# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## Study Information

| | |
|---|---|
| **Title** | Real-World Observational Study of Zavicefta® (ceftazidime-avibactam) to Characterize Use Patterns, Effectiveness and Safety – EZTEAM Study |
| **Protocol number** | C3591031 |
| **Protocol version identifier** | 4.0, amendment 3 |
| **Date of last version of protocol** | 29 April 2020 |
| **Active substance** | ceftazidime-avibactam, ACT: J01DD52 |
| **Medicinal product** | Zavicefta® (ceftazidime-avibactam) |
| **Research question and objectives** | The main objective of this non-interventional medical chart review study is to describe general treatment patterns, effectiveness, and safety of ceftazidime-avibactam in Europe including Russia and Latin America. |
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## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AEM | Adverse Event Monitoring |
| APACHE | Acute Physiology and Chronic Health Evaluation Score |
| BSI | Bloodstream Infection |
| CAI | Community-Acquired Infection |
| CI | Confidence Interval |
| cIAI | Complicated Intra-Abdominal Infection |
| CLABSI | Central Line Associated Blood Stream Infection |
| CRE | Carbapenem-Resistant *Enterobacteriaceae* |
| CT | Computerized Tomography |
| cUTI | Complicated Urinary Tract Infection |
| DCCI | Deyo-Charlson Comorbidity Index |
| eCRF | Electronic Case Report Form |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| GEP | Good Epidemiological Practice |
| 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 |
| ICU | Intensive Care Unit |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| LATAM | Latin America |
| LOS | Length of Stay |
| MDR | Multidrug-Resistant |
| MDRGN | Multidrug-Resistant Gram-Negative Organism |
| MRI | Magnetic Resonance Imaging |
| NI | Non-Interventional |
| NIS | Non-Interventional Study |
| NP | Nosocomial Pneumonia |
| SAE | Serious Adverse Event |

| Abbreviation | Definition |
|---|---|
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| 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

### Principal Investigators of the Protocol

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### Principal Investigator(s) of the Protocol

A full list of Principal Investigators and country coordinating investigators is available upon request.

## 4. ABSTRACT

### Title

Real-World Observational Study of Zavicefta® (ceftazidime-avibactam) to Characterize Use Patterns, Effectiveness and Safety

### Rationale and Background

Antimicrobial resistance and healthcare-associated infections (HCAIs) are well known public health threats. Gram-negative bacteria cause common hospital-acquired infections (HAIs) and infection with multidrug-resistant gram-negative organisms (MDRGNs), and have been associated with increased morbidity, mortality, and healthcare costs. Zavicefta® (ceftazidime-avibactam) is a unique combination of ceftazidime and avibactam developed to treat infections caused by gram-negative pathogens. In the European Union, Russia and several Latin American countries, ceftazidime-avibactam is an approved treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infections (cUTIs), hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), and infection due to aerobic gram-negative organisms with limited treatment options. Ceftazidime-avibactam has proven efficacious in non-inferiority Phase III trials but real-world evidence is needed about treatment characteristics, safety, and efficacy against *Pseudomonas* and multidrug-resistant (MDR) gram-negative bacteria, including carbapenem-resistant *Enterobacteriaceae* (CRE).

### Research Question and Objectives

The main objective of this medical chart review study is to describe general treatment patterns, effectiveness, and safety of ceftazidime-avibactam in real-world settings in Europe (including Russia) and Latin America.

### Study Design

This observational study will include approximately 700 hospitalized patients with a gram-negative infection, who have received at least one dose of ceftazidime-avibactam. Patients will be recruited in approximately 62 sites across 12 countries in Europe (including Russia) and Latin America. Patients will be followed from ceftazidime-avibactam initiation until 60 days post hospital discharge, mortality, withdrawal from the study, or loss-to-follow-up, whichever occurs first. Data will be abstracted from medical records using an electronic case report form (eCRF). Baseline data include patient socio-demographics, medical history, and clinical and microbiological characteristics of the infection treated. Follow-up data will include details of treatment over time and clinical, microbiological, and healthcare resource utilization outcomes. Evaluation of clinical success will be performed in patients with at least ≥72 hours of exposure to ceftazidime-avibactam. Safety will be evaluated in all patients exposed to at least one dose of the product.

### Population

Hospitalized patients with gram-negative infections treated with ceftazidime-avibactam.

**Variables**

- Exposure: ceftazidime-avibactam.
- Outcomes: clinical effectiveness, microbiological outcomes, adverse events (AEs), serious adverse events (SAEs), length of hospital stay, in-hospital healthcare resource utilization; mortality and hospital readmissions within 60 days of hospital discharge.
- Key covariates: patient demographics, indication, infection source (hospital/healthcare/community), treatment history, clinical characteristics.

**Data Sources**

Data from European and Latin American study sites will be used for this study. Sites will be qualified and then selected, based on responses to a series of questions intended to determine their capability of conducting the study and ability to contribute to the target patient population. Data will be abstracted from patient medical charts after treatment completion, and up to 60 days post hospital discharge or a censoring event (death, withdrawal from the study, or loss-to-follow-up).

**Study Size**

Overall, 700 patients with a gram-negative infection who have received at least one dose of ceftazidime-avibactam will be enrolled in this study.

Sample size was based on the following assumptions, assuming 75% of patients enrolled with at least 72 hours exposure to ceftazidime-avibactam and 70% clinical success, enrolling 300 patients in Europe would yield approximately 225 evaluable patients for clinical success and an expected 95% confidence interval (CI) of 70.0% (63.6% - 75.9%).

Assuming 10% of patients with at least 72 hours exposure to ceftazidime-avibactam have no pathogen identification, and 80% experience microbiological success, enrolling 300 patients in Europe would yield approximately 202 evaluable patients for microbiological success and a 95% CI of 80.0% (73.8% - 85.3%).

Based on the same assumptions for treatment outcomes as in Europe, 400 patients will be included in Latin America to obtain 300 evaluable patients for clinical success, and 270 evaluable patients for microbiological success. Using a two-sided exact method, enrolling 400 patients would yield an expected 95% CI of 70.0% (64.5% - 75.1%) of patients experiencing clinical treatment success and 80.0% (76.7% - 83.1%) of patients experiencing microbiological treatment success.

**Data Analysis**

Baseline characteristics will be summarized for ceftazidime-avibactam patients. Descriptive statistics will be used to summarize the treatment patterns (eg, dosage, indications, infection source), effectiveness (eg, clinical and microbiological outcomes), and safety (eg, mortality, AEs) of ceftazidime-avibactam and healthcare resource utilization by patients prescribed

ceftazidime-avibactam. AEs and SAEs will be recorded and summarized as the proportion of patients with each safety event out of all treated patients. Hospital readmissions will be analyzed as the proportion of patients readmitted to the hospital for recurrent infection within 60 days of hospital discharge out of all patients discharged from the initial hospitalization.

**Milestones**

Start of data collection: November 2018.

End of data collection: approximately December 2020 or later if the sample size is not reached.

Final study report: Q3 2021 for Europe and Q1 2022 for Latin America.

# 5. AMENDMENTS AND UPDATES

## **Amendment#1:** 04 October 2019

| Sections modified and updates | Reason |
|---|---|
| **Study information:** Update authors and milestones<br><br>**6. Milestones:** Final study report: Q3 2021 for Europe Q1 2022 for LATAM | Administrative |
| **Study information; 4. Abstract; 9. Research methods**<br><br>This observational study will include approximately 1030 hospitalized patients with a gram-negative infection, who have received at least one dose of ceftazidime-avibactam. Patients will be recruited in approximately 62 sites across 12 countries in Europe and Latin America. | Extension of the study to Latin American countries, after local approval and launch of ceftazidime-avibactam. |
| **8. Research question and objectives**<br><br>Describe the microbiological outcomes among patients treated with ceftazidime-avibactam during the 14 days after ceftazidime-avibactam initiation.<br><br>Describe safety outcomes in patients receiving ceftazidime-avibactam between treatment initiation and hospital discharge. | Microbiology results are collected for 14 days after treatment initiation with ceftazidime-avibactam.<br><br>Safety information is available only during the initial hospitalization. |
| **9.1. Study design**<br><br>Patients treated with at least one dose of ceftazidime-avibactam in routine clinical practice can be enrolled from the date of ceftazidime-avibactam launch in the country, or January 2018, or a maximum of 6 months before study start in the participating site, whichever is latest, onwards. | Extension of the study to Latin America. |
| **9.5 Study size**<br>• Europe: 630 enrolled patients.<br>• Latin America: 400 enrolled patients. | Extension of the study to Latin America. |
| **9.7.1. Exposure**<br><br>Addition of definitions for new line of therapy:<br>• A line of treatment is considered finished when at least one antibiotic given in combination is modified.<br>• Escalation after 4 days of treatment (dose increase or addition of another antibiotic for gram-negative) will be considered as a failure.<br>• Stream lining (stop an antibiotic) or conversion to oral therapy will be considered as a success. | According to the decision of the Steering Committee,<br>14 May 2019. |

| Sections modified and updates | Reason |
|---|---|
| **9.7.4. Planned analyses**<br>• Europe and Latin America will be analyzed separately.<br>• Outcomes of interest will be stratified by indication, by bacteria (Escherichia coli, Klebsiella spp., Enterobacter spp., Pseudomonas spp., others), and by country. | According to the decision of the Steering Committee, 14 May 2019 |

## **Amendment#2:** 9 December 2019

| Sections modified and updates | Reason |
|---|---|
| • Inclusion criterion 2: Change time period of ceftazidime-avibactam intake among participating patients (Patient received ≥1 dose of ceftazidime-avibactam in routine practice at participating site since 01 January 2018 OR the date of launch in the country if after 2018).<br>• Patient information and consent<br>1. Remote consent can be completed if approved by local legislation.<br>2. A Next of Kin informed consent will be sought for deceased patients. For out of reach patients a waiver may be used in countries where it is acceptable and approved by local regulations.<br>• Change number of sites to 62. | Administrative |

## **Amendment#3:** 29 April 2020

| Sections modified and updates | Reason |
|---|---|
| **3. Responsible parties**<br>Michael Begnino has been removed from the responsible parties | Administrative |
| **Study information; 4. Abstract; 9. Research methods**<br>This observational study will include approximately 700 hospitalized patients with a gram-negative infection, who have received at least one dose of ceftazidime-avibactam.<br>**9.5 Study size**<br>• Europe: 300 enrolled patients.<br>• Latin America: 400 enrolled patients. | Sample size reduction in Europe due to difficulty to recruit patients in this region. |

| Sections modified and updates | Reason |
|---|---|
| Table 1. Sample Size and Precision of the Estimate for Clinical Treatment Success and Table 2. Sample Size and Precision of the Estimate for Microbiological Treatment Success have been updated with a row for 200 subjects<br><br>**9.5.2. Study size in Latin America**<br>The part of the sentence below that is marked in bold has been added:<br>Based on the same assumptions for treatment outcomes as in Europe, **to obtain a 95% CI for treatment success that is approximately 10.0 percentage points for both clinical and microbiological treatment success,** 400 patients will be included in Latin America to obtain 300 evaluable patients for clinical success, and 270 evaluable patients for microbiological success. | |
| **9.1 Study design**<br>Section added: In France data abstraction should be retrospective only and in this case data abstraction should start after the 60 days follow-up date. Patient information sheet that is specific to France should be sent to patients before data abstraction starts. No follow-up calls with patients should occur in France. | Regulatory<br>To describe the data abstraction according to French regulatory framework. |
| **9.1 Study design**<br>Patients treated (for the indication that is approved in the country as per country label) with at least one dose of ceftazidime-avibactam in routine clinical practice at a participating site since 01 January 2018, or the date of launch in the country if after 2018, can be enrolled.<br>As this is an observational study, patients will be treated as per local label based on the standard of care at the discretion of their physician.<br><br>**9.7.3 Baseline participant and infection characteristics**<br>Indication for ceftazidime-avibactam prescription (will vary depending on country local label).<br>Other infection with limited treatment options: This indication is not approved in all participating countries. | Zavicefta® indications vary across countries, and prescriptions should follow the local label. |
| **9.4. Data sources**<br>Data will be abstracted from patient medical charts <u>after treatment completion</u>, and up to 60 days post hospital discharge or a censoring event (death, withdrawal from the study, or loss-to-follow-up). | Administrative.<br>Language alignment. |
| **9.9. Limitations of the research methods**<br>Some editorial changes have been done in this section:<br>• Deletion of the following sentences:<br>  • To address this issue, data will only be collected for a limited period prior to study start.<br>  • Characteristics of patients treated prior to and after study start will be compared to examine any bias from this source.<br>• Addition of the part of the sentence marked in bold below:<br>Finally, this study will only capture adverse events (AEs) **related to ceftazidime-avibactam or other products marketed by the sponsor** - that are reported in the patient medical records and not all AEs that occur. | Administrative. |

| Sections modified and updates | Reason |
|---|---|
| **10. Protection of human subjects**<br>10.1 Patient Information and 10.2. Patient consent: sections updated according to the current template.<br>**10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**<br><br>The following paragraph has been changed:<br><br>**There must be** prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, ICFs 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.<br><br>**11. Management and reporting of adverse events/adverse reactions**<br><br>The following paragraphs have been changed:<br><br>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.<br><br>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. | To update the protocol to current template |

# 6. MILESTONES

## Study Milestones

| Milestone | Planned date |
|---|---|
| Start of data collection | November 2018 |
| End of data collection | December 2020 or later if the sample size is not reached |
| Final study report | Q3 2021 for Europe, Q1 2022 for Latin America |

## 7. RATIONALE AND BACKGROUND

According to the World Health Organization (WHO), infections were among the top 3 leading causes of death worldwide as of 2012.[1] Antimicrobial resistance and healthcare-associated infections (HCAIs) are well known major public health threats.[2]

The annual number of patients with at least one HCAI in European acute care hospitals was estimated at 3.2 million (95% confidence interval [CI]: 1.9–5.2 million) in 2011-2012.[3] HCAI can result in prolonged hospital stay, long-term disability, high costs for patients and their families, and death, increased resistance of microorganisms to antimicrobial agents and financial burden for the health system.[4,5] In Europe, the 2008 WHO report on communicable diseases estimated that HCAIs cause an estimated 16 million days of hospitalization and 37,000 deaths annually, and contribute to an additional 110,000 deaths.[6] In Latin America, the prevalence of HCAIs is high and has been reported to be around 12.[7,8]

Gram-negative bacteria develop resistance to commonly prescribed antibiotics through mutation and gene acquisition.[9] Multidrug-resistant gram-negative organisms (MDRGNs) have emerged as a major threat to hospitalized patients and have been associated with mortality rates between 30% and 70%.[10-16] Infections caused by drug-resistant, gram-negative bacteria represent a considerable financial burden to healthcare systems due to the increased costs of managing the infection, especially resulting from extended hospital stays.[17] In 2009, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) estimated that the total healthcare cost incurred in Europe due to resistant infections totaled at least €1.5 billion each year, with more than half of this total accounted for by resistant gram-negative pathogens, €867 million. Costs include both healthcare treatment and societal costs such as lost productivity due to absence from work and.[18]

Gram-negative bacteria cause the 4 most frequent types of hospital-acquired infections (HAIs): hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia [VAP]), intra-abdominal infection (IAI), urinary tract infection (UTI), and bloodstream infection (BSI); and caused 43% of all HCAIs, 65% of catheter-associated UTIs, 65% of HAP, and 22% of central line associated bloodstream infections (CLABSI) from 2009 to 2010 in the United States.[9] The most important gram-negative pathogens in the hospital setting include *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which account for 27% of all pathogens and 70% of all gram-negative pathogens causing HCAIs.[9]

**Urinary tract infection (UTI)** is among the most common bacterial conditions in adults; it has been reported to represent 19% of the HCAIs in acute care hospitals in Europe and remains an important clinical problem with costly financial implications to society.[3,19,20] Complicated urinary tract infection (cUTI) occurs in both men and women, usually associated with some functional or structural abnormality: calculi or stones, indwelling catheters or other drainage devices, obstruction, immunosuppression, renal failure, renal transplantation and pregnancy.[19-21] Inappropriate practice, such as failure to remove a urinary catheter no longer needed for patient care, are associated with cUTI.[21] Most of the nosocomial UTIs are complicated infections.[20] The bacterial spectrum of

healthcare-associated urinary tract infections (HAUTIs) is broad, and antibiotic resistance is common.[22] One study reported that the most commonly isolated groups of microorganisms in UTI are gram-negative *Enterobacteriaceae* (63.8;[2] and the most commonly isolated microorganism overall was *Escherichia. coli* (15.2% overall, and 37.1% in UTIs), followed by *Staphylococcus aureus* (12.1% overall and 21.5% in surgical site infections [SSIs]).[2] The UTI antimicrobial resistance patterns restrict effective antibiotic therapy, evolve over time and show geographical variability.[20]

**Intra-abdominal infections (IAI**) can be divided into several groups based on the underlying process: peritonitis (primary or secondary), abscess (intraperitoneal, liver, pancreatic), perforation (complicating appendicitis, diverticulitis or gastric and duodenal ulcers), diverticula of intestine and other infectious process such as cholangitis or.[23,24] Complicated IAI (cIAI) occurs when the infection process affects more than one organ, causing localized or diffuse peritonitis. It requires both surgical and antibiotic therapy beyond the 24-hour regimen of perioperative antibiotics typically used in uncomplicated IAI. It is primarily a clinical diagnosis.[24] Patients with poor nutritional status, immunosuppression and high Acute Physiology and Chronic Health Evaluation (APACHE) score are at increased risk for cIAI and subsequent mortality. Most IAIs are polymicrobial, with enteric gram-negative pathogens contributing heavily. In healthcare-associated IAIs, highly resistant gram-negative pathogens may predominate. A study that evaluated a total of 3,160 clinical isolates of *E. coli* from IAIs from 13 European countries between 2008 and 2009 showed that 11% were found to produce extended-spectrum beta-lactamases (ESBLs).[25] Risk of mortality among patients with intra-abdominal sepsis have been estimated between 25% to 35% but can exceed 70% depending on risk.[26-29]

**Hospital-acquired pneumonia (HAP)** is a type of healthcare-associated pneumonia (HCAP) that consists of a lower respiratory infection that was not incubating at the time of hospital admission and that presents clinically 2 or more days after hospitalization.[30] The VAP is a type of HAP in persons who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-hour period before the onset of infection. It is associated with intubation, invasive mechanical ventilation, sedation, curarization, coma, trauma, the presence of enteral nutrition, and surgery.[31] A study reported that the most commonly isolated groups of microorganisms in pneumonia are gram-negative non-*Enterobacteriaceae* (36.5%).[2] The HAP has been associated with relatively high rates of antimicrobial resistance, especially in patients in intensive care units (ICUs) or those requiring mechanical ventilation.[32] Several epidemiologic studies have suggested that the empiric administration of inadequate antibiotic treatment for HAP is an important determinant of hospital,[33-35] which appears to be especially concerning with organisms associated with high resistance rates, including *Pseudomonas spp*., *Serratia spp*., *Enterobacter spp*., and *Acinetobacter spp*.[32] Estimates of the risk of death among patients with VAP have ranged from 7% to 30%.[36]

**For cUTI, cIAI and HAP/VAP and other HCAI,** antibiotics are usually prescribed empirically before physicians are able to identify the causative pathogen. Failure of initial empiric antibiotic therapy is associated with increased morbidity, mortality, and may be associated with additional healthcare resource utilization and costs.[37]

The available evidence shows that the proportion of gram-negative organisms resistant to commonly used antibiotics is increasing.[38,41] For the past 3 decades, carbapenems played a central role in treating severe infections caused by suspected drug-resistant bacteria. This has been compromised by the emergence of pathogens resistance to carbapenems, especially in *Enterobacteriaceae*.[42] In response to this threat, the novel beta-lactamase inhibitor avibactam was developed and is able to inactivate many of the class C and class A beta-lactamases, including *Klebsiella pneumoniae* carbapenemases (KPCs).[43]

**Zavicefta® (ceftazidime-avibactam)** is a unique combination of ceftazidime and avibactam administered intravenously that has been approved in the European Union, Russia and Latin American countries for the treatment of cIAI, cUTI, HAP/VAP, and infection due to aerobic gram-negative organisms with limited treatment options,[44] including carbapenem-resistant *Enterobacteriaceae* (CRE).[42]

Ceftazidime-avibactam efficacy and safety have been assessed in Phase II trials[45,46] and in non-inferiority Phase III trials. Ceftazidime-avibactam plus metronidazole was compared to meropenem in patients with cIAI, results demonstrated that ceftazidime-avibactam was non-inferior for clinical cure rate for;[47] ceftazidime-avibactam was compared to meropenem in patients with nosocomial pneumonia (NP) including VAP, results showed that ceftazidime-avibactam was non-inferior for clinical cure rate and 28-day mortality for NP patients;[48] ceftazidime-avibactam was compared to doripenem in patients with cUTI/acute pyelonephritis, ceftazidime-avibactam was proved non-inferior for symptomatic resolution and microbiological cure rate in.[49] Ceftazidime-avibactam *in vitro* activity against CRE has been shown.[42] In 7 Phase II and Phase III clinical trials, 2024 adult patients were treated with ceftazidime-avibactam. The most common adverse reactions occurring in ≥5% of patients treated with ceftazidime-avibactam were positive Coombs direct tests, nausea, and diarrhea. Nausea and diarrhea were usually mild or moderate in intensity.[44] Real-world data examining the treatment characteristics, safety, and efficacy of ceftazidime-avibactam against multidrug-resistant (MDR) pathogens including CRE is needed.

## 8. RESEARCH QUESTION AND OBJECTIVES

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

The primary objective of this study is to describe the patterns of use of ceftazidime-avibactam in real-world practice.

- Describe the indications and reasons for use of ceftazidime-avibactam; provide detailed information about its use for the treatment of infections due to aerobic gram-negative organisms with limited treatment options.
- Describe the usage patterns of ceftazidime-avibactam, including treatment line, dose, frequency of dose, duration, and polytherapy regimens.
- Describe the microbiological evidence available for patients treated with ceftazidime-avibactam.

- Describe the source of infection for which ceftazidime-avibactam is prescribed including community-acquired infections (CAIs), HCAIs, and HAIs.

The secondary objective of this study is to determine the effectiveness and safety of ceftazidime-avibactam in real-world practice.

- Describe the clinical outcomes of patients treated with ceftazidime-avibactam (ie, treatment success, failure, or indeterminate) in-hospital, and up to 30 and 60-days after hospital discharge.

- Describe the microbiological outcomes among patients treated with ceftazidime-avibactam during the 14 days after ceftazidime-avibactam initiation.

- Describe safety outcomes in patients treated with ceftazidime-avibactam between treatment initiation and hospital discharge.

- Describe the in-hospital length of stay (LOS), LOS in ICU and healthcare resource utilization in patients treated by ceftazidime-avibactam.

- Determine the prevalence of hospital readmissions for recurrence of the same infection within 30 and 60 days of hospital discharge among patients treated with ceftazidime-avibactam.

- Determine the in-hospital mortality and mortality up to 30 and 60 days after hospital discharge in patients treated by ceftazidime-avibactam.

## 9. RESEARCH METHODS

### 9.1. Study Design

This is a NI medical chart review study aiming to examine the treatment patterns, effectiveness, and safety of ceftazidime-avibactam in approximately 12 countries and 62 sites in Europe (including Russia) and Latin America.

Patients treated with at least one dose of ceftazidime-avibactam (for the indication that is approved as per country label) in routine clinical practice at a participating site since 01 January 2018 or the date of launch in the country if after 2018 can be enrolled.

As this is an observational study, patients will be treated as per local label based on the standard of care at the discretion of their physician. No drugs will be supplied for this study and patients will receive treatment through standard local practice. Patients treated as part of a compassionate program of ceftazidime-avibactam are not eligible to participate in the study.

Written informed consent will be provided by the patients prior to enrolling in the study in accordance with local regulations. In most cases, hospitalized patients or their legal delegate (when applicable) will provide written informed consent in person. For discharged patients or patients for whom the legal delegate is not available in person, remote consenting will be

performed via telephone calls if approved by local regulation. After study information is provided remotely, an informed consent form (ICF) will be mailed to the patient or legal representative. The patient or legal representative will be required to sign and return the ICF to the Principal Investigator (PI) prior to enrollment.

All data will be collected through the abstraction of hospital medical records. Collected study data will include but will not be limited to patient characteristics, clinical and microbiological characteristics of the infection, and treatment patterns, effectiveness, and safety of ceftazidime-avibactam. The study data collection and assessment schedule are described in Figure 1.

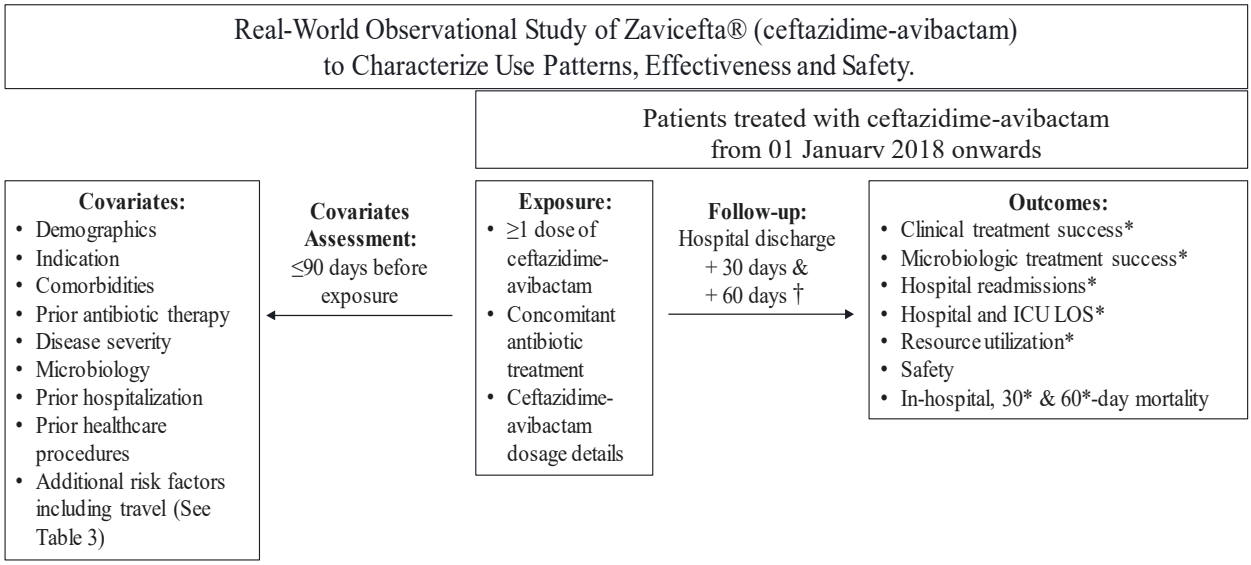
Patients who were exposed to ceftazidime-avibactam for ≥72 hours will be eligible for effectiveness analyses, including evaluation of treatment success. To avoid a selection bias that could result from restricting to patients with extended exposure, a small set of data elements will be collected and analyzed among patients with <72 hours of exposure. These data include details about exposure, indication and safety. Safety data will be analyzed for all patients enrolled.

Patients who meet all the inclusion and exclusion criteria will be followed through their medical records up to 60 days after hospital discharge, death, withdrawal from the study, or loss-to-follow-up, whichever occurs first.

Information about hospital readmissions or death after hospital discharge not available via medical chart abstraction will be ascertained by contacting the patient or their legal representative by phone >60 days after hospital discharge.

In France data abstraction should be retrospective only and in this case data abstraction should start after the 60 days follow-up date. Patient information sheet that is specific to France should be sent to patients before data abstraction starts. No follow-up calls with patients should occur in France.

**Figure 1. Study Design**




Note: Data collection will begin 01 January 2018 or since the date of launch if after 01 January 2018.
† Patients followed from ceftazidime-avibactam initiation until 60 days after hospital discharge or another censoring event.
* Indicates outcome that will be examined for patients exposed to ceftazidime-avibactam for ≥72 hours
Note: See Table 3 for an extended list of collected variables.
ICU=Intensive care unit; LOS=length of stay

## 9.2. Setting

Patients will be enrolled from approximately 62 sites in 12 countries in Europe and in Latin America. Sites will be qualified and then selected based on responses to a series of questions intended to determine capability of conducting the study and ability to contribute to the target patient population.

Participating study sites will aim to enroll consecutive eligible patients who initiated ceftazidime-avibactam based on physician prescribing. If an eligible patient was approached and does not agree to participate in the study, the reason for non-participation will be documented in the enrollment log.

Besides routine treatment, no clinic visits are required as part of participation in this study. All data are intended to be collected by referencing the medical records. For patients missing any of the requested information, data will be reported as missing. Eligibility in the study has been summarized below in Section 9.2.1 and Section 9.2.2. Patients participating in clinical trials are excluded from this study because protocol driven activities may be outside of normal practice and could confound safety assessments.

### 9.2.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible:

1. Hospitalized patient ≥18 years old or considered an adult in accordance with the age of majority in the participant's country of residence at the time of treatment with ceftazidime-avibactam.

2. Patient received ≥1 dose of ceftazidime-avibactam in routine practice at participating site since 01 January 2018 or the date of launch in the country if after 2018.

3. Patient underwent microbiological sampling ≤5 days before the initiation of ceftazidime-avibactam (irrespective of results and actual bacteriological identification).

4. Patient has all required essential data elements which include:

    a. Start and stop dates of ceftazidime-avibactam;

    b. Start and stop dates of prior antibiotic therapy used for the index infection;

    c. Type of combined antibiotic therapy (if applicable) and start and stop dates of any antibiotic combined with ceftazidime-avibactam.

5. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study where required by local regulations.

### 9.2.2. Exclusion Criteria

Patients must not meet any of the following exclusion criteria to be eligible:

1. The patient is enrolled in any clinical trial of an investigational product. Patients who are enrolled in non-interventional studies (NISs) (eg, registries) are eligible for inclusion.

2. The patient has received ceftazidime-avibactam in a compassionate care program setting.

3. The patient was exposed to ceftazidime-avibactam before use for the index infection.

## 9.3. Variables

Table 1 shows the list of exposures, outcomes, and other variables to be collected from the patient medical records including risk factors, comorbidities, and concomitant medications. All variables will be collected for patients exposed to ceftazidime-avibactam for ≥72 hours. For patients exposed to ceftazidime-avibactam for a duration of <72 hours, a limited set of variables will be collected, identified in Table 2.

**Table 1: List of Variables and Definitions for Patients Exposed to Ceftazidime-avibactam for ≥72 hours (non-exhaustive)**

| Variable | Role | Operational definition |
|---|---|---|
| Informed consent | Required for participation | Signed ICF submitted to study personnel. |
| Year of birth | Baseline characteristic | As reported by physician (if allowed by local regulations). |
| Sex | Baseline characteristic | As reported by physician. |
| Employment | Baseline characteristic | As reported by physician. |
| Height, weight | Baseline characteristic | Height and weight as reported by physician. |
| 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 procedure(s) | Baseline characteristic | Within the 30 days before ceftazidime-avibactam initiation: Date(s) and type(s) of healthcare procedure. |
| Pre-treatment disease severity (APACHE II or other prognostic assessment) | Baseline characteristic | Concurrent with index infection diagnosis (as close to diagnosis as possible, a maximum of 7 days prior to treatment); measured in patients directly admitted to the ICU; Date of assessment. |
| Additional risk factors | Baseline characteristic | Travel to foreign country within the past 3 months; country and date(s) of travel; comorbidities (Deyo-Charlson Comorbidity Index, see Annex 3 for detailed description); pregnancy (weeks of gestation since last menstrual period); alcohol use (drinks per week); tobacco use (current smoker and cigarettes per week). |
| Source of infection | Baseline characteristic/sub-group identifier | As reported by physician (HAI, HCAI, CAI). See Section 9.7 Data Analysis for extended definitions. |
| Indication for ceftazidime-avibactam | Baseline characteristic/sub-group identifier | As reported by physician (cIAI, cUTI, HAP/VAP, explain other; initial site of infection (organ)); See Section 9.7 Data Analysis for extended definitions. Date of diagnosis. |
| Indication for ceftazidime-avibactam: Other (1) | Baseline characteristic/sub-group identifier | Type of infection (eg, SSI, CLABSI, primary BSI, meningitis, other; initial site of infection [organ]). See Section 9.7 Data Analysis for details. |
| Pre-treatment microbiology sample | Baseline characteristic | Microbiological culture(s) of current infection during the 5 days of ceftazidime-avibactam initiation (sample date(s), sample source(s)). |
| Pre-treatment microbiology results | Baseline characteristic/sub-group identifier | Results from microbiological culture (method of testing, identified pathogen(s), susceptibility, MDR). See Section 9.7 Data Analysis for details. |

| Variable | Role | Operational definition |
|---|---|---|
| Antibiotic therapy: Prior lines of treatment | 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 discontinuation (AE, 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 | Use of ≥1 dose as reported in records. |
| Ceftazidime-avibactam dosage | Exposure | Dates of administration, dose(s), frequency, duration, reason for initiating and reason for discontinuation (if applicable) (eg, AE, 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/sub-group identifier | 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 (eg, AE, 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 within 48 and 72 hours of ceftazidime-avibactam initiation. |
| Post-treatment initiation microbiology sample | Outcome | Microbiological culture(s) during the 14 days after ceftazidime-avibactam initiation (sample date, sample site). See Section 9.7 Data Analysis for definitions. |
| Post-treatment initiation microbiology results | Outcome | Results from microbiological culture after treatment initiation (method of testing, identified pathogen(s), susceptibility, MDR). See Section 9.7 Data Analysis for definitions. |
| Clinical treatment outcome | Outcome | Success, failure, and indeterminate. See Annex 1 for definitions. |
| Microbiological treatment outcome | Outcome | Success, failure, emergent infections and unevaluable. See Annex 1 for definitions. |
| Lines of antibiotic therapy | Outcome | Number of lines, reason for change in line (eg, AE, 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). See Section 9.7 Data Analysis for definitions. |
| In-hospital mortality | Outcome | Death occurring after treatment initiation but before hospital discharge (date, cause of death). |

| Variable | Role | Operational definition |
|---|---|---|
| 30-day mortality | Outcome | Death occurring within the 30 days after hospital discharge (date, cause of death). |
| 60-day mortality | Outcome | Death occurring within the 60 days after hospital discharge (date, cause of death). |
| Safety | Outcome | All serious and non-serious AEs with explicit attribution to ceftazidime-avibactam that appear in the reviewed information and scenarios involving drug exposure to ceftazidime-avibactam, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of ceftazidime-avibactam. |
| Length of hospital stay | Outcome | Date(s) of hospital admission, date(s) of hospital discharge. See Section 9.7 Data Analysis for extended definition. |
| ICU length of stay | Outcome | Date(s) of ICU admission, date(s) of ICU discharge, diagnosis at admission. See Section 9.7 Data Analysis for an extended definition. |
| Hospital readmission | Outcome | Hospital readmission during the 30 and 60 days after initial discharge, reason for readmission. See Section 9.7 Data Analysis for an extended definition. |
| 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, other) and dates of service. See Section 9.7 Data Analysis for an extended definition. |
| 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 (eg, infectious disease, surgical). |
| Hospital information | Site characteristic | Care level, type number of beds, number of ICU beds. |
| Local gram-negative resistance patterns | Site characteristic | Most recent assessment of the proportion of gram-negative isolates exhibiting resistance to 3rd generation cephalosporins or carbapenem antibiotics, and dates of assessment. |

AE=adverse event; APACHE=Acute Physiology and Chronic Health Evaluation; BSI=bloodstream infection; CAI=community-acquired infection; CT: computerized tomography scan; cIAI=complicated intra-abdominal infection; CLABSI=central line associated blood stream infection; cUTI=complicated urinary tract infection; HAI=hospital-acquired infection; HAP=hospital-acquired pneumonia; HCAI= healthcare-associated infection; ICF=informed consent form; ICU=intensive care unit; MDR=multidrug-resistant; MRI: magnetic resonance imaging; SSI=surgical site infection; VAP=ventilator-associated pneumonia. (1) Other indications (infections due to aerobic gram-negative organisms with limited treatment options, see Section 7) are not included in the label for all participating countries.

**Table 2. List of Variables and Definitions for Patients Exposed to Ceftazidime-avibactam for <72 hours (non-exhaustive)**

| Variable | Role | Operational definition |
|---|---|---|
| Year of birth | Baseline characteristic | As reported by physician (if allowed by local regulations). |
| Sex | Baseline characteristic | As reported by physician. |
| Source of infection | Baseline characteristic/sub-group identifier | As reported by physician (HAI, HCAI, CAI). See Section 9.7 Data Analysis for extended definitions. |
| Indication for ceftazidime-avibactam | Baseline characteristic/sub-group identifier | As reported by physician (cIAI, cUTI, HAP/VAP, explain other; initial site of infection (organ)); See Section 9.7 Data Analysis for extended definitions. |
| Indication for ceftazidime-avibactam: Other (1) | Baseline characteristic/sub-group identifier | Type of infection (eg, SSI, CLABSI, primary BSI, meningitis, other; initial site of infection (organ)). See Section 9.7 Data Analysis for details. |
| Ceftazidime-avibactam | Exposure | Use of ≥1 dose as reported in records. |
| Ceftazidime-avibactam dosage | Exposure | Dates of administration, dose(s), frequency, duration, reason for initiating and reason for discontinuation (if applicable) (eg, AE, 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 | All serious and non-serious AEs with explicit attribution to ceftazidime-avibactam that appear in the reviewed information and scenarios involving drug exposure to ceftazidime-avibactam, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of ceftazidime-avibactam. |

AE=adverse event; BSI=bloodstream infection; CAI=community-acquired infection; cIAI=complicated intra-abdominal infection; CLABSI=central line associated blood stream infection; cUTI=complicated urinary tract infection; HAI=hospital-acquired infection; HAP=hospital-acquired pneumonia; HCAI= healthcare-associated infection; SSI=surgical site infection; VAP=ventilator-associated pneumonia. (1) Other indications (infections due to aerobic gram-negative organisms with limited treatment options, see Section 7 are not included in the label for all participating countries.

## 9.4. Data Sources

The data source for this study will be patient medical records. Data will be abstracted from patient medical charts after treatment completion, and up to 60 days post hospital discharge or a censoring event (death, withdrawal from the study, or lost-to-follow-up). Patients should be carefully tracked to identify censoring events.

AEs will be collected as part of standard practice. More information regarding the reporting of AEs is described in Section 11.

## 9.5. Study Size

### 9.5.1. Study Size in Europe

Sample size for this study was calculated with the goal of maximizing precision when estimating clinical and microbiological treatment success.

Clinical Treatment Success Assumptions:[47-49]

- 25% of the enrolled patients discontinue ceftazidime-avibactam before 72 hours of exposure (eg, due to AE, microbiological results);
- 75% of patients are exposed to ceftazidime-avibactam for ≥72 hours and are assessable for clinical effectiveness.70% of the assessable patients experience clinical treatment success, as defined in Annex 1.

**Table 3. Sample Size and Precision of the Estimate for Clinical Treatment Success**

| | | | Prevalence of Clinical Treatment Success | | | |
|---|---|---|---|---|---|---|
| N | | 60% | 65% | 70% | 75% | 80% |
| | 200 | (52.9% - 66.8%) | (58.0% - 71.6%) | (63.1% - 76.3%) | (68.4% - 80.8%) | (73.8% - 85.3%) |
| | 300 | (54.2% - 65.6%) | (59.3% - 70.4%) | (64.5% - 75.1%) | (69.7% - 79.8%) | (75.0 % - 84.4%) |
| | 400 | (55.0% - 64.8%) | (60.1% - 69.7%) | (65.2 % - 74.5%) | (70.5% - 79.2%) | (75.7% - 83.8%) |
| | 500 | (55.6% - 64.3%) | (60.6% - 69.2%) | (65.8% - 74.0%) | (71.0% - 78.7%) | (76.2% - 83.4%) |
| | 600 | (56.0% - 63.9%) | (61.0% - 68.8%) | (66.2% - 73.6%) | (71.3% - 78.4%) | (76.6% - 83.1%) |

Note: Displayed range is the 95% confidence interval (CI) around the estimate of treatment success.

Microbiological Treatment Success Assumptions:[47-49]

- 25% of the enrolled patients discontinue ceftazidime-avibactam before 72 hours of exposure (eg, due to AE, microbiological results);
- 75% of patients are exposed to ceftazidime-avibactam for ≥72 hours;
- 10% of patients exposed ≥72 hours (across all indications) have no pathogen identification and are not assessable for microbiological success;
- 80% of the assessable patients experience microbiological treatment success as defined in Annex 1.

**Table 4. Sample Size and Precision of the Estimate for Microbiological Treatment Success**

| | | | Prevalence of Microbiological Treatment Success | | | |
|---|---|---|---|---|---|---|
| N | | 70% | 75% | 80% | 85% | 90% |
| | **200** | (63.1% - 76.3%) | (68.4% - 80.8%) | (73.8% - 85.3%) | (79.3% - 89.6%) | (85.0% - 93.8%) |
| | **300** | (64.5% - 75.1%) | (69.7% - 79.8%) | (75.0% - 84.4%) | (80.4% - 88.8%) | (86.0% - 93.2%) |
| | **400** | (65.2% - 74.5%) | (70.5% - 79.2%) | (75.7% - 83.8%) | (81.1% - 88.4%) | (86.6% - 92.8%) |
| | **500** | (65.8% - 74.0%) | (71.0% - 78.7%) | (76.2% - 83.4%) | (81.6% - 88.0%) | (87.0% - 92.5%) |
| | **600** | (66.2% - 73.6%) | (71.3% - 78.4%) | (76.6% - 83.1%) | (81.9% - 87.8%) | (87.3% - 92.3%) |

Note: Displayed range is the 95% confidence interval (CI) around the estimate of treatment success.

Table 3 and Table 4 display estimates of clinical and microbiological treatment success, respectively, and the asymptotic precision of each estimate (95% CI), for sample sizes ranging from 300 to 600 evaluable patients.

To obtain a 95% CI for treatment success, that is approximately 12.3 percentage points or less for both clinical and microbiological treatment success, 225 evaluable patients are required. Given the assumptions above for both treatment outcomes, a minimum of 300 patients should be enrolled to obtain 225 evaluable patients. Minor gains in precision can be achieved by enrolling a larger number of patients.

Enrolling 300 patients would lead to 225 patients with ≥72 hours exposure to ceftazidime-avibactam evaluable for clinical success, and 202 patients evaluable for microbiological success. It would yield an expected 95% CI of 70.0% (63.6% - 75.9%) of patients experiencing clinical treatment success and 80.0% (73.8% - 85.3%) of patients experiencing microbiological treatment success using a two-sided exact method.

Note: The precision estimates were calculated using the Clopper Pearson (exact) CIs using statistical analysis system (SAS)® software version 9.2.[50]

### 9.5.2. Study Size in Latin America

Based on the same assumptions for treatment outcomes as in Europe, to obtain a 95% CI for treatment success that is approximately 10.0 percentage points for both clinical and microbiological treatment success, 400 patients will be included in Latin America to obtain 300 evaluable patients for clinical success, and 270 evaluable patients for microbiological success. Using a two-sided exact method, enrolling 400 patients would yield an expected 95% CI of 70.0% (64.5% - 75.1%) of patients experiencing clinical treatment success and 80.0% (74.7% - 84.6%) of patients experiencing microbiological treatment success.

## 9.6. Data Management

Data will be entered in the web-based data capture (WBDC) system at the investigator's site. The investigator (or delegate) will be responsible for entering data into the WBDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual will also provide the site with data entry instructions.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the investigator will be notified to sign the electronic case report form (eCRF) electronically as per the agreed project process. A copy of the eCRF will be archived at the investigator's site.

## 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. All analyses will be carried out using SAS® software version 9.4 or higher or another similar statistical software package.

Extended analytic definitions for primary variables can be found below, categorized by role. See Section 9.3 Variables for a full list of collected data.

### 9.7.1. Exposure

To qualify for participation, patients must have had ≥1 dose of ceftazidime-avibactam.

All analyses will be performed among patients with ≥72 hours of ceftazidime-avibactam exposure.

A limited number of analyses will be conducted among patients with <72 hours of ceftazidime-avibactam exposure. These sub-analyses will examine patient, infection, treatment characteristics, safety and mortality.

Antibiotic regimens including ceftazidime-avibactam will be examined. An antibiotic regimen is a planned therapeutic intervention which may involve 1 or more drugs. Each regimen is a line of therapy.

A new line of therapy is defined by:

1. Where a treatment regimen is *discontinued,* and a different regimen is started, the new regimen is considered a new line of therapy.

2. A line of treatment is considered finished when at least one antibiotic given in combination is modified.

3. *Escalation*, increasing the dosage, the dose or the unplanned addition or substitution of ≥1 drug(s) in an existing regimen is considered a new line of therapy.

- Escalation after 4 days of treatment (dose increase or addition of another antibiotic for gram-negative), will be considered as a failure.

4. *De-escalation*, or reducing the dosage or eliminating ≥1 drug(s) from an existing regimen, or switching to oral antibiotics, is not considered a new line of therapy.

    - Stream lining (stop an antibiotic) or conversion to oral therapy will be considered as a success.

### 9.7.2. Outcomes

- Clinical treatment outcome: please refer to Annex 1 for details on clinical treatment outcomes. Each line of therapy that includes ceftazidime-avibactam will be evaluated for the clinical outcome.

- Microbiological treatment outcome: please refer to Annex 1 for details on microbiological treatment outcomes. Each line of therapy that includes ceftazidime-avibactam will be evaluated for the microbiological outcome, providing that a pathogen was identified. Microbiological 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 hospital days 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/magnetic resonance imaging (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.

- Prevalence of hospital readmissions; analyzed as the proportion of patients readmitted to the hospital for a recurrence of the index infection out of all patients discharged from the initial hospitalization.

- Cumulative mortality, in-hospital, at 30- and 60-days post-discharge.

### 9.7.3. Baseline Participant and Infection Characteristics

- Indication for ceftazidime-avibactam prescription (will vary depending on country local label).

  - cUTI: a clinical diagnosis of UTI that occurs associated with calculi/stones, indwelling catheters or other drainage devices, obstruction, immunosuppression, renal failure, renal transplantation, pregnancy, functional or anatomical abnormalities of the urinary tract such as partial obstructive uropathy (acquired or congenital), elevated postvoiding residual volume (>100 mL residual), established diagnosis of neurogenic bladder or instrumentation of the urinary tract, including urogenital surgery in the 7 days prior to symptoms initiation, as registered in the medical chart or record, and the diagnosis of acute prostatitis is excluded by physical exam. Hospital-acquired (nosocomial) cUTI will be defined as cUTI that develops at least 48 hours after the hospital admission. Healthcare-associated cUTI will be defined as cUTI among patients with presence of chronic indwelling urinary catheters, residence in nursing home or long-term care facility, regular hemodialysis clinic visits, or evidence of urological procedures within 3 months prior to the inpatient admission or during the inpatient admission.[51]

  - cIAI: a clinical diagnosis of IAI (ie, peritonitis, intraperitoneal abscess, liver abscess, pancreatic abscess, appendicitis, diverticulitis, gastric or duodenal ulcers, cholangitis, cholecystitis) and evidence of involvement of more than one organ, causing peritonitis and requiring both surgical and antibiotic therapy (beyond 24 hours regimen), as registered in the medical chart or record. Hospital-acquired cIAI will be defined as cIAI that develops at least 48 hours after the hospital admission. Healthcare-associated cIAI will be defined as cIAI that occurs while receiving treatment for other conditions in a healthcare facility (eg, nursing home, long-term care, hemodialysis clinic, hospital) within 3 months prior to the inpatient admission or during the inpatient admission.[52]

  - HAP/VAP: a clinical diagnosis of pneumonia and evidence of nosocomial origin (HAP/VAP) as registered in the medical chart or record. HAP is defined as pneumonia that occurs at least 48 hours after hospital admission; VAP is defined as pneumonia that occurs at least 48 hours after endotracheal intubation or tracheostomy.

  - Other infection with limited treatment options: any infection, based upon empiric or microbiological evidence, for which ceftazidime-avibactam is prescribed. Detailed information on the infection should be collected for analysis including type of infection (eg, primary BSI, SSI, CLABSI, meningitis), and original source of infection (ie, specific organ/locale). This indication is not approved in all participating countries.

- Pathogen susceptibility: All susceptibility information will be collected for the isolated pathogens including tested antibiotic by classes (eg, 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 antibiotic susceptible, intermediate, resistant).

- Multidrug-resistance: The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories, excluding antibiotic classes to which the pathogen is intrinsically resistant. Categories include but are not limited to aminoglycosides, carbapenems, cephalosporins, cephamycins, fluoroquinolones, folate pathway inhibitors, glycylcyclines, penicillins, monobactams, phosphonic acids, polymyxins, tetracyclines.[53]

- Source of infection (healthcare-associated, hospital-acquired, community-acquired).[54]

    - 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 3 months before baseline enrollment;

            - Resided in a nursing home or other long-term care.[55]

    - HAI.

        - Infection that occurred ≥48 hours after hospital admission that were not incubating at the time of admission.

    - CAI.

        - Infection detected ≤48 hours after hospital admission that does not qualify as a HCAI.

- Infection site: This refers to the origin of the infection (eg, appendix, bladder, kidney, large intestine, lungs, liver, gallbladder, pancreas, peritoneum small intestine, stomach, urethra, other).

- 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 (ie, active ingredient) of the drug (ie, change in trade name with same active ingredient, dose and strength will not be classified as a treatment line change).

- APACHE II score[56] 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 (eg, 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[57] 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 3.

### 9.7.4. Planned Analyses

All computations and generation of tables, listings and data for figures will be performed using SAS® software version 9.4 or higher or another similar statistical software package. The analysis plan will be fully described in a written and approved SAP.

Baseline (where baseline is defined as study entry) characteristics will be summarized for ceftazidime-avibactam patients. Descriptive statistics will be used to summarize the treatment patterns (eg, dosage, indications, infection source), effectiveness (eg, clinical and microbiological outcomes), and safety (eg, mortality, AEs) of ceftazidime-avibactam and healthcare resource utilization by patients prescribed ceftazidime-avibactam. AEs will be recorded and summarized as the proportion of patients with each safety event out of all treated patients. Hospital readmissions will be analyzed as the proportion of patients readmitted to the hospital for recurrent infection out of all patients discharged from the initial hospitalization.

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied.

Continuous variables will be described by the mean with standard deviation and 95% CI, median, upper and lower quartiles and maximum and minimum values. Categorical variables will be reported as number and percentages with 95% CIs.

Missing data will be described in all summaries.

A detailed flow diagram will be provided to describe the patient selection process. Patient and treatment characteristics of the analytic cohort will be summarized using descriptive statistics as described above.

The outcomes of interest will be derived as necessary from collected data and examined descriptively. Outcomes will be further examined after stratification by patient characteristics including baseline disease severity.

Outcomes of interest will be also stratified by indication, by bacteria (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., others) and by country.

Data from Europe and Latin America (LATAM) will be analyzed separately.

### 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 (ie, 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

There are some limitations in this study. First, because data will be collected via medical chart abstraction, 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, checking 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 imputations, when appropriate.

It is also possible that this study will have a selection bias. Some patients will be treated prior to the start of the study-related data collection. Obtaining informed consent from patients with good outcomes will be more difficult than among patients who died and as a result, would be eligible for waived informed consent. Further, remote consenting will increase the likelihood of capturing patients discharged from hospitalization prior to study start.

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. For example, patients at healthcare facilities capable of participating in research may be sicker, on average, than those who attend smaller tertiary care facilities. Results will be interpreted within this context.

Outcome misclassification may occur in this study. Patients will be followed for 60 days after hospital discharge for any indication of readmission for the same infection. It will be difficult to distinguish patients who were lost to follow-up from those who were readmitted at a different healthcare facility. This may result in an underestimate of some outcomes. To mitigate this risk, best effort will be made to identify outcome information by contacting patients or their legal representatives by telephone at the end of the follow-up period to ascertain information about hospital readmissions or mortality.

Finally, this study will only capture AEs related to ceftazidime-avibactam or other products marketed by the sponsor - 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 (eg, hospital regulation). Evaluation of safety results will be interpreted within this context.

## 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.

### 10.2. Patient Consent

The ICF must be in compliance with local regulatory requirements and legal requirements.

The ICF used in this study, and any changes made during the course of the study, must be prospectively approved by both the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. When the informed consent cannot be completed in person, patients or their legal representative will be consented remotely via telephone and will be mailed an ICF to sign, date, and return by mail, if approved by local legislation. The investigator will retain the original of each patient's signed consent form. A Next of Kin informed consent will be sought for deceased patients. And for out of reach patients a waiver may be used in countries where it is acceptable and approved by local regulations.

### 10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved AEs.

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

### 10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, ICFs 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.

### 10.5. Ethical 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 Food and Drug Administration (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

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 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 studies (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 WBDC system at the investigator's site 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 research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training.

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.

### 11.1. Single Reference Safety Document (SRSD)

The region-specific product label will serve as the SRSD during the study, which will be used by Pfizer Safety to assess any safety events reported to Pfizer Safety by the investigator during this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be generated after all data collection is complete. The final report will encompass all planned analyses, including a description of the complete study population. Study details will be described in the SAP.

## 13. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, 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.

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

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## 15. LIST OF TABLES



## 16. LIST OF FIGURES

## ANNEX 1. DEFINITIONS OF DIFFERENT SUBCATEGORIES OF OUTCOME

### Detail criteria for evaluation of clinical and microbiological outcome[58]

| | | | |
|---|---|---|---|
| Clinical Evaluation | Clinical Success | Cure | Resolution of all signs and symptoms of infection with no need for escalation of antimicrobials.<br><br>De-escalation of antibiotic therapy is considered a treatment success unless ceftazidime-avibactam was used in a regimen with one or more other antibiotics and is the only antibiotic de-escalated. |
| | Clinical Failure | Failure | Inadequate response to ceftazidime-avibactam therapy or resistant, worsening, or new recurrent signs and symptoms at the end of ceftazidime-avibactam therapy.<br><br>This may include antimicrobial escalation (ceftazidime-avibactam dose increase, or additional antibiotic) after 4 days of treatment, discontinuation of ceftazidime-avibactam without clinical cure (eg, AE, insufficient effect), or readmission to a hospital with same infection within 60 days of the initial hospital discharge date. This may also include cIAI patient who required an additional unplanned source control procedure after ceftazidime-avibactam initiation. |
| | 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. |
| | | Colonization | Detection of new pathogen from the site of infection during therapy without signs of infection and need for antimicrobial treatment, or a superinfection with a microbiological agent outside the treatment spectrum of ceftazidime-avibactam (G+/fungi). |
| | 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 | 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. |

AE=adverse event; cIAI=complicated intra-abdominal infection; MIC=minimum inhibitory concentration; IV=intravenous.

## ANNEX 2. LIST OF STAND-ALONE DOCUMENTS

Documents in the list below are available upon request. Note that changes to this list do not require a protocol amendment.

| Number | Document reference number | Date | Title |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

NA=Not applicable.

## ANNEX 3: 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 | 1 |
| Peripheral Vascular Disease | 1 |
| Cerebrovascular Disease | 1 |
| Dementia | 1 |
| Chronic Obstructive Pulmonary Disease | 1 |
| Rheumatologic Disease | 1 |
| Peptic Ulcer Disease | 1 |
| Depression | 1 |
| Use of Warfarin | 1 |
| Hypertension | 1 |
| Mild Liver Disease | 1 |
| Diabetes Mild to Moderate | 1 |
| Hemiplegia or Paraplegia | 2 |
| Moderate or Severe Renal Disease | 2 |
| Diabetes with Complications | 2 |
| Skin Ulcers/Cellulitis | 2 |
| Malignancy (solid, non-metastatic) | 2 |
| Hematological malignancy (leukemia, lymphoma) | 2 |

| Comorbidity | Deyo-Charlson Weight |
|---|---|
| Moderate to Severe Liver Disease | 3 |
| Metastatic Solid Tumor | 6 |
| AIDS | 6 |
| Any transplant (bone marrow, solid organ) | 6 |

AIDS=acquired immunodeficiency syndrome.