hospital stay, length of hospital stay, in-hospital mortality, healthcare resource utilization

- Key covariates: patient demographics, indication, infection source (hospital/healthcare/community), treatment history, clinical characteristics

- *Data sources*

Data (defined in the data collection plan)will be abstracted from electronic health records if available or individual patient medical records, in case electronic records are not available

- *Study size:*

500 hospitalized patients who have received at least 48 hours of Ceftazidime- Avibactam. Data will be collected for the period of 01 June 2019 till 01 April 2020. The data collection will stop once data from 500 patients has been abstracted.

- *Data analysis*

- Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

- *Milestones*

Completion of feasibility assessment: 01 October 2020

Start of data collection: 01 December 2020

End of data collection: 31 January 2021

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.	15 October 2020	Study information	Version number changed to version 2 and the date changed to 15 October 2020	Protocol amendment
		3. Responsible parties	Number of sites changed to 9 instead of 12	Change made basis feasibility assessment
		6. Milestones	Milestones updated as follows: Completion of feasibility assessment: 01 October 2020 Start of data collection : 01 December 2020 End of data collection: 31 January 2021 Study progress report: 01 January 2021 Final study report: 01 February 2021	Milestones updated per the current status of the study
		8. Research question & objective	<u>Version 1: Primary objective:</u> 1. Describe the clinical outcomes of patients treated with ceftazidime-avibactam (i.e. treatment success, failure, or indeterminate) 2. Describe the microbiologic outcomes among patients treated with ceftazidime-avibactam 3. Describe safety outcomes in patients receiving ceftazidime-avibactam during the treatment <u>Changed to the following in version 2:</u> 1.Describe the treatment success of patients treated with ceftazidime-avibactam at Day 7 and Day 14/ end of treatment after ceftazidime-avibactam initiation, whichever is earlier. 2.Describe the microbiological success among patients treated with ceftazidime-avibactam at day 7 and Day 14/ end of treatment after Ceftazidime avibactam initiation whichever is earlier. 3.Number of patients with serious and non-serious AEs with explicit attribution to Ceftazidime avibactam for upto 30 days post treatment completion with Ceftazidime- Avibactam, death or discharge; whatever is first <u>Version 1: Secondary objective:</u>	Reassessment of protocol post suggestions from clinicaltrials.gov

Amend ment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			1. Describe the source of infection for which ceftazidime-avibactam was used. 2. Describe the indications and reasons for use of ceftazidime-avibactam 3. Describe the usage patterns of ceftazidime-avibactam, including dose, frequency of dose, duration, and polytherapy regimens. Any prior antimicrobial therapy will also be documented. 4. Describe the microbiologic evidence available for patients treated with ceftazidime-avibactam. & describe the enzymes identified from the genotyping tests (if done). 5. Describe the in-hospital length of stay (LOS), LOS in ICU and healthcare resource utilization in patients with infections treated by ceftazidime-avibactam. 6. Determine the incidence of recurrent infections during the hospital stay, including re-infection and relapse up to 30 days post treatment completion with Ceftazidime- Avibactam death or discharge; whatever is first. <u>Changed to the following in version 2:</u> 1. Describe the source of infection at baseline for which ceftazidime-avibactam was used. 2. Describe the indications and reasons for use of ceftazidime-avibactam at baseline. 3. Describe the usage patterns of ceftazidime-avibactam, includingthe dose in mg, frequency of dose in hours, duration in days, and polytherapy regimenscombination antibiotic regimen given till 14 days/ End of treatment whichever is earlier. 4. Describe at baseline any prior antimicrobial therapy administered in the 90 days prior to current admission. 5. Describe the gram negative organisms identified and the susceptibility to ceftazidime -avibactam along with molecular typing at baseline. 5. Describe the in-hospital length of stay (LOS) in days , LOS in ICU in days and percentage of various healthcare resource utilization in patients with infections treated by ceftazidime-avibactam up to 30 days post treatment completion with Ceftazidime- Avibactam death or discharge; whatever is first. 6. Determine the incidence of recurrent infections during the hospital stay, including re-infection and relapse up to	

Amend ment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			30 days post treatment completion with Ceftazidime-Avibactam, death or discharge; whatever is first	
		9. Research method- Section 9 2 Settings	Number of sites changed to 9 from 12	Basis the feasibility assessment
		9 3 Variables Table 1: Variables and operational definition	Operational definition of source of infection, indication for ceftazidime-avibactam, clinical outcome, microbiological outcome and safety changed as per the changes in outcome.	Basis the change in the outcomes in section 'Research question and objectives.'
		Annex 2.1	Clinical success and failure criteria updated	

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	01 October 2020
Start of data collection	01 December 2020
End of data collection	31 January 2020
Study progress report	01 January 2021
Final study report	01 February 2021

7. RATIONALE AND BACKGROUND

Antimicrobial resistance (AMR) is a global threat today and has overshadowed the potential gain in reducing deaths due to infections. It is estimated that by the year 2050, Asia will have 4.7 million deaths that could be directly attributed to AMR.[1] Data from 13,086 patients across 10 tertiary care hospitals in India between January and December 2015 showed highest mortality rates in patients infected with Gram-negative bacteria (17.7%), as opposed to those caused by Gram-positive bacteria (10.8%), particularly in the ICU, where 26.9% of patients with Gram-negative MDR infections died. [2]

Antimicrobial resistance is increasing in India with up to 12-59 % of E. coli being extended beta lactamase (ESBL) producers and up to 30% being carbapenemase producers (CP).[1] Among the infections caused by Gram-negative bacteria (GNB), the most common drug-resistant organisms are Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae) and non-fermentors (Pseudomonas aeruginosa, Acinetobacter baumannii). ESBL rates are as high as 70% in E. coli and K. pneumoniae. Carbapenem resistance (CR) rates were found significantly varied with different organisms (10%, 40%, 25% and 70% for E. coli, K.pneumoniae, P. aeruginosa and A. baumannii, respectively). [3]

Klebsiella pneumoniae has emerged over the last few years as a highly resistant pathogen with up to 50% resistance to carbapenems and rapidly increasing resistance to polymyxins.[1] Increasing incidence of infections due to carbapenem resistance organisms is becoming difficult to treat, due to the limited availability of therapeutic agents. Very few agents such as colistin, fosfomycin, tigecycline and minocycline are widely used, despite its toxicity.[4]

Ceftazidime-avibactam is a combination of the third-generation cephalosporin ceftazidime and the novel, non-β-lactam β-lactamase inhibitor avibactam. Avibactam has a broad spectrum of activity, inhibiting Ambler class A (e.g. TEM-1, CTX-M-15, KPC-2, KPC-3), class C (e.g. AmpC) and certain class D β-lactamases (e.g. OXA-10, OXA-48); it is not active against class B enzymes

(metallo-β-lactamases). In vitro studies have shown that avibactam can restore the antimicrobial activity of the third-generation, extended-spectrum cephalosporin ceftazidime against many ESBL-, AmpC-, Klebsiella pneumoniae carbapenemase (KPC)- and OXA-48-producing Enterobacteriaceae and drug-resistant P. aeruginosa isolates. [5] It is approved in India for the management of cIAI (complicated Intra-abdominal infections),cUTI (complicated urinary tract infections) and HAP/VAP (Hospital Acquired Pneumonia/ Ventilator associated pneumonia).

The clinical efficacy of intravenous ceftazidime-avibactam in the treatment of cUTI, cIAI and HAP (including VAP) in adults was demonstrated in pivotal phase III non-inferiority trials (all versus carbapenem comparators), where ceftazidime-avibactam treatment was associated with high response rates.[5]Ceftazidime-avibactam was non-inferior to doripenem in the treatment of hospitalized adults with cUTI (including pyelonephritis) in the RECAPTURE trials, based on primary endpoint analyses. Ceftazidime-avibactam plus metronidazole was non-inferior to meropenem in the treatment of hospitalized adults with cIAI, based on clinical cure rates at the TOC visit in the RECLAIM-1 and -2 trials as well as in the RECLAIM-3 trial in Asian populations. As demonstrated in the pivotal REPROVE trial, ceftazidime-avibactam was also non-inferior to meropenem in the treatment of adult patients with HAP (including VAP), with REPROVE being the first randomized controlled trial to demonstrate non-inferiority of a new antimicrobial therapy versus a carbapenem targeting Gram-negative pathogens in this setting.[5] In seven Phase 2 and Phase 3 clinical trials, 2024 adult patients were treated with Zavicefta. The most common adverse reactions occurring in ≥ 5% of patients treated with Zavicefta were Coombs direct test positive, nausea, and diarrhoea. Nausea and diarrhoea were usually mild or moderate in intensity.[6] REPROVE and RECLAIM trials also had 90 and 142 Indian patients respectively. Qualitative analyses of the India subset showed that the efficacy and safety outcomes were in line with global population. [7]

However real-world data examining the treatment characteristics, safety, and efficacy of Ceftazidime-avibactam against Gram negative organisms especially multidrug-resistant (MDR) pathogens including CRE is lacking in Indian setting.This retrospective study aims to understand the real world usage, efficacy and safety of Ceftazidime avibactam in treating Gram negative infections.

8. RESEARCH QUESTION AND OBJECTIVES

The main objective of this non-interventional (retrospective) study is to describe the general treatment patterns, effectiveness, and safety of ceftazidime-avibactam in real-world settings.

Primary objective:

1. Describe the treatment success of patients treated with ceftazidime-avibactam at Day 7, Day 14/ end of treatment after ceftazidime-avibactam initiation, whichever is earlier.
2. Describe the microbiological success among patients treated with ceftazidime-avibactam at day 7, Day 14/ end of treatment after Ceftazidime avibactam initiation whichever is earlier.

3. Number of patients with serious and non-serious AEs with explicit attribution to Ceftazidime avibactam for upto 30 days post treatment completion with Ceftazidime- Avibactam, death or discharge; whatever is first

Secondary objective:

1. Describe the source of infection at baseline for which ceftazidime-avibactam was used.
2. Describe the indications and reasons for use of ceftazidime-avibactam at baseline.

3. Describe the the dose in mg, frequency of dose in hours, duration in days, and combination antibiotic regimen given till 14 days/ End of treatment whichever is earlier.

4. Describe at baseline any prior antimicrobial therapy administered in the 90 days prior to current admission.

5. Describe the gram negative organisms identified and the susceptibility to ceftazidime - avibactam along with molecular typing at baseline.

6. Describe the in-hospital length of stay (LOS) in days , LOS in ICU in days and percentage of various healthcare resource utilization in patients with infections treated by ceftazidime-avibactam up to 30 days post treatment completion with Ceftazidime- Avibactam death or discharge; whatever is first.

7. Determine the incidence of recurrent infections during the hospital stay, including re-infection and relapse up to 30 days post treatment completion with Ceftazidime-Avibactam, death or discharge; whatever is first.

9. RESEARCH METHODS

9.1 Study design

This is a non-interventional retrospective study to examine the real world usage, effectiveness, and safety of ceftazidime-avibactam for the treatment of Gram negative infections in India. 500 hospitalized patients who have received atleast 48 hours of Ceftazidime- Avibactam. Data will be collected for the period of 01 June 2019 till 01 April 2020. The patient should have completed treatment with ceftazidime-avibactam before 01 April 2020. The data collection will stop once data from 500 patients has been abstracted.

Data will be collected through the abstraction of hospital medical records (electronic) if available or through the individual patient case files (paper) in case electronic records are not available. Collected study data will include but will not be limited to patient characteristics, clinical and microbiologic characteristics of the infection, and treatment patterns, effectiveness, and safety of ceftazidime-avibactam.

9.2 Setting

Data will be abstracted from approximately 9 sites in India. Data from the patients who have received Ceftazidime-Avibactam as a part of the routine clinical management for Gram negative infections will be recorded as per the defined outcomes. Data will be abstracted from electronic health records .Individual patient medical records, in case is necessary. The data will be abstracted by a CRO (clinical research organization), the principal investigator (PI) or a reviewer (clinical research associate) nominated by the PI. For the records missing any of the requested information, data will be reported as missing. Data from patients that were part of the named access program will be excluded.

9.2.1 Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. >18 years of age
2. Admitted to hospital with documented gram negative infection
3. Has received treatment for atleast 48 hours (complete) with Ceftazidime-Avibactam as a part of his routine clinical management

9.2.2 Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. The patient is enrolled in any clinical trial of an investigational product
2. Age <18 years
3. Received Ceftazidime avibactam for less than 48 hours.
4. Patient with documented Acinetobacter infection.
5. Patient was a part of named access program or any other interventional study

9.3 Variables

The source of the data will either be the electronic medical records or patient files (if electronic record is not available)

Table 1: Variables and Operational definition

Variable	Role	Operational definition
Patient initials	Baseline characteristic	As documented in the records
Gender	Baseline characteristic	As documented in the records
Age	Baseline characteristic	As documented in the records
Weight	Baseline characteristic	As documented in the records
Date of hospitalization	Baseline characteristic	As documented in the records
Diagnosis	Baseline characteristic	Date and details of the diagnosis including the severity of the disease as reported by physician
Comorbidities (Deyo-Charlson Comorbidity Index)	Baseline characteristic	The score will be assessed/ calculated basis the patient records. (See annexure)
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, dates of administration, route, dose and frequency.
Recent healthcare procudures	Baseline characteristic	Within the 30 days before ceftazidime-avibactam initiation: Date(s) and type(s) of healthcare procedure.
Reason for admission to ICU	Current admission	Reason for admission to ICU will be documented along with the date of admission
Source of infection	Baseline characteristic	As documented in the records at baseline
Indication of Ceftazidime-Avibactam	Baseline characteristic	As documented in the records at baseline
Pre-treatment microbiology sample	Baseline characteristic	Microbiological culture(s) of current infection before ceftazidime-avibactam initiation (sample date(s), sample source(s)).
Pre-treatment microbiology results	Baseline characteristic	Results from microbiological culture (method of testing, identified pathogen(s), susceptibility, MDR).
	Baseline characteristic	Antibiotic(s) used for current infection before ceftazidime-avibactam initiation. Dates of administration, dose(s), frequency, duration, route of administration, reason for initiating (microbiology, progression on previous antibiotic), reason for

Variable	Role	Operational definition
Antibiotic therapy: Prior lines of treatment		discontinuation (adverse event, perceived clinical failure, isolation of a resistant pathogen, preference for empiric coverage, secondary infection requiring regimen change, switch to oral therapy, de-escalation).
Ceftazidime-avibactam	Exposure	Minimum exposure for ≥48 hours as per the records
Ceftazidime-avibactam dosage	Exposure	Dates of administration, dose(s), frequency, duration, reason for initiating and reason for discontinuation (if applicable) (e.g. adverse event, perceived clinical failure, isolation of a resistant pathogen, preference for empiric coverage, secondary infection requiring regimen change, switch to oral therapy, de-escalation, cure, death).
Concomitant antibiotic therapy	Exposure	Name(s) of antibiotic(s) used concurrently with ceftazidime-avibactam, dates of administration, dose(s), frequency, duration, route of administration, reason for initiating and reason for discontinuation (e.g. adverse event, perceived clinical failure, isolation of a resistant pathogen, preference for empiric coverage, secondary infection requiring regimen change, switch to oral therapy, de-escalation, cure, death) (if applicable).
Clinical symptom improvement	Outcome	Symptom improvement or worsening as reported by the physician using clinical judgement at 72 hours (day 3).
Post-treatment initiation microbiology sample	Outcome	Microbiological culture(s) during treatment with Ceftazidime-Avibactam (sample date, sample site) will be abstracted if done as per the medical records
Post-treatment initiation microbiology results	Outcome	Results from microbiological culture after treatment initiation (method of testing, identified pathogen(s), susceptibility, MDR) to determine the microbiological outcomes (defined below)
Clinical outcome	Outcome	Success, failure, and indeterminate (defined in annexure) at day7 and 14 days/ end of treatment from Ceftazidime/avibactam initiation whichever is earlier
Microbiological outcome	Outcome	Success, failure (defined in annexure) at day 14 from ceftazidime-avibactam initiation
Lines of antibiotic therapy	Outcome	Number of lines, reason for change in line (e.g. adverse event, perceived clinical failure, isolation of a resistant pathogen, preference for empiric coverage, secondary infection requiring regimen change, switch to oral therapy, de-escalation, cure, death).
In-hospital mortality	Outcome	Death occurring after treatment initiation but before hospital discharge (date, cause of death).
Safety	Outcome	Number of patients with serious and non-serious AEs with explicit attribution to Ceftazidime avibactam for upto 30 days post

Variable	Role	Operational definition
		treatment completion with Ceftazidime- Avibactam, death or discharge; whatever is first
Length of hospital stay	Outcome	Date(s) of hospital admission, date(s) of hospital discharge.
ICU length of stay	Outcome	Date(s) of ICU admission, date(s) of ICU discharge, diagnosis at admission
Healthcare utilization	Outcome	Detailed list of healthcare utilization (diagnosis at admission, departments admitted/discharged, discharge diagnosis, mechanical ventilation, dialysis, CT/MRI imaging, tracheostomy, surgical intervention, percutaneous procedures,) and dates of service.
Hospital ward	Outcome	All wards attended, ward of admission, ward of diagnosis (surgical, medical, onco-hematology, infectious disease, ICU, other)
Physician specialty	Site characteristic	Medical specialty of the treating physician indicating CAZ-AVI (e.g. infectious disease, surgical).
Hospital information	Site characteristic	Care level, type number of beds, number of ICU beds.
Recurrence of infection	Outcome	Patient showing symptoms and signs of a new infection after completion of treatment with Ceftazidime avibactam till 30 days. The site of infection/micro-organism may be same or different. This will be abstracted if the patient has inpatient stay for >30 days.

9.4 Data sources

Data will be abstracted from electronic health records .Individual patient medical records, in case is necessary. The data will be abstracted by a CRO (clinical research organization), the principal investigator (PI) or a reviewer (clinical research associate) nominated by the PI.

9.5 Study size

500 hospitalized patients who have received atleast 48 hours (complete) of Ceftazidime-Avibactam. Data will be collected for the period of 01 June 2019 till 01 April 2020. The data collection will stop once data from 500 patients has been abstracted

9.6 Data management

An electronic e-CRF will be used to abstract the records and INES data management system will be used for data entry and management.

9.6.1 Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to an electronic data record.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

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9.6.2 Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRF and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless *CRO and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years* if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7 Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Exposure

To qualify for participation, patients must have had atleast 48 hours (or three doses)of ceftazidime-avibactam.

All analyses will be performed among patients with ≥48 hours of ceftazidime-avibactam exposure.

Antibiotic regimens including ceftazidime-avibactam will be examined. An antibiotic regimen includes one or more medications, a planned therapeutic intervention which may involve one or more drugs. Each regimen is a line of therapy.

A new line of therapy is defined by where a treatment regimen is *discontinued* and a different regimen is started, the new regimen is considered a new line of therapy.

Outcome

- Clinical treatment outcome: please refer to Annex 3 for details on clinical treatment outcomes. Each line of therapy that includes ceftazidime-avibactam will be evaluated for the clinical outcome.
    - Microbiologic treatment outcome: please refer to Annex 3 for details on microbiologic treatment outcomes. Each line of therapy that include ceftazidime-avibactam will be evaluated for the microbiologic outcome. Microbiologic treatment outcome should be assessed at the end of each regimen containing ceftazidime-avibactam.
    - Hospital LOS will be calculated as: 1) the total number of consecutive days the patient was treated in the hospital from admission to discharge during their initial hospitalization; 2) the total number of days hospitalization between diagnosis of infection and discharge; 3) the total number of days the patient was treated in the hospital after ceftazidime-avibactam initiation up to hospital discharge, including the first day of treatment.
    - ICU LOS will be calculated as: 1) the total number of consecutive or non-consecutive days the patient was treated in the ICU during their initial hospitalization; and 2) the total number of days the patient was treated in the ICU after ceftazidime-avibactam initiation, including the first day of treatment.
    - Healthcare resource utilization data (medical/surgical/percutaneous procedures, CT/MRI imaging, days of mechanical ventilation, days of dialysis) will be abstracted from the patient medical records.

- Reasons for initiating or discontinuing antibiotic therapy (any line) include but are not limited to AE, perceived clinical failure, isolation of a resistant pathogen, secondary infection requiring regimen change, switch to oral therapy, de-escalation, cure, death.

Baseline Participant and Infection Characteristics

- Any hospitalized adult patient with an infection caused by Gram negative pathogens
- Pathogen susceptibility: All susceptibility information will be collected for the isolated pathogens including tested antibiotic by classes (e.g. aminoglycosides, amphenicol, beta-lactams, carbapenems, cephalosporins, glycopeptides, glycylcyclines, lipopeptides, macrolides, monobactams, nitroimidazoles, oxazolidinones, penicillins, penicillins and beta-lactamase inhibitors, quinolones, streptogramins, tetracyclines, other) and within class, and sensitivity to each (susceptible, intermediate, resistant).
- Multidrug-resistance: The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories. Categories include but are not limited to aminoglycosides, carbapenems, cephalosporins, cephamycins, fluoroquinolones, folate pathway inhibitors, glycylcyclines, penicillins, monobactams, phosphonic acids, polymyxins, tetracyclines (54).
- Source of infection (healthcare-associated, hospital-acquired, community-acquired) (55)
    - HCAI
        - Infection present ≤48 hours after hospital admission in patients who met one or more of the following criteria:
            - Received home healthcare (intravenous [IV], wound care, specialized nursing) during the past 30 days, excluding oxygen use,
            - Received healthcare in a clinical setting or received IV chemotherapy during the past 30 days,
            - Hospitalized in an acute care hospital for 2 or more days in the 3 months before baseline enrollment,
            - Resided in a nursing home or other long-term care facility (56).
    - HAI
        - Infection that occurred ≥48 hours after hospital admission that were not incubating at the time of admission.

- CAI
  - Infections detected ≤48 hours after hospital admission that do not qualify as a HCAI.

- Infection site: This refers to the origin of the infection

- Treatment line number: A new line of therapy starts when the antibiotic therapy is modified because an antibiotic is discontinued, the dose increased, patient is switched to an oral antibiotic therapy/regimen or a new antibiotic is added. Up to 5 lines of therapy will be collected. Assessment of treatment line will be based on generic name (i.e. active ingredient) of the drug (i.e. change in trade name with same active ingredient, dose and strength will not be classified as a treatment line change).
- APACHE II score will be collected from medical records for patients directly admitted to the ICU among sites that routinely calculate this measure. If the APACHE II score is not present in the medical records, it will not be calculated for the purpose of this study. Other common measures of disease severity (e.g. Sequential Organ Failure Assessment [SOFA], simplified acute physiologic score [SAPS], multiple organ dysfunction score [MODS], organ dysfunction and infection system [ODIN], APACHE III) will be collected, if reported in medical records.

- The Deyo-Charlson Comorbidity Index (DCCI) will be used to predict patients' 10-year probability of survival and will be used as a measure of overall health. The comorbidities evaluated in the DCCI will be collected at baseline from medical records to calculate the score. Details of this index are provided in Annex 2.2.

9.8 Quality control

Data will be collected and entered by site personnel for all data. The team will receive training that will include protocol/eCRF training and training on the electronic data capture (EDC) system that will be used for the study. All data will be entered directly into the database through web-based eCRFs. The eCRFs include programmable edit checks to provide feedback (automatic queries) on potential errors or missed fields. Data collection and validation procedures will be detailed in appropriate operational documents. All data collection will be performed in compliance with regulations.

Each study site will be responsible for ensuring that data entered into the study database are accurate and reflect the data found in the source documents (i.e. medical records). Data monitoring may be performed, as applicable, considering data privacy requirements in each of the participating countries.
Data entered into the database will be reviewed on a periodic basis to ensure plausibility; data queries may be issued to the participating sites as needed.

9.9 Limitations of the research methods

Because this is retrospective study, it is likely that some of the requested information will be missing, incomplete, or inaccurate. Safeguards against missing and inaccurate data will be employed throughout the research process. This includes choosing qualified sites, ensuring primary variables of interest are those that are routinely collected, using required fields and validation techniques in eCRFs, and employing analytic techniques including evaluating and describing patterns of missingness and using multiple imputation, when appropriate.
It is possible that patients treated at study sites, or patients selected for treatment with ceftazidime-avibactam, are not representative of the patient population that would be eligible for treatment. Results will be interpreted within this context.

Finally, this study will only capture AEs that are reported in the patient medical records and not all AEs that occur. Reported AEs are likely only those deemed clinically significant or those that need to be captured in the medical records for other reasons (e.g. hospital regulation). Evaluation of safety results will be interpreted within this context.

9.10 Other aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

10.1 Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and

protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Unstructured data analysis:

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a

temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.
The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the *Case record form* and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.
"All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.
Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.">
All research staff members must complete the following Pfizer training requirements:
• "YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)".
These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.
Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be published in a scientific journal. In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the

world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13 REFERENCES

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14 LIST OF TABLES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title

ANNEX 2. ADDITIONAL INFORMATION

ANNEX 2.1. DEFINITIONS OF DIFFERENT SUBCATEGORIES OF OUTCOME
Detail criteria for evaluation of clinical and microbiological outcome

Clinical Evaluation	Clinical Success	Cure	Resolution of all signs and symptoms of the infection. This will be as per the clinicians judgement and the treatment protocol/algorithm followed at the respective centers.
	Clinical Failure	Failure	Persistence of signs and symptoms from baseline This will be as per the clinicians judgement and the treatment protocol/algorithm followed at the respective centers.
	Clinical Indeterminate	Indeterminate	There is not enough information to conclude whether the antibiotic regimen containing ceftazidime-avibactam was a clinical failure or a success.
Microbiological Evaluation	Microbiological Success	Eradication	Absence of causative pathogen from appropriately obtained specimens at the site of infection
		Presumed Eradication	Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure.
	Microbiological Failure	Verified Persistence	The failure to eradicate the original pathogen from the site of isolation after completion of therapy.
		Presumed Persistence	Absence of appropriate material for culture or absence of results of control microbiological tests coupled with lack of clinical improvement after a pathogen was initially isolated.
		Persistence with Increasing minimal inhibitory concentration	Continued presence of the causative organism in a culture during or upon completion of treatment with IV study therapy that displays a ≥4-fold higher MIC to IV study therapy after treatment with IV study therapy.
	Emergent Infections	Superinfection	Detection of a new pathogen from the site of infection during therapy with need for antimicrobial treatment.
		New Infection	Detection of a new pathogen from the site of infection after therapy with need for antimicrobial treatment.

	Microbiological Unevaluable	Unevaluable	Patients without cultures or evident pathogens from the presumed site of infection.

IC=minimum inhibitory concentration; IV=intravenous

ANNEX 2.2: DEYO-CHARLSON COMORBIDITY INDEX

This table outlines the Deyo-Charlson Comorbidity Index. To quantify comorbidity, the Deyo-Charlson Comorbidity score is computed by adding the weights that are assigned to the specific diagnoses. A score of 1 is attributed to myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, depression, use of warfarin, hypertension and diabetes mild to moderate. The following diseases are scored as 2: hemiplegia or paraplegia, moderate or severe renal disease, skin ulcers/cellulitis, diabetes and complications and malignancy including leukemia and lymphoma. Moderate or severe liver disease is scored 3. Finally, a score of 6 is assigned to metastatic solid tumor and AIDS.

Comorbidity	Deyo-Charlson Weight
Myocardial Infarction	1
Congestive Heart Failure	
Peripheral Vascular Disease	
Cerebrovascular Disease	
Dementia	
Chronic Obstructive Pulmonary Disease	
Rheumatologic Disease	
Peptic Ulcer Disease	
Depression	
Use of Warfarin	
Hypertension	
Mild Liver Disease	
Diabetes Mild to Moderate	
Hemiplegia or Paraplegia	2
Moderate or Severe Renal Disease	
Diabetes + Complications	
Skin Ulcers/Cellulitis	

Comorbidity	Deyo-Charlson Weight
Malignancy	
Moderate to Severe Liver Disease	3
Metastatic Solid Tumor	6
AIDS	