NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	**T**reatment outcomes from **R**etrospective **A**nalysis of patient **C**harts for Aztr**E**onam/Avibactam (TRACE)
Protocol number	C3601019
Protocol version identifier	Version 1.0
Date	8 June 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000956
Active substance	Aztreonam-Avibactam (ATM-AVI, Emblaveo®) ATC code: J01DF51
Medicinal product	Emblaveo®
Product reference	Aztreonam-avibactam (MARKETING AUTHORISATION NUMBER(S) EU/1/24/1808/001)
Marketing Authorization Holder(s)	[redacted]
Joint PASS	No
Research question and objectives	**Research question:** What are the real-world outcomes observed among hospitalized adults with infections caused by confirmed or suspected multidrug-resistant Gram-negative organisms who are treated with ATM-AVI? **Primary Objective** To estimate the clinical cure rate (proportion) of hospitalized adult patients receiving ATM-AVI for infections caused by multidrug-resistant Gram-negative organisms. **Secondary Objectives** 1. To describe the demographic, clinical, and infection characteristics of hospitalized adults with multidrug-resistant Gram-negative infections who receive ATM-AVI.

	2. To evaluate healthcare resource utilization during the index hospital stay following ATM-AVI treatment in adults with infections caused by multidrug-resistant Gram-negative organisms 3.To describe in-hospital all-cause mortality in adults with infections caused by Gram-negative organisms who receive ATM-AVI **Exploratory objective** To evaluate time between microbiology samples obtained from the patient and treatment initiation with ATM-AVI
Countries of study	France, Italy, Romania, Spain
Author	[redacted]

Marketing Authorization Holder(s).

Marketing Authorization Holder(s)	[redacted]
MAH contact person	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABG	Arterial Blood Gas
AE	Adverse event
APACHE	Acute Physiology and Chronic Health Evaluation
APS	Acute Physiology Score
ASSEMBLE	Aztreonam-avibactam Study for Safety and Efficacy in Metallo-Beta-Lactamase Producing Gram-negative Bacterial Infections
ATM-AVI	Aztreonam-avibactam
ATM	Aztreonam
AVI	Avibactam
ATC	Anatomical Therapeutic Chemical
BAT	Best Available Therapy
CI	Confidence Interval
cIAI	Complicated Intra-Abdominal Infection
CRE	Carbapenem-Resistant Enterobacterales
CRF	Case Report Form
CT-24	Pfizer Non-Interventional Study Classification
cUTI	Complicated Urinary Tract Infection
EAP	Expanded Access Program
EDC	Electronic Data Capture
EC	Ethics Committee
eCRF	Electronic Case Report Form

EDP	Exposure During Pregnancy
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
EnCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOT	End of Therapy
ESBL	Extended-Spectrum β-Lactamase
EU	European Union
GMA	Global Medical Affairs
GNB	Gram-negative bacteria
GSOP	Global Standard Operating Procedure
HAP	Hospital-Acquired Pneumonia
HEOR	Health Economics and Outcomes Research
HMA	Head of Medicines Agency
HTA	Health Technology Assessment
IA	Interim Analysis
ICU	Intensive Care Unit
IMP	Imipenemase
IRB	Institutional Review Board
KPC	*Klebsiella pneumoniae* carbapenemase
LOS	Length of Stay
LTO	Limited Treatment Options
MA/MAH	Marketing Authorization Holder

MBL	Metallo-β-Lactamase
MDR	Multidrug-Resistant
MDRO	Multidrug-Resistant Organism
NDM	New Delhi Metallo-β-lactamase
NGS	Next generation sequencing
NI	Non-interventional
NIS AEM	Non-interventional Study Adverse Event Monitoring
PASS	Post-Authorization Safety Study
PAS	Post-Authorization Study
PI	Principal Investigator
PK	Pharmacokinetics
RWD	Real-World Data
RWE	Real-World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
TD	Treatment Difference
VAP	Ventilator-associated pneumonia
VIM	Verona Integron-Encoded Metallo-β-Lactamase
WHO	World Health Organization
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title

Treatment outcomes from **R**etrospective **A**nalysis of patient **C**harts for Aztr**E**onam/Avibactam (TRACE)

Protocol Version 1.0, 8 June 2026

Main author: [redacted]

Rationale and Background
Antimicrobial resistance among Gram-negative bacteria (GNB), including metallo-β-lactamase (MBL)–producing organisms, is an increasing global public health concern. Aztreonam-avibactam (ATM-AVI) is approved in the EU and UK for the treatment of several serious Gram-negative infections in adults with limited treatment options. While randomized clinical trials have established efficacy and safety, evidence from routine clinical practice describing outcomes and utilization remains limited.

Research Question and Objectives

Research question: What are the real-world outcomes observed among hospitalized adults with infections caused by confirmed or suspected multidrug-resistant Gram-negative organisms who are treated with ATM-AVI?

Primary Objective

To estimate the clinical cure rate (proportion) of hospitalized adult patients receiving ATM-AVI for infections caused by multidrug-resistant Gram-negative organisms.

Secondary Objectives

1.To describe the demographic, clinical, and infection characteristics of hospitalized adults with multidrug-resistant Gram-negative infections who receive ATM-AVI

2. To evaluate healthcare resource utilization during the index hospital stay following ATM-AVI treatment in adults with infections caused by multidrug-resistant Gram-negative organisms

3.To describe in-hospital all-cause mortality in adults with infections caused by Gram-negative organisms who receive ATM-AVI

Exploratory objective

To evaluate time between microbiology samples obtained from the patient and treatment initiation with ATM-AVI

Study Design

International, multi-center, non-interventional, retrospective medical chart review conducted as a voluntary Post-Authorization Safety Study (PASS).

Population

Hospitalized adults (≥18 years) treated with ATM-AVI according to approved indications at selected hospitals in Europe.

Variables

Exposure is defined as receipt of ATM-AVI prescribed as part of routine clinical care for an approved indication, independent of study participation. Co-variates include patient sociodemographics, comorbidities, and risk factors for a multidrug-resistant Gram-negative infection. Index infection characteristics (e.g., source and type), ATM-AVI treatment details (dose and duration), and concomitant antibiotic therapy will be recorded. Comorbidity burden will be assessed using the Charlson Comorbidity Index (CCI) and severity of illness will be assessed using an Acute Physiology and Chronic Health Evaluation (APACHE II) score. Microbiological covariates include causative organisms, phenotypic (antimicrobial susceptibility) and genotypic characteristics (e.g., metallo-β-lactamase enzyme type). Hospitalization-related covariates will include index admission timing and intensive care unit (ICU) stay. Outcomes evaluated will include clinical cure or failure, in-hospital mortality, length of hospital stay, ICU utilization, 30-day readmission, and reason for readmission, when applicable. Additional details are provided in Table 2.

Data Sources

Secondary data will be abstracted from both unstructured sources (e.g. clinician notes) and structured data sources such as electronic health records and/or hospital laboratory information systems. All data will be entered into standardized electronic case report forms (eCRFs) to ensure consistency and harmonization across study sites.

Study Size

Approximately 400 patients. The sample size calculation is based on the primary objective to estimate the clinical cure rate (proportion) of hospitalized adult patients receiving ATM-AVI for infections caused by multidrug-resistant Gram-negative organisms.

Data Analysis

Planned analyses will include descriptive statistics for all variables. Continuous variables will be summarized using standard summary statistics such as number of observations (n), mean, standard deviation (SD), median, first and third quartile, minimum and maximum values. Categorical variables will be summarized in frequency tables as counts and proportions of the total study population. The proportion of missing data will be reported for each variable.

For the primary endpoint, the frequency and proportion of clinical cure will be calculated. The Clopper Pearson exact method will be used to calculate the 95% confidence interval.

For the secondary and exploratory endpoints, descriptive summary will be performed as appropriate. Survival analysis using the Kaplan–Meier method will be applied for time-to-event outcomes (e.g. mortality and cure), accounting for differing follow-up times and censoring. Cox proportional hazards regression will be conducted to analyze the impact of multiple covariates (e.g., antimicrobial genotypic/phenotypic resistance, specific pathogens, infection sites, potential risk factors for resistance and marker of disease severity) and time-to-event outcomes, including mortality or cure.

Milestones

Milestone	Planned Date
Completion of feasibility assessment	16 December 2025
Registration in the HMA-EMA Catalogues of RWD studies	16 March 2026
Start of data collection	10 August 2026
End of data collection	24 February 2028
Interim analysis	31 December 2026
Study progress report # 1	31 March 2027
Final study report	01 June 2028

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Completion of feasibility assessment	16 December 2025
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Final study report	01 June 2028

7. RATIONALE AND BACKGROUND

7.1. Background

The World Health Organization's (WHO) 2025 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report highlighted the rise in global antimicrobial resistance rates and the threat of increasing antibiotic resistance among Gram-negative bacteria (GNB).[1] The increasing prevalence of multidrug-resistant organisms (MDROs) is linked to increasing global morbidity and mortality rates.[2] Traditionally, MDROs have primarily affected patients in healthcare settings due to factors such as increased exposure to antibiotics, frequent or prolonged inpatient stays, use of in-dwelling devices, and host-related vulnerabilities (immunosuppression, special populations, etc.).[3,4] Enterobacterales, an order of GNB in particular, are responsible for a variety of healthcare-associated infections. For GNB, the major driving force of antibiotic resistance is the presence of β-lactamases (encoded by *bla)* with a rapidly expanding list of β-lactam hydrolyzing enzymes.[2]

β-lactams have long been the cornerstone of therapy for MDRO infections due to their broad spectrum of activity, effectiveness, and safety. However, there is growing concern over the emergence and dissemination of β-lactamase enzymes that degrade β-lactams, threatening their efficacy as the safe first line of defense against multidrug-resistant MDR bacteria.[2] Ambler's classification divides β-lactamases into four classes based on amino acid sequences: classes A, B, C, and D. Classes A, C, and D β-lactamases rely on serine to cleave the β-lactam ring. In contrast, class B β-lactamases, also known as metallo-β-lactamases (MBLs), use zinc (Zn^{2+}) as a metal cofactor to destroy the β-lactam ring.[5,6] Carbapenem-resistant pathogens including those producing Ambler class B MBLs, are becoming increasingly prevalent in clinical settings worldwide.[7-9] These include carbapenem-resistant organisms such as carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Stenotrophomonas maltophilia*.[9] Specifically, MBLs such as Verona integron-encoded MBL (VIM), imipenemase (IMP) and New Delhi MBL (NDM), which are generally co-expressed with other resistance mechanisms such as extended-spectrum β-lactamases (ESBLs), represent a significant threat to patients and healthcare systems as treatment options are extremely limited.[10]

Aztreonam-avibactam (ATM-AVI, Emblaveo®) is a fixed-dose, intravenous combination of the established antibiotic aztreonam (ATM) and the β-lactamase inhibitor avibactam (AVI). ATM, a monobactam antibiotic, is resistant to hydrolysis by MBLs but can be degraded by other β-lactamases. AVI, a non-β-lactam β-lactamase inhibitor, effectively neutralizes both Ambler class A

and class C β-lactamases and some class D enzymes, including extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48 carbapenemases, and AmpC enzymes restoring ATM's efficacy against resistant pathogens.[11] ATM-AVI was approved in 2024 in the EU and the UK for the treatment of complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), complicated urinary tract infection (cUTI), including pyelonephritis and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (LTOs).[12,13]

ATM-AVI is administered via 3-hour intravenous infusion every 6 to 12 hours depending on renal function for a 5–14 day duration of therapy based on infection type and severity.[14]Furthermore, ATM-AVI has demonstrated *in-vitro* activity against multidrug-resistant (MDR) Enterobacterales, including those that produce ESBLs, serine carbapenemases and MBLs.[15-19]

The Phase 3 REVISIT trial assessed the safety and efficacy of ATM–AVI (± metronidazole for patients with cIAI who were randomized to the ATM-AVI group) against an active comparator regimen of meropenem (± colistin at the discretion of the investigator) for the treatment of HAP, VAP, or cIAI caused by confirmed or suspected GNB, including those due to organisms with MBL production.[20] The results of the intent-to-treat analysis revealed similar rates of clinical cure between the treatment arms, occurring in 68.4% (193/282) of those in the ATM-AVI arm versus 65.7% (92/140) in the meropenem arm (treatment difference (TD) 2.7%, 95% confidence interval [CI]: −6.6 to 12.4). Among patients with cIAI, clinical cure was achieved in 76.4% (159/208) for the ATM–AVI arm versus 74.0% (77/104) in the meropenem arm (TD 2.4%, 95% CI −7.4 to 13.0). For patients with HAP/VAP, the clinical cure rate was 45.9% (34/74) in the ATM–AVI arm versus 41.7% (15/36) in the meropenem arm (TD 4.3%, 95% CI –15.5 to 23.1). However, only 10 patients in this study possessed MBL-positive isolates.

The ASSEMBLE trial specifically evaluated ATM-AVI against the best available therapy (BAT) for infections due to MBL-producing GNB.[21] This Phase 3, randomized, open-label study enrolled hospitalized adults with serious infections, including cIAI, HAP/VAP, cUTI, or bloodstream infections. Results of the microbiological intention-to-treat population indicated that five out of 12 (41.7%) of the ATM-AVI ± metronidazole patients achieved clinical cure versus none of the three (0%) BAT patients, however only 15 total patients with infections due to MBL-producing bacteria were enrolled.

The majority of the isolates identified across these trials were Enterobacterales, with very few isolates of *Stenotrophomonas maltophilia* or *Pseudomonas aeruginosa* isolated.

7.2. Rationale

ATM-AVI offers broad-spectrum activity against β-lactamase-producing bacteria, including MBL producers and provides optimized ATM and AVI exposure.[14,22] While clinical studies have established ATM-AVI's pharmacokinetics/pharmacodynamics profile, effectiveness and safety data from routine clinical practice are scarce – particularly with regards to patient characteristics and clinical outcomes.[23-28] The ASSEMBLE study specifically evaluated ATM-AVI activity against MBL-producing pathogens.[21] Although the study's results suggested a promising role for ATM-AVI in treating serious infections caused by MBL-producing GNB,[21] the study's relatively small sample size limits the generalizability of these findings.

This existing evidence gap will be addressed by conducting an international, multi-center, descriptive retrospective medical chart review to comprehensively describe the real-world clinical outcomes associated with the use of ATM-AVI in adult patients. Conducting a retrospective chart review is a well-established way of collecting comprehensive data on patient demographics, clinical indications and therapeutic outcomes.

Assessing the real-world performance of ATM-AVI and understanding its utilization for approved indications are critical from a public health perspective. Real world evidence generation provides insights into the drug's performance across diverse patient populations and clinical settings and complements findings from controlled clinical trials. This information may contribute to the descriptive evidence available to clinicians on the role of ATM-AVI in combatting MDR GNB infections, which pose a significant growing public health threat.[29] Furthermore, understanding the specific clinical scenarios in which ATM-AVI is prescribed may inform future research, support healthcare policy, guide resource allocation, and enable public health authorities to monitor the emergence of resistance patterns to ensure that ATM-AVI remains a viable treatment option. In summary, evaluating the real-world application of ATM-AVI is critical, as it provides descriptive evidence to inform clinical practice, provides insights towards effective healthcare planning and contributes to the global effort against antimicrobial resistance.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

This retrospective multi-center chart review study aims to answer the following question through data collection to meet the primary and secondary objectives:

What are the real-world outcomes observed among hospitalized adults with infections caused by confirmed or suspected multidrug-resistant Gram-negative organisms who are treated with ATM-AVI?

Primary Objective

To estimate the clinical cure rate (proportion) of hospitalized adult patients receiving ATM-AVI for infections caused by multidrug-resistant Gram-negative organisms.

Secondary Objectives

1. To describe the demographic, clinical, and infection characteristics of hospitalized adults with multidrug-resistant Gram-negative infections who receive ATM-AVI

2. To evaluate healthcare resource utilization during the index hospital stay following ATM-AVI treatment in adults with infections caused by multidrug-resistant Gram-negative organisms

3. To describe in-hospital all-cause mortality in adults with infections caused by Gram-negative organisms who receive ATM-AVI

Exploratory objective

To evaluate time between microbiology samples obtained from the patient and treatment initiation with ATM-AVI.

These objectives are structured according to the PICOT[30] framework, as detailed in Table 1 below.

Table 1- PICOT framework for evaluating ATM-AVI use in hospitalized adult patients

Population (P)	Hospitalized adults (≥18 years of age) recruited from a representative sample of hospitalized patients across Europe who received ATM-AVI for the treatment of MDR Gram-negative infections	
Intervention(I)	Treatment with ATM-AVI for at least 72 hours, for one of the following therapeutic indications as per country label [12,13] - cIAI, HAP or VAP, cUTI (including pyelonephritis), or infections caused by aerobic GNB in patients with LTOs	
Comparator (C)	No formal comparator (descriptive non-interventional cohort)	
Outcomes (O)	Patient demographics, clinical history, comorbidities, index infection characteristics, microbiological results, ATM-AVI use patterns, clinical cure/failure, healthcare resource utilization including length of stay (LOS), Intensive Care Unit (ICU) LOS, and readmissions within 30 days, in hospital all-cause mortality	
Timeframe (T)	Case accrual timeframe	1 September 2024† – 27 December 2027 ‡
	Data abstraction timeframe*	10 August 2026 to 27 January 2028
†Or earliest available date that ATM-AVI is commercially available in each country (see Annex 4). ‡ Allows for the last cases identified to have the maximum 30-day observation period following the discharge date of the index hospitalization, * Data will be abstracted in retrospective intervals; country-specific intervals to be determined depending on earliest date that ATM-AVI is commercially available.		

9. RESEARCH METHODS

9.1. Study Design

This study is a multi-center, non-interventional, retrospective exposure-based secondary data collection study that will be conducted through medical chart review of both structured and unstructured data. It is intended to describe patient characteristics and real-world clinical outcomes associated with ATM-AVI use in hospitalized adults. There are no comparison groups.

The primary endpoint is clinical cure (or clinical cure rate), as measured by the resolution or improvement in signs and symptoms at end of therapy (EOT) with no additional therapy required for index infection and no patient death recorded during ATM-AVI treatment. Additionally, for cIAI pts – there should be no unplanned drainage or surgical intervention required since the initial procedure. Juxtaposed to the clinical cure is clinical failure, which is defined as the absence of clinical cure. Secondary endpoints include healthcare resource utilization, characterization of clinical and infection

characteristics in patients treated with ATM-AVI, and to describe in-hospital all-cause mortality as defined in Section 9.3.

The chosen design of this study is based on published methodology of similar trials in anti-infective products [31,32] and is intended to address the study objectives while reflecting real-world use of ATM-AVI in routine clinical practice. The retrospective secondary data collection approach enables efficient evaluation of real-world clinical outcomes, managing the operational constraints associated with prospective data collection in acutely ill hospitalized patients. [33,34] The selection of patients across multiple countries allows for capturing heterogeneity among institutions, healthcare systems, and clinical practices, and is intended to provide representativeness of results across geographic regions/countries.

This chart review will evaluate data derived from existing medical records from enrolled patients. All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this study is being conducted. The retrospective nature of the study will not interfere with treatment decisions, and dosing and intervals will reflect real-world clinical practice. No additional subject visits, diagnostic tests, follow-up procedures, or treatments beyond routine clinical care will be required as part of this study. Since all of the patient-level data necessary to conduct the study are expected to be readily available in medical charts, there is no need to prospectively collect data and the study approach will be non-interventional.

An exposure-based framework was selected to ensure the inclusion of patients who received ATM-AVI as part of routine care, thereby minimizing selection bias associated with outcome-based sampling and allowing assessment of outcomes following a defined treatment exposure. Exposure based cases are defined as adults (≥18 years) who received their first recorded course of ATM-AVI during a hospitalization, in accordance with the locally approved therapeutic indications, and whose documented duration of ATM-AVI therapy was at least 72 hours. This exposure definition is intended to ensure sufficient treatment duration to assess real-world clinical outcomes while reflecting routine clinical practice. The index infection date is defined as the date (and time, if available) of the first microbiological culture collection, reflecting clinical suspicion of infection for which treatment with ATM-AVI would be required and occurring near the initiation of antibiotic therapy. To avoid within-patient correlation (i.e., the statistical association between repeated measurements taken from the same individual over time) and selection bias, only the first eligible treatment episode will be analyzed. Subsequent ATM-AVI treatment courses will not be included.

Data will be abstracted retrospectively from existing medical records of qualifying hospitalized patients with a prescription of ATM-AVI between September 1, 2024 (or the earliest date ATM-AVI was commercially available in the specific country as per Annex 4) and January 27, 2028. Medical information, such as patient demographics and infection characteristics, past medical history 90 days prior to the index hospitalization (defined as the first hospitalization during which first prescription of ATM-AVI was recorded in the healthcare record), ATM-AVI dosing and duration information, healthcare resource utilization, and clinical and microbiological features of the infection, will be collected from the patients' medical records. Clinical outcome will be assessed at EOT and in the subsequent time period following the index infection and responses will be categorized as clinical cure or failure. Outcomes will be evaluated by the investigator and recorded in the electronic case report form (eCRF). Figure 1 provides a schematic of the overall patient timeline for the study.

Records lacking complete documentation of ATM-AVI treatment details will be excluded. The enrollment period may be adjusted based on study progress or enrollment plan.

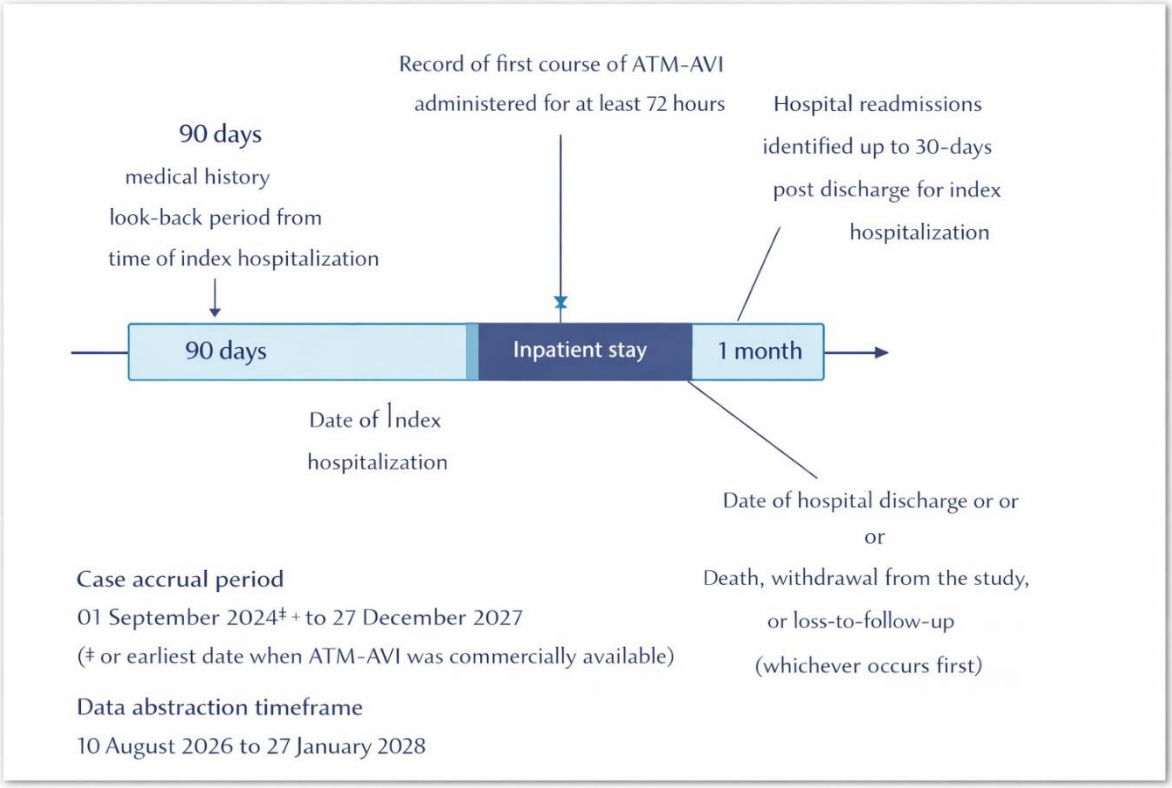

Figure 1- Study timeline per included patient, illustrating the index hospitalization (during which first prescription of ATM-AVI was recorded in the healthcare record), 90 day lookback period from the time of index hospitalization to ascertain patient medical and treatment history, and hospital readmissions identified up to 30 days post-discharge

9.2. Setting

This study is an international study intended to be conducted in select hospitals in Europe that provide inpatient acute medical care for adults with serious GNB infections where ATM-AVI is prescribed as part of routine inpatient care following clinical suspicion of infection and microbiological evaluation. Participating hospitals may include tertiary referral centers and secondary care hospitals, with patient management occurring in settings such as intensive care units and general medical wards, depending on local clinical practice.

Participating sites were preliminarily identified based on a feasibility assessment performed between July and December 2025. Initial sites identified for potential evaluation were provided by the Pfizer medical team but assessed using an external vendor. Site feasibility assessments evaluated factors such as the expected availability of eligible patients, routine use of ATM-AVI in clinical practice, accessibility and completeness of medical records, and the ability to comply with applicable data protection and data quality requirements. Final sites enrolled into the study will be based on local regulatory requirements, institutional approvals and study enrollment needs.

Site selection is based on geographic regions within each country, and every attempt will be made to ensure proportional representation from different locales and clinical practice settings. Broad inclusion criteria support the capture of as many patients as possible to better reflect how ATM-AVI is being utilized in the real-world. This approach aims to enhance the representativeness of our findings, providing a comprehensive understanding of ATM-AVI's application across diverse clinical environments. By including data from a wide range of healthcare settings, geographic locations, and infection types we aim to obtain data that span the spectrum of severity within the indication of ATM-AVI in each country.

Selected hospitals are required to have medical record systems capable of supporting reliable retrospective review, including access to documentation of past medical history and risk factors for MDR GNB up to 90 days before index hospitalization, microbiological testing capabilities, medication exposure, and relevant clinical and healthcare utilization outcomes documented during hospitalization. They should also be able to access medical records up to 30 days post discharge to determine if the patient was readmitted to the facility and the reason for the readmission, if available.

Each participating hospital/site will appoint a principal investigator (PI). The designated PI will be responsible for site-level oversight, scientific integrity, and communication with the sponsor or coordinating center. Data abstraction will be performed by trained personnel under the supervision of the site PI. PIs and data abstractors will receive training on the eCRF system, data entry standards, patient eligibility criteria, and compliant data handling practices.

Confidentiality agreements and contracts will be executed with participating institutions and investigators. Study conduct at each site will be subject to applicable local regulatory and ethics committee approvals prior to initiation.

9.2.1. Inclusion Criteria

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

1. Individual ≥18 years of age, hospitalized with a suspected or documented Gram-negative bacterial infection, and received ATM-AVI for at least 72 hours.
2. Microbiological sampling: Patient underwent microbiological sampling within the 5 days prior to initiation of ATM-AVI.
3. Treatment timeline: Record of receiving ATM-AVI treatment between September 1, 2024, or the earliest date ATM-AVI is commercially available in each country, and December 27, 2027.
4. Patient is receiving ATM-AVI treatment for the first time during study eligibility period.

9.2.2. Exclusion Criteria

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

1. Incomplete documentation of ATM-AVI treatment details (i.e. start/stop date of ATM-AVI treatment)
2. Enrollment in a clinical trial for another antibiotic during the time that the patient is being treated with ATM-AVI.

3. Patient enrolled in any other Pfizer sponsored ATM-AVI study

9.3. Variables

The variables to be collected for this study will be obtained from the patient's medical records via human review of unstructured data (e.g. clinical notes as part of routine medical care) and structured data (e.g. laboratory information system), except for information related to the hospital antibiogram. These items will be provided by the site investigator. Detailed definitions of study variables will be included in the statistical analysis plan (SAP).

Table 2: Study Variables, Outcomes and Operational Definitions for Data Collected

Variable	Role	Operational Definition
Socio-demographics		
Age	Baseline characteristic	Age in completed years on index infection date calculated from date of birth or abstracted from the medical record
Sex	Baseline characteristic	As recorded in hospital records [Male, Female, or unknown when not specified]
Height/weight	Baseline characteristic	Height [cm or inches] and weight [kg or pounds] as recorded in hospital records on or before closest date to index infection date
Location prior to hospitalization	Baseline characteristic	Area of residence prior to hospitalization, if reported in hospital records [e.g. home, other hospital, long term care facility]
Medical and treatment history		
Comorbidities	Baseline characteristic	Selected diagnoses documented in the medical record prior to or on index infection date
Charlson Comorbidity Index	Derived baseline characteristic	Comorbidity burden will be assessed using the Charlson Comorbidity Index, calculated through medical chart review according to the original methodology described by Charlson et al.[35]
Acute Physiology and Chronic Health Evaluation (APACHE II) [36]	Derived baseline characteristic/ subgroup identifier	APACHE II score (Annex 3) will be collected from medical records for patients directly admitted to the ICU among sites that routinely calculate this measure. Ideally the score should be calculated during the first 24 hours in the ICU and based on the worst values recorded during this time period. If the

		APACHE II score is not present in the medical records, it will not be calculated for the purpose of this study.
Recent hospital admission	Baseline characteristic	Identified from patient hospital records and pertains to any hospitalizations documented within 90 days prior to the index hospitalization. Information to be collected includes date(s) of admission and discharge(s), reason(s) for hospitalization and admission to the ICU during the stay (yes/no/unknown).
History of antibiotic exposure /previous infections	Baseline characteristic	Identified within 90 days of the index infection date; includes type(s) and date(s) of infection(s), organism identified and receipt of carbapenem therapy (yes/no) to treat the infection
History of healthcare procedure(s)	Baseline characteristic	Within the 30 days before the index infection date; record date(s) and type(s) of healthcare procedure: invasive procedures (e.g., surgery, central line placement, tracheostomy), intubation, Extracorporeal membrane oxygenation (ECMO)
Risk factors for a multidrug-resistant GNB infection [37-40]		
Antibiotic exposure within 90 days prior to index hospital admission	Baseline characteristic	Yes /No
History of multidrug-resistant Gram-negative bacterial infection or colonization within the last 90 days	Baseline characteristic	Yes /No
Prior hospitalization in the last 90 days	Baseline characteristic	Yes /No
Use of devices such as ventilators, central lines, or urinary catheters in the index hospitalization prior to ATM-AVI treatment	Baseline characteristic	Yes /No ; If yes, record type of device(s) utilized
Previous ICU stay within 90 days prior to index hospitalization	Baseline characteristic	Yes /No

Hemodialysis within 90 days prior to index infection	Baseline characteristic	Yes /No ; If yes, record type of hemodialysis (e.g. intermittent hemodialysis, continuous renal replacement therapy)
Transplant within 90 days prior to index infection	Baseline characteristic	Yes /No
Major surgery in the last 30 days before index infection	Baseline characteristic	Yes /No
Cytotoxic chemotherapy in the last 90 days prior to index infection	Baseline characteristic	Yes /No
History of recent travel or receipt of medical care in a country known to have a high prevalence of MBL producing organisms	Baseline characteristic	Yes/No; If yes, country or countries will be recorded
Receipt of high dose corticosteroids for ≥ 14 days in the last 90 days prior to index infection	Baseline	Yes/No
Hospitalization details		
Admission date	Outcome	Date of admission of index hospitalization as recorded in the medical record [DD/MM/YYYY]
Discharge date	Outcome	Date of discharge of index hospitalization as recorded in the medical record [DD/MM/YYYY]
Reason for index hospitalization	Baseline characteristic	Categorical classification of overall reason for index hospitalization
Admission diagnosis	Baseline characteristic	The primary clinical diagnosis documented at the time of hospital admission that reflects the principal reason for the patient's hospitalization, as recorded in the medical record

Discharge diagnosis	Baseline characteristic	The primary clinical diagnosis documented at the time of hospital discharge that reflects the principal final reason for the patient's hospitalization, as recorded in the medical record
Discharge status	Baseline characteristic	Discharge status including home, healthcare facility, assisted living, hospice, other institution, other (not classified), in-hospital death
Infection diagnosis and antibiotic treatment details		
Therapeutic indication for use of ATM-AVI	Baseline characteristic/ subgroup identifier	ATM-AVI is an antibiotic indicated for the treatment of several serious infections in adult patients. This inclusion criteria will be reported as part of the description of ATM-AVI use, and will correspond to one of the following based on the approved therapeutic indication for use in the product labeling:[12,13] • Complicated intra-abdominal infections • Hospital acquired pneumonia, including ventilator-associated pneumonia • Complicated urinary tract infection, including pyelonephritis • Infections due to aerobic gram-negative organisms in patients with limited treatment options.
Index infection date	Baseline characteristic	The date and time of the first microbiological culture collection**,** reflecting clinical suspicion of infection for which treatment with ATM-AVI would be required and occurring near the initiation of antibiotic therapy. [DD/MM/YYYY]
Primary infection site(s)	Baseline characteristic/ subgroup identifier	The site(s) of the infection that resulted in ATM-AVI prescription, as reported by physician

Description of the index culture	Baseline characteristic	The sample collected prior to starting ATM-AVI that resulted in ATM-AVI prescription Description must include: date and type of culture sample, the pathogen(s) identified, patient's location when the index culture was obtained (outpatient clinic, emergency room, general ward, ICU, operating room [intra-operative sample], other),the drugs tested for susceptibility and the antimicrobial susceptibility testing results [phenotypic results] , molecular resistance [genotypic results] and the time at which results were available and reported to treating physician (if available).
ATM-AVI utilization	Exposure	Dates of administration, loading dose administered (yes/no), maintenance doses administered, frequency of dosing.
ATM-AVI treatment rationale	Baseline characteristic/subgroup identifier	Corresponds to the physician-documented reason for the prescription of ATM-AVI treatment. Selected from one of the following pre-defined categories: • Use for a documented infection (i.e., the pathogen and susceptibilities were known, ATM-AVI use was due to failure of a prior antibiotic regimen, documented adverse event or clinician therapy preference.) • Empirical use (i.e., ATM-AVI use started before the pathogen and/or susceptibilities were available to help guide the choice) • Salvage therapy (i.e., ATM-AVI was used after a prior antibiotic regimen has failed) • Note: ATM-AVI might have been given in combination with another antibiotic agent.

Reason for stopping ATM-AVI treatment	Outcome	Physician documented reason for stopping ATM-AVI treatment.
Concomitant antibiotics	Baseline characteristic/ subgroup identifier	Any antibiotics given concurrently with ATM-AVI treatment; this variable will be binary [Yes/No]. If yes, identification of the generic name is required only (i.e. no dosing information required). Medications will be classified using the WHO Anatomical Therapeutic Chemical (ATC) classification system [41]
Duration of ATM-AVI treatment	Outcome	Duration of ATM-AVI treatment; (must fall within pre-determined range: ≥72 hours)
Infectious diseases physician consult	Baseline characteristic	Indicate if an Infectious Diseases physician was consulted in the care of the patient receiving ATM-AVI (YES/NO)
Post Treatment Outcomes		
Clinical cure	Outcome	Defined as resolution or improvement in signs and symptoms at EOT with no additional therapy required for index infection and no patient death recorded during ATM-AVI treatment. Additionally, for cIAI pts – no unplanned drainage or surgical intervention required since initial procedure
Clinical failure	Outcome	Inadequate response to ATM-AVI based on worsening signs and symptoms related to the index infection, lack of resolution or documented relapse of index infection (judged by physician and recorded in patient's medical chart), and/or need to re-initiate therapy directed to the index pathogen after stopping ATM-AVI. Patients who died during therapy during current hospitalization will be considered as clinical failure.[32]
Microbiological result	Baseline characteristic/ subgroup identifier	Results from microbiological culture(s) of current infection obtained within 5 days prior to ATM-AVI initiation. Record sample collection date(s), date(s) of testing, sample source(s), method of testing (e.g., E-test, Kirby Bauer disc diffusion, etc.), enzyme testing methods (e.g., Carba-5, NGS, etc.), identified

		pathogen(s) (e.g., *Escherichia coli*, *Klebsiella pneumoniae* etc.), MBL enzymes (NDM/IMP/VIM), date(s) and results of antimicrobial susceptibility Antimicrobial susceptibility: All susceptibility information (susceptible/intermediate/ resistant) will be collected for the isolated Gram-negative pathogens including tested individual antimicrobial (e.g., gentamicin, ceftazidime/avibactam, ATM-AVI, meropenem etc., other) Note: For pathogens detected other than GNB (e.g., Gram-positive bacteria, fungi), only the organism's name will be recorded; susceptibility data will not be collected.
In-hospital all-cause mortality	Outcome	Death occurring after ATM-AVI treatment initiation but before hospital discharge (date). Cause of death should be recorded (if known) [32]
Healthcare utilization resources		
Hospital ward	Baseline characteristic	All wards attended during index hospitalization, including ward admission and discharge/transfer date.
Length of hospital stay	Outcome/subgroup identifier	Date(s) of hospital admission, date(s) for index hospitalization and hospital discharge or death, whichever occurs earlier [measured in days]
Infection associated length of stay	Outcome/subgroup identifier	Difference between the index infection date (defined by the date/time of first microbiological sample for index infection as documented in the medical record) and the last day of ATM-AVI therapy
ICU admission	Outcome/subgroup identifier	ICU admission is defined as any documented transfer of a patient into an ICU at any point during the index hospitalization, as recorded in the medical chart. [yes/no]

ICU length of stay	Outcome/subgroup identifier	Date(s) of ICU admission, date(s) of ICU discharge, [measured in days]
Hospital readmission	Outcome/subgroup identifier	Hospital readmission to same facility/system within 30 days after initial discharge[yes/no]
Readmission reason (infection associated)	Outcome/subgroup identifier	Hospital readmission due to index infection recurrence [yes/no]
Local epidemiology		
Local Gram-negative resistance patterns	Baseline characteristic	Most recent assessment of the proportion of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* isolates exhibiting resistance to ceftazidime and meropenem, and dates of assessment (e.g. from antibiogram or equivalent report). This information will be used to assess local epidemiology and will not be linked to individual patient outcomes.

9.4. Data Sources

The data source for this study will be patient medical records and hospital laboratory information management systems (for detailed microbiological results data). The data generated at participating sites will be collected by trained site personnel and entered into the research platform through eCRFs. Data will be abstracted from patient medical charts (either electronic or hard copies) after treatment completion and records of hospital readmissions will be identified up to 30 days post discharge for the index hospitalization. Censoring events will be tracked by Investigator sites during data abstraction activities. The clinical outcomes will be obtained from investigator assessments. **Table 3** below provides an overview of the data collection schedule for the study.

Table 3: Data Collection Schedule

Variable	**Baseline** *	**Hospitalization Period**	**Post-discharge‡**
Study eligibility requirements (inclusion/exclusion criteria)	X		
Demographics	X		
Past medical and antibiotic treatment history	X †		
Clinical characteristics	X		
Hospitalization details	X	X	
Infection diagnosis	X	X	

Antibiotic treatment details	X	X	
Clinical outcomes		X	
Microbiology testing and results (if available)	X	X	
Healthcare Resource Utilization		X	X
Mortality		X	

* Baseline is the date of inclusion in the study

† Includes retrospective review of health record data up to 90 days prior to index admission

‡ 30-day observation period following the discharge date of the index hospitalization

9.5. Study Size

Since there are no a *priori* hypotheses specified and the present study is descriptive in nature, no sample size calculation based on hypothesis testing has been performed. However, a sample size of 400 patients was the target for enrollment that was determined to ensure adequate precision in estimating the clinical cure rate (proportion) of hospitalized adult patients receiving ATM-AVI for infections caused by MDROs.

Specifically, the sample size of 400 patients is justified by the anticipated precision of two-sided 95% confidence intervals for key proportions, assuming a conservative expected proportion of 50%, which maximizes the required sample size under a binomial model; using the Clopper Pearson exact method, a sample of 400 patients would yield a 95% confidence interval of approximately 45.1% to 54.9% (total width 9.8). This sample will allow reliable estimates to be obtained for the study objectives.

The study will continue until each of the recruited sites has enrolled the anticipated number of patients resulting from previous feasibility estimates, without any single site dominating the total number of enrolled patients. A detailed patient recruitment plan will list the target study size for each country and will be continually evaluated in an attempt to ensure balanced representativeness of patient demographics and distribution of resistant phenotypes/genotypes, as epidemiological patterns vary across countries and patient populations.[42]

The SAP will detail pooled and country level analysis of the data required to evaluate primary and secondary endpoints in the study, as well as the exploratory analyses.

9.6. Data Management

All data in the context of this study will be collected by clinical abstraction from medical charts, processed, stored, and evaluated in accordance with the protocol and regulatory requirements and applicable guidance for electronic records. To maintain consistency in the process throughout the course of the study, all procedures will be defined and detailed in a data management plan created before the start of data collection to ensure clean and accurate data for analysis.

An electronic data capture (EDC) system will be used to capture study site data collected by site personnel and to monitor and report data as specified in the protocol. Investigators or authorized staff will enter clinical data into the system (eCRFs). All study staff will be fully trained in the use of the online data capture system, including the eCRF, completion guidelines and help files. Training

records and certificates will be stored in the investigator site file and checked through routine monitoring visits. The sponsor will also retain copies of all training records in the study trial master file.

Data processing will involve electronic edit checks and manual checks. During data entry, electronic edit checks will indicate the site personnel entering the data of any non-plausible or incoherent errors (e.g., identification of missing values or values that are outside pre-defined range, logical and consistency checks) made during the data capture process. Missing or unclear data will be queried and sent to the investigator for resolution. All modifications on data will be automatically documented in the audit trail generated by the system.

For data protection purposes, the patient's identity will be maintained pseudonymized throughout the study. No study team member will have access to the patient's private details including name, email, or phone number. For each patient, a patient ID will be generated. The patient ID is a pre-specified number of digits unique to the country, site, and patient.

At every stage of the data management process, the data collected will be securely stored and patient confidentiality will be always maintained in accordance with data protection laws. Access to the EDC system will be by username/password combination only and available to authorized personnel. When data entry is performed at the investigator site, investigators will not have access to the whole database but only to the data entered by the individual site on their own enrolled patients. Patient identification list will remain in the investigator file; neither patient name nor any combination of patient identifiable details will appear on the eCRF to avoid disclosure of patient identification or sharing external to the site.

9.6.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

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 and/or paper 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, laboratory or the physician's chart. In these cases, data collected on the CRFs must match those charts. Where required by local regulations, additional safeguards related to secondary use of healthcare data and cross-border data transfer will be implemented in compliance with applicable data protection laws.

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., CRFs and hospital records), all original signed informed consent documents (if required by Regulatory Authority or Ethics Committee), 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, 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 or as 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

Continuous variables will be summarized using descriptive statistics such as number of observations (N), mean, SD, median, first and third quartile, minimum and maximum values. Categorical data will be summarized with the N and percentage (%) of patients in each category. Missing observations will be presented in tables as a separate category. The calculation of percentages will not include the missing category. Missing values in this study will not be imputed.

All statistical tests performed are 2-sided with a significance level of 5%. No adjustment for multiple testing is performed.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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.

For primary endpoint, the frequency and proportion of clinical cure will be calculated. The Clopper Pearson exact method will be used to calculate the 95% confidence interval.

For the secondary and exploratory endpoints, descriptive summary will be performed as appropriate. Survival analysis using the Kaplan–Meier method will be applied for time-to-event outcomes (e.g. mortality and cure), accounting for differing follow-up times and censoring. Cox proportional hazards regression will be conducted to analyze the impact of multiple covariates (e.g., antimicrobial genotypic/phenotypic resistance, specific pathogens, infection sites, potential risk factors for resistance and marker of disease severity) on the time it takes for mortality or cure. The first dose of ATM-AVI therapy will be defined as time 0 for survival analysis.

9.8. Quality Control

This study will utilize secondary data collected from participating sites in the context of routine clinical practice. Quality control of site-reported data will be performed to ensure data completeness, internal consistency, accuracy, and plausibility across the full data lifecycle, from source record creation through database lock.

Source Records and Data Origination

Clinical data will originate from source records routinely generated at participating sites (e.g., medical charts, electronic health records, laboratory or microbiology databases) in accordance with local clinical practice. Site personnel are responsible for ensuring that source records are complete, accurate, and legible, and that data abstraction for the purposes of this study reflects the information documented in those records in compliance with applicable regulatory and ethical requirements.

Owner Database and Source System Quality Checks

Where data are extracted from local or regional owner databases (e.g., hospital information systems, laboratory databases, or registries), quality control checks performed by the database owner as part of routine database governance will support baseline data integrity. These checks may include access controls, audit trails, predefined validation rules, and routine consistency checks in accordance with local procedures.

CRF Completion and Review

Study data will be captured using standardized eCRFs as defined in the Data Management Plan. eCRFs will incorporate programmed edit checks, data type restrictions, mandatory fields, and range checks to minimize missing or implausible data at the point of entry. Initial review of entered data will be performed to identify incomplete, inconsistent, or illogical entries.

Risk-Based Source Data Verification

Risk-based source data verification may be performed, taking into account the non-interventional design of the study and the secondary nature of the data. Verification activities will focus on predefined critical data elements and key variables relevant to the study objectives, as described in the Monitoring Plan. Verification may be conducted centrally or remotely and will be proportionate to identified risks.

Central Data Review and Data Cleaning

Ongoing central data review will be conducted to assess data completeness, internal consistency, temporal logic, and plausibility across sites and data sources. Data cleaning activities will include predefined automated and manual checks for missing values, out-of-range results, duplicate records, and logical inconsistencies between variables. The scope and frequency of data reviews will be defined in the Data Management Plan.

Query Management and Resolution

Identified data discrepancies will be documented and, where appropriate, communicated to the reporting site through a structured query process. Queries will be reviewed and resolved by site personnel in a timely manner, with updates documented in the data capture system. All query activities and resolutions will be traceable and auditable.

Final Data Review and Database Lock

Prior to database lock, a final review of data quality will be performed to confirm that all predefined quality control checks have been completed, outstanding queries have been resolved or appropriately documented, and data are suitable for analysis. Database lock will be conducted in accordance with the Data Management Plan following confirmation that quality control activities are complete.

Oversight and Compliance

Quality control procedures, including data checks, query management, and oversight activities, will be conducted in accordance with the Data Management Plan and aligned with the analyses described in the SAP. Oversight activities will follow a risk-based approach, as defined in the Monitoring Plan. All quality control and oversight activities will be performed in compliance with Good Clinical Practice principles and applicable regulatory requirements.

9.8. 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 (non-critical) information will be missing, incomplete, or inaccurate. It is also possible that a complete picture of patient demographics is not obtained if certain parameters are inconsistently provided for specific groups of patients. 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.

Second, ensuring a geographically diverse sample is essential to accurately capture the full spectrum of clinical scenarios for which ATM-AVI is employed. Achieving a representative sample necessitates the inclusion of varied healthcare settings and the implementation of sampling across different regions within a specific country. Specific strategies will be implemented to obtain a diverse and generalizable sample of study sites as outlined in Sections 9.1 (Study Design) and 9.2 (Setting) above.

Another limitation is the potential for an unequal distribution of infection types captured based on specific indications (e.g. HAP/VAP vs cUTI). Because of the real-world nature of this study, the distribution of infections documented may not be even across all infection types. We will evaluate the distribution of infection types at both interim and final analysis, but no required lower or upper bound on the numbers of patients per indication type will be applied.

Moreover, susceptibility results will be based on local testing reports; therefore, susceptibility rates identified in this study cannot necessarily be extrapolated beyond the study population. Furthermore, microbiological assessments are unlikely to be performed consistently in patients who achieve clinical cure and presumed eradication, (e.g. those with cUTIs at low risk for relapse).[43] As a

result, true microbiological success or failure rates will not always be obtained in this real-world study setting.

The study's reliance on physician judgment in the determination of the clinical outcomes, including clinical cure or failure also has the potential to introduce variation and bias into the study; yet, the retrospective, real-world nature of the study makes the standardization of the outcomes impossible. To mitigate that, the analyses may consider accounting for random effects, clustering, or other statistical approaches, depending on the observed data.

Furthermore, as this study is meant to describe real-world use of ATM-AVI, it is expected, that other drugs are administered concomitantly with ATM-AVI, and thus clinical response and cure will not be attributable solely to ATM-AVI treatment without sophisticated statistical analyses beyond the anticipated scope of the study. It will be important to consider the study results in the context of the indications for use of ATM-AVI (e.g., cIAI where ATM-AVI may be used in combination with metronidazole or combination Gram-negative therapy for HAP/VAP).

An additional limitation of the study is that it only includes patients who received ≥72 hours of antibiotic therapy. The rationale for this limit is that a 72-hour period allows for stabilization before potentially switching from intensive IV therapy to other effective oral treatments. This criterion may introduce survivor bias, however, as patients who discontinued therapy before 72 hours—whether due to early death, rapid clinical deterioration, transition to comfort care, or early clinical improvement leading to discontinuation—will not be captured in the cohort. As a result, the analytic population may overrepresent patients who were clinically stable enough to remain on therapy for at least 72 hours and may underestimate adverse outcomes occurring early in the treatment course.

Lastly, it is anticipated that routine clinical practice and patient care may differ across the centers when physicians prescribe ATM-AVI based on previous experience with other antibiotics that are used for the treatment of multidrug-resistant Gram-negative infections.[9,44,45] This impacts the interpretation of the study as the variability can lead to differences in baseline characteristics of the study population, making it difficult to draw general conclusions about the outcomes associated with ATM-AVI use, and outcomes may be influenced more by the standard of care than by ATM-AVI itself. However, this will be evident if the outcomes appear to vary by country.

9.9. Other Aspects

The primary risk to the study is the inability to recruit the target sample, potentially due to the limitation of patients using ATM-AVI strictly as per indication. To mitigate this risk, we are commencing data abstraction as early as possible in each country (i.e. the earliest date that ATM-AVI is commercially available) and utilizing a multi-pronged approach to ensure a geographically representative sample. In addition, the enrollment period for the study could be extended to recruit the target sample.

10. PROTECTION OF HUMAN PARTICIPANTS

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

In accordance with applicable local laws and regulatory requirements in each participating country, patient informed and privacy consent requirements may vary. Depending on local regulations, patients may be required to provide written or oral informed and privacy consent, or to confirm their agreement through a non-opposition mechanism prior to inclusion in the study.

Where permitted by applicable local laws and regulations, and given the retrospective, non-interventional nature of this multicenter study—which involves only secondary use of existing medical records, —an exemption from the requirement to obtain individual informed and privacy consent will be sought.

Any waiver of informed and privacy consent must be reviewed and approved by the Local Privacy Authority, where applicable, and/or the relevant Ethics Committee (EC) or Institutional Review Board (IRB) in each participating country prior to the inclusion of patient data in the study. In the absence of an approved waiver, written informed and privacy consent will be obtained from each patient or, where applicable, from the patient's legally acceptable representative, in accordance with local laws and regulations.

Further details on patient consent for each participating country are provided in Annex 5 COUNTRY-SPECIFIC PATIENT CONSENT REQUIREMENTS

10.3. Patient Withdrawal

Patients in France may oppose to their data collection in the study at any time.

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 subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events. 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 after the patient withdrawal. The sponsor may retain and continue to use any data collected before such withdrawal of informed consent

10.4. Institutional Review Board (IRB)/ Ethics Committee (EC)

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/ECs and/or Local Privacy Authority. All correspondence with the IRB/EC must be retained. Copies of IRB/EC applications, communications, notifications approvals must be forwarded to Pfizer and filed in Investigator Site File.

In France, because the study has a retrospective design based on secondary data collection and is conducted according to MR004 (Deliberation n° 2018-155 of 3 May 2018 approving the reference methodology relating to the processing of personal data carried out in the field of researches not involving human subjects, studies and evaluations in the area of health), the study is not subject to review by the national ethics committee called CESREES under national legislation (Title 8 of MR(004). However, a submission is required on the Health Data Hub platform.

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 External Guidance Documents for the Design and Conduct of Non-Interventional Studies and references to any additional relevant guidance.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves a combination of existing secondary structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

11.1. Secondary Data Collection of Structured Data

In these data sources, it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Secondary Data Collection Required Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refers 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 safety events (AEs/SAEs) with explicit attribution to any Pfizer product that appears 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 with such causality documented in the medical chart.

The requirements for reporting safety events, as defined below, on the "*Non-Interventional Study Adverse Event Report Form for Protocols with Stipulated Active Collection of Adverse Events"*, herein after referred to as the NIS AEM Report Form are as follows:

- All safety events with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy[(a)], breastfeeding, medication error, overdose, misuse, extravasation, *lack of effectiveness*, occupational exposure, and off-label use associated with the use of any Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

(a) Exposure during pregnancy (EDP) reports are reportable using the NIS AEM Report Form and the EDP Supplemental Form, irrespective of the presence of an associated safety event.

For these safety events with an explicit attribution or scenarios involving exposure to any 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 them. No follow-up 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, 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 day/month/year (DD/MMM/YYYY) format.

All site/research staff members must complete the following Pfizer training requirement:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

This training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (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 statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current "*Your Reporting Responsibilities (YRR) with Supplemental Topics*" training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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.

An interim analysis will be conducted, and interim results may be considered for submission in abstract form to a scientific conference if sufficient data are available at the time of analysis.

A final study report summarizing the study results will be prepared upon completion of the study. The results may be disseminated through scientific publications or presentations in accordance with applicable policies and guidelines.

Any publications from the results of this study must be consistent with Pfizer's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated December 2019. All reporting will be consistent with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Initiative checklist for cohort studies.[46]

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION - APACHE II SCORE

Table S1: Acute Physiology and Chronic Health Evaluation - APACHE II SCORE [36]

PHYSIOLOGIC VARIABLE		(Check one range per variable and write the severity score in the column to the right									
		HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE				
		+4	+3	+2	+1	0	+1	+2	+3	+4	Severity Score
1.	Temperature – Rectal (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9	
2.	Mean arterial pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49	
3.	Heart rate (ventricular response) (bpm)	≥180	140-179	110-139		70-109		55-69	40-54	≤39	
4.	Respiratory rate (non-ventilated or ventilated) (breaths per minute)	≥50	35-49		25-34	12-34	10-11	6-9		≤5	
5.	Oxygenation A-aDO_2 or PaO_2 (mm Hg) a) FiO_2 ≥0.5:record A-aDO_2	≥500	350-499	200-349		<200					
	b) FiO_2<0.5: record only PaO_2					>70	61-70		55-60	<55	
6.	Arterial pH* (see footnote)	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15	
7.	Serum Sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110	
		+4	+3	+2	+1	0	+1	+2	+3	+4	
8.	Serum Potassium (mmol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5	

PHYSIOLOGIC VARIABLE		(Check one range per variable and write the severity score in the column to the right							
		HIGH ABNORMAL RANGE				LOW ABNORMAL			
9.	Serum Creatinine (mg/dL) (Double points for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4	<0.6		
10.	Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9	20-29.9	<20	
11.	White Blood Count (total/mm^3) (in 1000s)	≥40		20-39.9	15-19.9	3-14.9	1-2.9	<1	
12.	Glasgow Coma Scale (Score = 15 minus actual GCS)	(Best GCS in the 24 hours prior to screening) Eye	Verbal	Motor	GCS total=(Eye+Verbal+Motor)				(15–GCS total)
A. Total Acute Physiology Score (APS)		Total severity points indicated for in the column to the right							
*Serum -HCO3 (VENOUS-mmol/L) Not preferred, use if no ABGs		≥52	41-51.9		32-40.9	22-31.9	18-21.9	15-17.9	<15

Glasgow Coma Scale	(Circle appropriate response)	B Age	Points	C	Chronic Health Points	Apache-II Score (sum of A+B+C)
Eyes open	verbal - nonintubated	Age	Points		If any of the 5 CHE categories is answered yes give +5 points for non-operative or emergency postoperative patient and give +2 points if elective postoperative patient	A APS points
4 - spontaneously	5 - oriented	<=44	0			+ B Age points
3 - to speech	4 - confused	45-54	2			+ C Chronic Health Points
2 - to pain	3 - inappropriate words	55-64	3			
1 - no response	2 - incomprehensible sounds	65-74	5			= Total Apache II
	1 - no response	>=75	6	Liver	Cirrhosis with PHT or encephalopathy	
Motor response				CV	Class IV angina or at rest or with minimal self care activities	
6 - to verbal command	verbal - intubated	Age points =		Pulmonary	Chronic hypoxemia or hypercapnia or polycytaemia of PHT > 40mmHg	
5 - localizes to pain	5 - seems able to talk			Kidney	Chronic peritoneal or hemodialysis	
4 - withdraws to pain	3 - questionable ability to talk			Immune	Immune compromised host	
3 – flexion to pain	1 - generally unresponsive				Chronic Health Points =	
2 – extension to pain						
1 - no response						

Abbreviations: A-aDO2 = alveolo-arterial oxygen difference; ABG = arterial blood gas; APS = Acute Physiology Score; CHE = Chronic Health Evaluation; CV = cardiovascular; FiO2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; HCO3 = hydrogencarbonate or bicarbonate; PaO2 = partial pressure of oxygen in arterial blood; PHT = pulmonary hypertension

ANNEX 4: COUNTRY-SPECIFIC CASE ACCRUAL TIMEFRAME

The case-accrual timeframe for each country is dependent upon the earliest available date on which ATM-AVI is commercially available in that country.

In this context, “commercially available” is defined as when drug product is available for purchase. A drug product provided free of charge for a named patient through a Pfizer CT16-GSOP expanded access program (EAP) would not be deemed as commercially available.

Table S2: Date Range of Case-Accruals by Country and EAP participation

Country	CT16-GSOP EAP (Y/N) *	Earliest Case-Accrual Date	Latest Case-Accrual Date
France	No	16 September 2024	27 December 2027
Italy	Yes	24 September 2025	27 December 2027
Romania	No	24 September 2025	27 December 2027
Spain	No	08 October 2024	27 December 2027

* CT16-GSOP is a Pfizer-internal Standard Operating Policy (SOP) that outlines the requirements and conditions for a free of charge named patient expanded access program. All expanded access programs undertaken under CT16-GSOP must comply with local regulations for pre-approval supply and / or provision of an unlicensed pack (e.g. foreign pack).

ANNEX 5: COUNTRY-SPECIFIC PATIENT CONSENT REQUIREMENTS

France

According to article 74 of the French Data Act n°78-17, 6th January 1978, patients have a discretionary right to object to the data processing of their personal health data. This right may be exercised by the patient without justification.

Regarding living patients, the investigator must ensure that each of them or their legal representatives are fully informed about the nature and objectives of the study, the sharing of study-related data, and any potential risks associated with the processing of the patient's personal data; Patients will be informed of the use of his/her existing medical data for the purpose of the study with an information letter sent by postal mail with an acknowledgement of receipt, by the participating centers. Participating centers will also contact patients by phone to inform them of the study objectives and the sending of the specific information letter. Patients will have 21 days to oppose to the data collection following its reception. If they do not oppose, their data will be collected in the study. Patients are also informed that they can oppose to the data collection at any time during the study. The proof of delivery of the information letter will be kept in patient’s medical records.

Regarding deceased patients and in accordance with the application of Decision No. 2018-155, Article 2.5 of May 3, 2018: personal data may be collected for research purposes provided that the professional participating in the research knows the vital status of the patient and that the patient did not object in writing during their lifetime to the collection of their personal data. An information letter will be sent to their family based on contact details available in patients' medical records

Romania

The IRB/IEC is requested to grant a waiver for having patients sign an informed consent form (ICF) on the following grounds:

- This is a non-interventional study that only will abstract data from existing hospital medical records.
- Requesting that patients sign an ICF is not practical because patients will no longer be receiving care at the hospital after discharge and some patients will have died since the index hospital admission.
- Requesting that patients sign an ICF may introduce selection bias, which would have a negative impact on the representativeness of the study results.
- Requesting that patients sign an ICF will cause unnecessary inconvenience to patients and their families in view that no patient identifiers will be disclosed by the site; and hence, the study data will be pseudonymized to protect the privacy rights of patients (see preceding paragraph).

Should IRBs/IECs reject the request for a waiver of consent, then the investigator will 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. The investigator will retain the original of each patient's signed consent form. If local IRBs/IECs require consent for deceased patients, next of kin will be contacted for remote informed consent as described above. The informed consent form must be in compliance with local regulatory requirements and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

Spain

The IRB/IEC is requested to grant a waiver for having patients sign an informed consent form (ICF) on the following grounds:

- This is a non-interventional study that only will abstract data from existing hospital medical records.
- Requesting that patients sign an ICF is not practical because patients will no longer be receiving care at the hospital after discharge and some patients will have died since the index hospital admission.
- Requesting that patients sign an ICF may introduce selection bias, which would have a negative impact on the representativeness of the study results.

• Requesting that patients sign an ICF will cause unnecessary inconvenience to patients and their families in view that no patient identifiers will be disclosed by the site; and hence, the study data will be pseudonymized to protect the privacy rights of patients (see preceding paragraph).

Should IRBs/IECs reject the request for a waiver of consent, then the investigator will 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. The investigator will retain the original of each patient's signed consent form. If local IRBs/IECs require consent for deceased patients, next of kin will be contacted for remote informed consent as described above. The informed consent form must be in compliance with local regulatory requirements and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

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