A PHASE 1, OPEN-LABEL, SINGLE-DOSE STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF CEFTAZIDIME-AVIBACTAM (CAZ-AVI) IN CHILDREN FROM 3 MONTHS TO LESS THAN 18 YEARS OF AGE WHO ARE HOSPITALIZED AND RECEIVING SYSTEMIC ANTIBIOTIC THERAPY FOR SUSPECTED OR CONFIRMED NOSOCOMIAL PNEUMONIA, INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA

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Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	17 September 2018	Not applicable (N/A)
Amendment 1	12 June 2019	In addition to minor administrative changes and clarifications, protocol amendment 1 includes the following: As needed in the document, text was updated to indicate that when screening assessment procedures are performed the day prior to the dose of CAZ-AVI, weight is also to be collected at day of dose administration. The weight collected on the date of dose administration will be used to properly calculate the dose of CAZ-AVI to be administered. The protocol summary, the introduction and study design were updated to include the CAZ-AVI pediatric approval in children from 3 months of age and older in 2019 received in the US for the treatment of cIAI (when combined with metronidazole), and for the treatment of cUTI. Text now also has been updated to show that CAZ-AVI has received regulatory approval in 51 countries worldwide. Text has been updated to show that this study is planned to be performed at approximately 43 sites and 14 countries in the Americas, Europe, and Asia. At the Screening Visit (Day -1 to 1), text was updated to clarify that standard of care assessments performed will not replace the study specific Screening and Baseline laboratory assessments. Study Design text was updated to provide a definition of nosocomial pneumonia as pneumonia with onset ≥48 hours after admission or within 7 days of discharge from an inpatient care facility, including ventilator-associated pneumonia (VAP), defined as a parenchymal lung infection arising ≥48 hours after endotracheal intubation and mechanical ventilation. Inclusion Criteria text for criterion 4b was update to clarify that the imaging result of "new or worsening infiltrate" was not limited to X-ray, but could be

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		demonstrated on chest X-ray or other imaging modality that had been performed as part of the subject's medical care. Pharmacokinetic (PK) Blood Sample Assessments for all cohorts was updated so that the first PK sample is obtained at the end of CAZ-AVI infusion/flush +0 to 5 minutes. End time of IV flush has been added to the data points to be collected at the Baseline Visit. Text was also updated to clarify that the PK sample obtained immediately after the CAZ-AVI infusion/flush must not be drawn from any lumen of a catheter used for drug delivery. Pharmacokinetics Analysis (Primary Endpoint) text in the objectives and endpoint section has been updated to show that plasma concentration of ceftazidime and of avibactam will be listed, and summarized by nominal time for all cohorts, using appropriate descriptive statistics such as number, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and coefficient of variation. The text update also clarifies that the NCA PK parameters will be summarized for Cohorts 1 and 2 using descriptive statistics. Text was updated to use the term nominal time for all cohorts so that the primary endpoint related to plasma concentration now describes CAZ and AVI plasma concentration by nominal time. Tertiary/Exploratory Endpoints text updated to state endpoint as CAZ and AVI ELF:plasma concentration ratios, and to clarify that this collection is considered for subjects who have BAL after bronchoscopy. Text also clarified that lab results will be medically reviewed. End of Trial text was updated to define the end of the study as the last visit of the last patient undergoing the study, or the date of study closure in the case of early study termination, whichever date is later. Text was also updated to state that the study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow."

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Background and Rationale

Ceftazidime is an injectable third generation cephalosporin antibiotic which has been in clinical use worldwide for more than 25 years for the treatment of infections caused by aerobic Gram-negative pathogens. Ceftazidime has been shown to be safe and effective in adult and pediatric patients (neonates to adolescents <18 years of age) for a range of indications. However, over the past 15 years, resistance to ceftazidime has been increasing worldwide. The most common mechanism of resistance is bacterial production of β-lactamases, in particular, extended spectrum β-lactamases (ESBLs).

In order to counter ceftazidime resistance and restore antibacterial activity to ceftazidime, a combination product has been developed in which ceftazidime is combined with avibactam, a novel non-β-lactam β-lactamase inhibitor. Although avibactam itself possesses no intrinsic antibacterial activity, it has been shown to restore activity of ceftazidime against clinically relevant β-lactamases of class A and class C varieties, including extended spectrum β-lactamases (ESBLs) and serine-based *Klebsiella pneumoniae* carbapenemases (KPCs) and AmpC producing strains. Although avibactam has no inhibitory effect on class B metallo-β-lactamases, it does inhibit the activity of some class D β-lactamases (eg, OXA-48 type carbapenemase). A fixed dose combination of ceftazidime and avibactam (CAZ-AVI) was approved for use in adults in the United States in 2015, and for use in children three months of age and older (with cIAI in combination with metronidazole, or cUTI) in 2019, under the brand name AVYCAZ.[1] A fixed dose combination of ceftazidime and avibactam (CAZ-AVI) was approved for use in adults in Europe in 2016 under the brand name Zavicefta.[2] This fixed-dose combination of CAZ-AVI is currently being evaluated globally for pediatric use.

Study Sites and Number of Subjects Planned

This study is planned to be performed at approximately 43 sites and 14 countries in the Americas, Europe, and Asia.

The study will enroll approximately 32 children aged 3 months to <18 years who are hospitalized and receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia (NP), also known as hospital-acquired pneumonia (HAP), including the subtype of ventilator-associated pneumonia (VAP).[1]

[1] Note that the word "bacterial" is sometimes added to these descriptions, ie, hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) to emphasize the bacterial nature of pneumonia requiring antibacterial treatment. Throughout this document the disease entity will be referred to using the traditional nomenclature of HAP/VAP.

Subjects will be divided into 4 age cohorts, all enrolling simultaneously:

Cohort	Age	Number
1	Age 12 years to <18 years	n=8
2	Age 6 years to <12 years	n=8
3	Age 2 years to <6 years	n=8
4	Age 3 months to <2 years (born ≥37 weeks gestational age)	n=8
4a	Age 1 year to <2 years	n=4
4b	Age 3 months to <1 year	n=4

Objectives and Endpoints

Primary Objective:	**Primary Endpoints:**
• To characterize the pharmacokinetics (PK) of a single intravenous dose of CAZ-AVI in pediatric subjects aged 3 months to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia, including ventilator-associated pneumonia.	• CAZ and AVI Plasma concentrations by nominal time. • CAZ and AVI PK parameters calculated by non-compartmental analysis (Cohorts 1 and 2 only).
Secondary Objective:	**Secondary Endpoints:**
• To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in pediatric subjects aged 3 months to less than 18 years with nosocomial pneumonia, including ventilator-associated pneumonia.	• Safety and tolerability endpoints include adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.
Exploratory Objectives:	**Exploratory Endpoints:**
• To determine CAZ-AVI concentrations in bronchial epithelial lining fluid (ELF) by bronchoalveolar lavage (BAL) from subjects undergoing bronchoscopy for their clinical management if bronchoscopy with BAL is performed within the PK sampling interval after CAZ-AVI infusion.	• CAZ and AVI ELF:plasma concentration ratios.

Study Design

This is a multicenter, multinational, open-label single-dose pharmacokinetic (PK) study enrolling at least 32 subjects. The study aims to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single intravenous (IV) infusion. Subjects will be hospitalized pediatric patients who are receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia (NP) defined as pneumonia with onset ≥48 hours after admission or within 7 days of discharge from an inpatient care facility, including ventilator-associated pneumonia (VAP), defined as a parenchymal lung infection arising ≥48 hours after endotracheal intubation and mechanical ventilation. Subjects will be enrolled in 4 cohorts of descending age, each consisting of at least 8 evaluable subjects. An evaluable subject is one who has received the complete single IV dose of CAZ-AVI and provided PK blood samples at ≥50% of the sampling time points. The definition of an evaluable subject is used for enrollment purposes only, and it does not impact the definition of the PK analysis set in Section 9.3. Each subject will receive a single IV dose of CAZ-AVI administered as an infusion over a 120 minute period. Blood samples will be collected from all subjects at the end of/after the infusion to evaluate the PK of ceftazidime and avibactam. Subjects will be followed for 48 hours after the end of the infusion.

The study will consist of a Screening visit (Visit 1, Day -1 to 1), during which consent will be obtained and subject eligibility will be confirmed, a Baseline/Treatment visit (Visit 2, Day 1) during which subjects will receive a single IV infusion of CAZ-AVI, and then two follow-up assessment visits at 24 hours (Visit 3, Day 2) and 48 hours (Visit 4, Day 3). Blood samples for PK analyses (0.5 mL per sample) will be obtained over 22 hours for Cohort 1 (7 samples), over 13 hours for Cohort 2 (6 samples), and over 6 hours for Cohorts 3 and 4 (4 samples). A Late Follow-up (LFU) visit, that may be performed by telephone, will be conducted 28-35 days after the CAZ-AVI infusion in order to identify, assess, and record any new Serious Adverse Event (SAE).

In addition to routine clinical monitoring all available safety and tolerability data from each cohort will be reviewed by a Safety Review Committee (SRC) after the first 4 subjects in each cohort are enrolled. The SRC will consist of the study team physician, international coordinating Investigator or delegate, global safety risk lead or delegate, therapeutic area director or delegate and the clinical pharmacologist/pharmacometrician or delegates. Any SRC recommendation to alter the conduct of the study or modify dosing will be incorporated into a protocol amendment, as appropriate, and forwarded to regulatory authorities.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The Investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Protocol Activity	Screening[a]	Baseline/IV Infusion	24 hr Assessment	48 hr Assessment	Late Follow- up (LFU)
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Day	**Day -1 to 1**	**Day 1**	**Day 2**	**Day 3**	**Day 28-35**
Clinic Assessments					
Informed consent	X				
Demography	X				
Medical/surgical history	X				
Physical examination	X			X	
Inclusion/exclusion criteria	X				
Height	X[b]				
Weight	X[b]	X[a]		X	
Vital signs evaluation[c]	X	X	X	X	
Oxygen saturation (if available)	X	X	X	X	
Adverse Event and Serious Adverse Event assessment	X	X	X	X	X
Adjunctive therapeutic procedures (if any)		X	X	X	
Contraception check	X	X	X	X	X
CXR, CT scan, or other imaging tests	X[d]		X[e]		
Laboratory					
Hematology	X			X	
Blood chemistry	X	X[f]		X	
Urinalysis	X			X	
CrCL estimation[g]	X			X	
Pregnancy test[h]	X			X	

Protocol Activity	Screening[a]	Baseline/IV Infusion	24 hr Assessment	48 hr Assessment	Late Follow- up (LFU)
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Day	**Day -1 to 1**	**Day 1**	**Day 2**	**Day 3**	**Day 28-35**
Study Medication					
CAZ-AVI Infusion		X			
Pharmacokinetic (PK) blood sampling[i]		X			
BAL fluid collection for CAZ-AVI PK[j]		X			
Prior/Concomitant treatment[k]	X	X	X	X	

Abbreviations: CT scan = computed tomography scan; CXR = chest x ray; IV = intravenous.

a. Screening (Day -1 to 1) assessments will serve as baseline and can be completed on the same calendar day as Day 1, prior to CAZ AVI infusion, but must be completed no earlier than the day before the start of CAZ AVI infusion. If Screening and Baseline assessments are performed on different days, weight should be collected at both Screening and Baseline, and weight at Baseline should be used to calculate dose.
b. BMI will only be calculated at screening. The BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.
c. Vital signs (blood pressure, pulse rate, respiratory rate and temperature) will be taken at the following time points: before infusion and at 2, 4, 6, 12, 24, and 48 hours after the end of CAZ AVI infusion. Additional vital signs may be taken as needed.
d. At screening, obtain results of CXR, CT scan, or other imaging tests (eg, MRI, ultrasound) if performed diagnostically as part of the subject's regular medical care for the current diagnosis of pneumonia.
e. If clinically indicated.
f. Blood sample (0.5 mL) for blood urea analysis to be collected at the time of BAL only for subjects undergoing BAL as part of their clinical management.
g. Creatinine values will be used to calculate CrCL using the Bedside Schwartz equation [eGFR (ml/min/1.73 m2) = 0.413 * (length(cm)/serum creatinine (mg/dL)], Schwartz, Munoz, et al., 2009.[3]
h. A serum or urine pregnancy test with sensitivity for human chorionic gonadotropin (hCG) of at least 25 mIU/mL to be performed on all female subjects of childbearing potential (postmenarcheal), as determined by the Investigator.
i. PK samples will be drawn at time points indicated in Table 3, Table 4 and Table 5 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively.
j. BAL fluid collection to be performed at selected sites only for subjects undergoing bronchoscopy with BAL as part of their clinical management during the time window for collection of PK blood samples after CAZ AVI infusion. A matching blood sample to replace one of the PK blood samples is to be collected at the same time as the BAL, along with a blood sample for blood urea analysis.
k. Review prior and concomitant treatments. For Cohort 3 and 4 subjects who are being breast fed, record all medications taken by the lactating mother for 3 days before the CAZ AVI infusion through Day 3.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Ceftazidime is an injectable bactericidal third generation cephalosporin antibiotic which has been in clinical use worldwide for more than 25 years. Ceftazidime is approved for the treatment of aerobic Gram-negative bacterial infections in adults and children including neonates (from birth). Many years of experience using ceftazidime have accrued in numerous countries worldwide and its tolerability profile is well characterized. Included among the infections treated by ceftazidime are complicated urinary tract infection (cUTI) caused by P. aeruginosa, Enterobacter spp., Proteus spp., Klebsiella spp., and E. coli; complicated intra-abdominal infection (cIAI), including peritonitis, caused by E. coli, Klebsiella spp., Staphylococcus aureus (methicillin-susceptible strains); and lower respiratory tract infections caused by P. aeruginosa, Klebsiella spp. E. coli, Enterobacter spp, and S. aureus (methicillin susceptible strains). Ceftazidime is also approved for use in a wide range of other infections, including, but not limited to complicated skin and soft tissue infections (cSSTI), bone and joint infections, bronchopulmonary infections in cystic fibrosis, and bacteremias (Fortum Summary of Product Characteristics [SmPC] 2016;[4] FORTAZ United States Package Insert [USPI] 2014).[5] Like other β-lactam antibiotics, ceftazidime is susceptible to hydrolysis by β-lactamases, in particular, extended spectrum β-lactamases (ESBLs), thereby rendering it inactive. The high and increasing prevalence of β-lactam resistance worldwide over the last 15 years has reduced the utility of ceftazidime in many countries.

Avibactam is a novel, non β-lactam, β-lactamase inhibitor. Beta-lactamase inhibition by avibactam is effected through the formation of a stable covalent carbamoyl linkage to the enzyme complex. Although avibactam itself possesses no intrinsic antibacterial activity, it has been shown to restore in vitro activity of ceftazidime against Class A, Class C and some Class D β-lactamases (eg OXA-48 type carbapenemse) restoring activity against pathogens commonly associated with cIAI, cUTI, and nosocomial pneumonia (NP). Avibactam, when combined with ceftazidime, has also been shown to be active against strains that express a combination of β-lactamase types, as well as strains that are concomitantly resistant to other antibacterial classes such as fluoroquinolones. Unlike currently available β-lactamase inhibitors, avibactam does not induce β-lactamase production (Miossec, Claudon, et al., 2013).[6]

A fixed dose combination of ceftazidime-avibactam (referred to hereafter as CAZ-AVI) was approved for use in adults by the FDA on 25 February 2015, and in children three months of age and older (cIAI in combination with metronidazole, or cUTI) on 18 Mar 2019 and is marketed under the tradename AVYCAZ.[1] On 24 June 2016, the European Commission granted European Union marketing authorization for the use of CAZ-AVI in adults under the tradename Zavicefta.[2] The fixed dose combination ceftazidime-avibactam is currently being evaluated for pediatric use.

CAZ-AVI has received regulatory approval in 51 countries worldwide. CAZ-AVI is indicated in the US and Europe for the treatment of adults with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), and hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). It is also indicated in Europe for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options. CAZ-AVI is indicated in the US for the treatment of children three months of age and older with cIAI when used in combination with metronidazole, and in children with cUTI.

1.2. Background

Ceftazidime-avibactam is currently being evaluated for use in pediatric patients. Single-dose PK of CAZ-AVI was previously investigated in Study D4280C00014, which included the same age cohorts as the present study, but did not target specific types of infection and enrolled only a few children with pneumonia. CAZ-AVI was subsequently evaluated at multiple doses in children with cIAI (D4280C00015/C3591004) and cUTI (D4280C00016/C3591005), corresponding to two of the approved indications for CAZ-AVI in adults.

1.3. Rationale for Conducting this Study

The long-established efficacy and safety of ceftazidime in children, the mode of action of avibactam, the available Phase 2 clinical data for CAZ-AVI in pediatrics, and the established efficacy and safety of CAZ-AVI for the treatment of HAP/VAP in adults provide a strong rationale for extending the evaluation of CAZ-AVI into the pediatric HAP/VAP population. This study will extend the pediatric evaluation of CAZ-AVI into children with HAP/VAP, the third indication for CAZ-AVI in adults. Observed PK data from the adult Phase 3 studies in patients with cIAI (Studies D4280C00001 and D4280C00005, Mazuski, Gasink, et al 2016)[7] and HAP/VAP (Study D4281C00001, Torres, Zhong, et al 2018)[8] suggest that the plasma PK of both ceftazidime and avibactam are comparable in patients with cIAI and NP following the administration of CAZ-AVI 2000 mg/500 mg as a 120 minute infusion. The present study will confirm whether the plasma PK of ceftazidime and avibactam in children with NP are comparable with the plasma PK in children with cIAI and cUTI.

Based on the assumptions that the disease, mechanism of action, and the PK/PD are the same in pediatric and adult HAP/VAP patients; the appropriate dose of CAZ-AVI for pediatric patients will be one that achieves comparable plasma exposures to those in adults. If the adult dose is efficacious, the same exposure in pediatric patients should also be associated with clinical efficacy. CAZ-AVI is expected to provide positive clinical outcomes in those pediatric HAP/VAP patients infected with pathogens resistant to β-lactam antibiotics due to the presence of avibactam sensitive β-lactamases. Therefore, CAZ-AVI has the potential to address the significant unmet clinical need associated with antibiotic resistance in pediatric HAP/VAP patients.

As an exploratory endpoint in this study in a limited number of subjects who are undergoing bronochoscopy with bronchoalveolar lavage (BAL) for clinical purposes, and for whom informed consent is obtained specifically for the collection of BAL samples, an epithelial

lining fluid (ELF) sample will be collected for estimation of CAZ-AVI concentrations. An adult BAL study in normal volunteers has shown that both ceftazidime and avibactam penetrate dose-proportionally into ELF, with ELF exposure to both drugs being about 30% of plasma exposure (Nicolau, Siew, et al., 2015).[9] Since the clinical efficacy of CAZ-AVI has been demonstrated in adults with HAP/VAP, ELF penetration is known to be adequate to achieve efficacy, and plasma exposure is validated as a suitable surrogate target.

The inclusion and exclusion criteria for this study have been chosen in order to select appropriate pediatric patients who are being treated for suspected or confirmed HAP/VAP infection. The PK sampling and safety assessments are judged to be sufficient to fulfill the primary and secondary objectives of the study.

1.4. Dose Rationale

Dosing for this study is based on modelling and simulation study CAZ-MS-PED-02 (Pediatric Investigation Plan [PIP] Study 7) which included data from the adult Phase 1, 2, and 3 studies including studies of cIAI, cUTI, and NP, and three prior pediatric studies: 1) D4280C00014, an open-label, single-dose study in hospitalized pediatric patients from 3 months to <18 years of age receiving systemic antibiotic therapy for suspected or confirmed infection; 2) D4280C00015/C3591004 a phase 2, single-blind, randomized, multicenter, active-controlled, multiple-dose study of CAZ-AVI when given in combination with metronidazole and compared with meropenem in hospitalized pediatric patients from 3 months to <18 years of age with cIAI; and 3) D4280C00016/C3591005 a phase 2, single-blind, randomized, multicenter, active-controlled, multiple-dose study of CAZ-AVI compared with cefepime in hospitalized pediatric patients from 3 months to <18 years of age with cUTI.

In all population pharmacokinetic (PK) analyses both CAZ and AVI concentration time courses have been well described by a linear 2-compartment PK model with first-order elimination. Simulations based on the final population described above were used to provide dose recommendations for all pediatric patients from pre-term neonates to <18 years of age with normal renal function in addition to pediatric patients 2 to <18 years of age with mild, moderate, or severe renal impairment. Per dose regimen and age scenario sets of 1,000 pediatric PK parameters were simulated with between-subject variability simulated non-parametrically through resampling of individual random effect estimates from the final CAZ and AVI models. The exposure target was defined as achieving at least 50 percent of time on treatment that CAZ and AVI are simultaneously above the minimum inhibitory concentration (MIC) of 8 mg/mL for CAZ and Critical threshold concentration (C_T) of 1.0 mg/L for AVI, respectively. The Probability of Target Attainment (PTA) was defined as the probably of achieving the exposure target. The PTA for PK/PD CAZ MIC 8 mg/L and AVI C_T 1.0 mg/L is the same joint PK/PD target used to support approval in adults.

A range of mg/kg doses were simulated, with the total dose capped at the absolute adult CAZ-AVI label doses of 2000/500 mg every 8 hours over a 120 minute infusion for normal renal function/mild renal impairment (or adjusted label dose for moderate renal impairment). Simulations were based on steady-state exposures; however, single CAZ-AVI doses will be administered in this study.

The doses for this study (see Table 2) when administered q8h as a 120 minute intravenous [IV] infusion were predicted to achieve ≥92% PTA in NP, which is above the target PTA of 90%. In subjects with normal renal function, average exposure (C_{max} and AUC) were predicted to be comparable to or higher than corresponding adult reference values. Average ceftazidime maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values ranged from 110-124% and 97-110%, respectively, of corresponding adult reference values. Average avibactam C_{max} and AUC values were 126-148% and 112-129%, respectively, of corresponding adult reference values. Additionally, these values were below the average for CAZ C_{max} and AUC and AVI AUC and slightly higher for AVI C_{max} as compared to the adult with mild renal impairment population, which are the group with the highest ceftazidime and avibactam exposures that have been studied in Phase II and III clinical studies, with data suggesting that CAZ-AVI is well-tolerated in this adult reference population (Muller, et al., 2013).[10]

In mild renal impairment (CrCL ≥50 to <80 mL/min/1.73 m^2), the dose of CAZ-AVI 50/12.5 mg/kg when administered q8h as a 120 minute intravenous [IV] infusion (subjects ≥2 years of age) was predicted to achieve ≥99% PTA in NP, which is well above the target PTA of 90%. In subjects with mild renal impairment, average exposure (C_{max} and AUC) were predicted to be comparable to or higher than corresponding adult reference values. For the CAZ-AVI 50/12.5 mg/kg q8h dose, the CAZ C_{max} and area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24}) were between 108 and 124% and between 98 and 112% respectively, of the values for adult subjects with mild renal impairment. The AVI C_{max} and AUC_{0-24} were between 124 and 148% and between 111 and 131% respectively, of the values for adult subjects with mild renal impairment. As noted previously, the lack of a dose adjustment is consistent in adult patients with mild renal impairment. Although not assessed in CAZ-MS-PED-02, the study doses in subjects ≥3 months to <6 months and ≥6 months to <2 years are 40/10 mg/kg and 50/12.5 mg/kg, respectively, consistent with dosing in mild renal impairment for Studies D4280C00015/C3591004 and D4280C00016/C3591005.

In moderate renal impairment (CrCL ≥30 to <50 mL/min/1.73 m^2), the dose of CAZ-AVI 25/6.25 mg/kg when administered q8h as a 120 minute intravenous [IV] infusion (subjects ≥2 years of age) was predicted to achieve ≥99% PTA in NP, which is well above the target PTA of 90%. In subjects with moderate renal impairment, average exposure (C_{max} and AUC) were predicted to be comparable to or higher than corresponding adult reference values. For the 25/6.25 mg/kg q8h dose, the CAZ C_{max} and AUC_{0-24} were between 114 and 149% and between 99 and 143% respectively, of the values for adult subject with mild renal impairment. The AVI C_{max} and AUC_{0-24} were between 134 and 171% and between 114 and 154% respectively, of the values for adult subjects with mild renal impairment. Although not assessed in CAZ-MS-PED-02, doses in subjects ≥3 months to <6 months and ≥6 months to <2 years in this study are 20/5 mg/kg and 25/6.25 mg/kg, respectively, consistent with dosing in moderate renal impairment for Studies D4280C00015/C3591004 and D4280C00016/C3591005. These doses are 50% of the total daily dose for normal subjects which are consistent with the dose adjustment applied in adult patients with moderate renal impairment.

As noted previously, these are the same doses as used in the recently completed pediatric studies with CAZ-AVI in cIAI (D4280C00015/C3591004) and cUTI (D4280C00016/C3591005). The doses for this study are listed Table 2. For the ceftazidime component these doses are within the mg/kg/day range of the approved doses of 30-50 mg/kg q8h for children 1 month to 12 years (FORTAZ USPI 2014)[5] and 100-150 mg/kg/day in three divided doses for children <40 kg (Fortum SmPC 2016).[4]

1.5. Benefit/Risk and Ethical Assessment

The potential benefit of the study, in general, is the confirmation that a novel antibiotic combination product is an appropriate treatment for infections in children, including nosocomial pneumonia, in the face of the changing pattern of antibiotic resistance. The subjects enrolled into this clinical study will have infections that are of sufficient severity to require hospitalization and treatment with systemic antibiotics. CAZ-AVI will not be used in this study to treat the infection for which the patient has been admitted as this is not a therapeutic study.

The risk considerations for this study encompass the known and potential risks for the development product CAZ-AVI and its component products ceftazidime and avibactam.

The full risk profile for ceftazidime is described in the prescribing information for the product (refer to local ceftazidime product labeling). Important risks as laid out in the warnings and precautions in product labeling for ceftazidime include the following:

- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae such as tremor, myoclonus, seizures, encephalopathy and coma.

The adverse events (AEs) described below for ceftazidime may occur with multiple administrations and are unlikely to occur with the single dose that subjects in this study will be receiving:

- Antibiotic-associated diarrhea, Clostridium difficile diarrhea, colitis, and pseudomembranous colitis;

- Bacterial overgrowth with nonsusceptible organisms.

The risks for CAZ-AVI in children have not been fully elucidated; however, it is assumed that known or potential risks for CAZ-AVI should include those identified in the approved local label for CAZ-AVI, eg the US Package Insert (USPI) (AVYCAZ, 2019)[1] or the EU Summary of Product Characteristics (SmPC) (Zavicefta, 2018).[2] Thus far, no unique risks have been identified for the combination of ceftazidime and avibactam in children. In recently completed study D4280C00015/C3591004, CAZ-AVI plus metronidazole was well tolerated for the treatment of pediatric patients 3 months of age to <18 years of age with cIAI. Highly favorable clinical and microbiological response rates were observed across all patients in the study and against the predominant cIAI pathogens (E. coli and P. aeruginosa), and no new safety concerns were identified. In recently completed study

D4280C00016/C3591005 CAZ-AVI was generally well tolerated and appeared effective for the treatment of pediatric patients 3 months of age to <18 years of age with cUTI, and no new safety concerns were identified. Side effects identified for the avibactam component of CAZ-AVI include injection site redness and injection site bruising.

Additional information for CAZ-AVI may be found in the single reference safety document (SRSD), which for this study is the CAZ-AVI Investigator Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
• To characterize the pharmacokinetics (PK) of a single intravenous dose of CAZ-AVI in pediatric subjects aged 3 months to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia, including ventilator-associated pneumonia.	• CAZ and AVI plasma concentrations by nominal time. • CAZ and AVI PK parameters calculated by non-compartmental analysis (Cohorts 1 and 2 only).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in pediatric subjects aged 3 months to less than 18 years with nosocomial pneumonia, including ventilator-associated pneumonia.	• Safety and tolerability endpoints include adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
• To determine CAZ-AVI concentrations in bronchial epithelial lining fluid (ELF) by bronchoalveolar lavage (BAL) from subjects undergoing bronchoscopy for their clinical management if bronchoscopy is performed within the PK sampling interval after CAZ-AVI infusion.	• CAZ and AVI ELF:plasma concentration ratios.

3. STUDY DESIGN

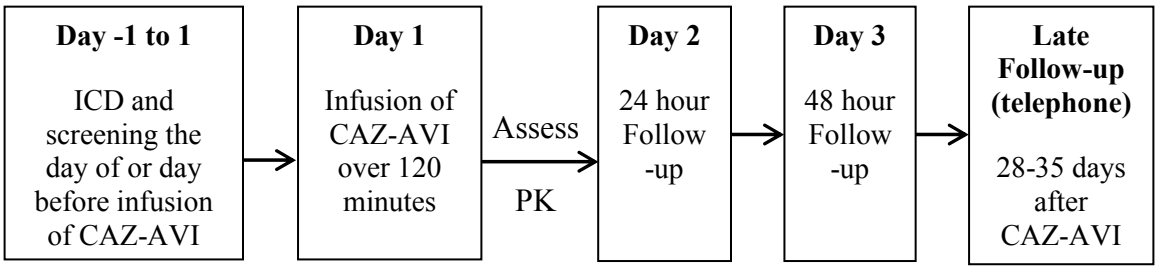
This is a multicenter, multinational, open-label single-dose PK study enrolling approximately 32 subjects. This study is planned to be performed at approximately 43 sites and 14 countries in the Americas, Europe, and Asia. The study outline is shown in Figure 1.

This study aims to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single IV infusion. Subjects will be hospitalized pediatric patients who are receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia (NP), defined as pneumonia with onset ≥48 hours after admission or within 7 days of discharge from an inpatient care facility, including ventilator-associated pneumonia (VAP), defined as a parenchymal lung infection arising ≥48 hours after endotracheal intubation and mechanical ventilation. Subjects will be enrolled in 4 cohorts of descending age, each consisting of at least 8 evaluable subjects. An evaluable subject is one who has received the complete single IV dose of CAZ-AVI and provided PK blood samples at ≥50% of the sampling time points. The definition of an evaluable subject is used for enrollment purposes only, and does not impact the definition of the PK analysis set in Section 9.3. Each subject will receive a single IV dose of CAZ-AVI administered as an intravenous infusion over a 120 minute period. Blood samples will be collected from all subjects after the infusion to evaluate the PK of ceftazidime and avibactam. Subjects will be followed for 48 hours after the end of the infusion.

The study will consist of a Screening visit (Visit 1, Day -1 to 1), during which consent will be obtained and subject eligibility will be confirmed, a Baseline/Treatment visit (Visit 2, Day 1) during which subjects will receive a single IV infusion of CAZ-AVI, and then two follow-up assessment visits at 24 hours (Visit 3, Day 2) and 48 hours (Visit 4, Day 3). A Late Follow-up (LFU) telephone visit will be conducted 28-35 days after the CAZ-AVI infusion to identify, assess, and record any new Serious Adverse Event (SAE). Blood samples for PK analyses (0.5 mL per sample) will be obtained over 22 hours following the CAZ-AVI infusion for Cohort 1 (7 samples), over 13 hours for Cohort 2 (6 samples), and over 6 hours for Cohorts 3 and 4 (4 samples). A Late Follow-up (LFU) visit, that may be performed by telephone, will be conducted 28-35 days after the CAZ-AVI infusion in order to identify, assess, and record any new Serious Adverse Event (SAE).

In addition to routine clinical monitoring all available safety and tolerability data from each cohort will be reviewed by a Safety Review Committee (SRC) after the first 4 subjects in each cohort are enrolled. The SRC will consist of the study team physician, international coordinating Investigator or delegate, global safety/risk lead or delegate, therapeutic area director or delegate and the clinical pharmacologist/pharmacometrician or delegates. Any SRC recommendation to alter the conduct of the study or modify dosing will be incorporated into a protocol amendment, as appropriate, and forwarded to regulatory authorities.

Figure 1. Study Outline



4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject's parent(s), legal guardian, or legally acceptable representative has been informed of all pertinent aspects of the study. As appropriate per local requirements informed assent of subjects must also be documented.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male or female children age ≥3 months to <18 years at Screening:

    a. Cohort 1: age 12 years to <18 years;

    b. Cohort 2: age 6 years to <12 years;

    c. Cohort 3: age 2 years to <6 years;

    d. Cohort 4: age 3 months to <2 years (must be born ≥37 weeks gestational age).

4. Hospitalized, receiving systemic antibiotic therapy for the treatment of a suspected or confirmed HAP, including VAP, meeting the following criteria, and expected to require hospitalization until after the follow-up evaluations are completed on Day 3 (48 hours after the end of infusion):

    a. Onset of symptoms ≥48 hours after admission or <7 days after discharge from an inpatient acute or chronic care facility;

    b. Evidence of new or worsening infiltrate as demonstrated on chest X-ray or other imaging modality that has been performed as part of the subject's regular medical care;

c. At least 1 of the following systemic signs prior to the initiation of treatment for Nosocomial Pneumonia:

   i. Fever (temperature >38°C) or hypothermia (rectal/core temperature <35°C);

   ii. White blood cell (WBC) count >10,000 cells/mm^3, or WBC count <4,500 cells/mm^3, or >15% band forms.

d. At least 2 of the following respiratory signs or symptoms:

   i. A new onset of cough (or worsening of cough);

   ii. Production of purulent sputum or endotracheal secretions;

   iii. Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds, dullness to percussion, egophony);

   iv. Dyspnea, tachypnea or hypoxemia (O_2 saturation <90% or PaO_2 <60 mmHg while breathing room air);

   v. A need for mechanical ventilation or, for already ventilated subjects, acute changes made in the ventilator support system to enhance oxygenation, as determined by, for example arterial blood gas or worsening PaO_2/FiO_2.

5. Likely to survive the current illness or hospitalization.

6. Sufficient IV access (peripheral or central) to receive study drug and dedicated access for PK sampling.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

4. Past or current history of epilepsy or seizure disorder (excluding childhood febrile seizures.

5. Severe renal impairment defined as creatinine clearance (CrCL) ≤30 mL/min/1.73 m^2 calculated using the child's measured height (length) and serum creatinine with the Bedside Schwartz equation (Schwartz, Munoz, et al., 2009):[3]

$$\text{CrCL (mL/min/1.73 m}^2\text{)} = \frac{\mathbf{0.413 \times height\ (cm)}}{\mathbf{serum\ creatinine\ (mg/dL)}}$$

6. Documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic.

7. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are sexually active and unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of CAZ-AVI.

8. Acute hepatitis in the prior 6 months, a prior history of cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure; and/or any of the following blood test results, for any individual, when assessed for eligibility:

    a. Bilirubin >3 × upper limit of normal (ULN), unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease;

    b. ALT or AST >3 × ULN values used by the laboratory performing the test. Subjects with values >3 × ULN and <5 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented;

    c. ALP >3 × ULN. Subjects with values >3 × ULN and <5 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

9. Any condition (eg, septic shock, burns, cystic fibrosis, acute hemodynamic instability, including those conditions not responding to pressor support) that would make the patient, in the opinion of the Investigator, unsuitable for the study (eg, would place a patient at risk; compromise the quality of the data; or interfere with the absorption, distribution, metabolism, or excretion of CAZ-AVI).

10. Receipt of a blood or blood component or scheduled for transfusion within the PK sampling period (eg, red blood cells, fresh frozen plasma, platelets) transfusion during the 24-hour period before enrollment.

11. Body mass index (BMI) below the 5th percentile or above the 95th percentile for height, age, and weight except for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

12. Treatment with ceftazidime within 12 hours of CAZ-AVI administration or treatment with ceftazidime within 24 hours of CAZ-AVI administration in subjects with renal impairment (CrCL ≤50 mL/min/1.73 m^2).

13. Treatment with potent inhibitors of OAT1 and/or OAT3 (eg, probenecid, p-aminohippuric acid (PAH), or teriflunomide).

4.3. Randomization Criteria

This study is not randomized. All enrolled subjects will receive a single dose of CAZ-AVI. The Investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the single dose of investigational product. The Investigator or his or her designee will confirm that the subject has selected an appropriate method of contraception from the list of permitted contraception methods (see below). At time points indicated in the Schedule of Activities, the Investigator or designee will instruct the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the Investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

Additionally, all sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the time of dose of investigational product and continuing for at least 28 days after the dose of investigational product.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the Investigator site, and contact details for a contact center in the event that the Investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by Investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the Investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the Investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the Investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is Zavicefta (ceftazidime-avibactam [CAZ-AVI]).

5.1. Allocation to Treatment

This is an unblinded, single treatment arm PK study. All subjects will receive CAZ-AVI.

5.2. Breaking the Blind

This is an open-label study. Blinding procedures are not applicable.

5.3. Subject Compliance

Qualified study center personnel will administer the IV study treatment and assure treatment compliance. At a minimum the dose, date, and exact start and stop time of administration of the IV study treatment will be recorded in the appropriate sections of the Case Report Form (CRF) and checked by the monitor at monitoring visits. Deviations from study treatment will be reported and documented.

5.4. Investigational Product Supplies

All sites will be provided with an Investigational Product (IP) Manual containing detailed instructions on the receipt, storage, dispensing, preparation, and administration of the investigational product, as outlined below. If there is any conflict between this protocol and the IP Manual regarding the handling of the investigational product, the IP Manual will control.

5.4.1. Dosage Form(s) and Packaging

The investigational product, Zavicefta (ceftazidime 2 g/avibactam 0.5 g), will be supplied by Pfizer as a white to yellow powder for concentrate for solution for infusion in a 20 mL glass vial. Each vial contains a fixed dose combination of ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.

Table 1. Identity of Investigational Product

Investigational product	Dosage form and strength
Zavicefta (ceftazidime-avibactam)	2 g/0.5 g powder for concentrate for solution for infusion

5.4.2. Preparation and Dispensing

Detailed instructions for the preparation of CAZ-AVI powder for concentrate for solution for infusion will be provided in the separate IP Manual. The investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. The preparation and administration of all sterile products must be performed using aseptic technique.

Ceftazidime/avibactam powder for concentrate for solution for infusion vials should be reconstituted with 10 mL of sterile water for injection. After reconstitution, 1 mL of solution contains 167.3 mg of ceftazidime and 41.8 mg of avibactam. The reconstituted solution is pale yellow and free of particles. Each vial is for single use only and should be used immediately after reconstitution. The reconstituted solution in the vial should be diluted with a compatible diluent for administration in an IV bag or IV syringe at the appropriate concentration for intravenous infusion.

Any unused product or waste material should be disposed of in accordance with local requirements.

5.5. Administration

The single dose intravenous infusion of CAZ-AVI is based on age and weight of the subject, with adjustment according to renal function, as detailed in Table 2. Administration should be via either an appropriately sized sterile syringe and calibrated syringe pump or IV infusion bag and calibrated IV pump over 120 minutes. The 120 minute infusion should be followed by an IV flush of the line. Details regarding drug administration will be provided in the IP Manual.

Table 2. CAZ-AVI Doses in Relationship to Age, Weight, and Renal Function

Cohort	Age range	Body weight	CAZ-AVI dose CrCL ≥50 mL/min/1.73 m^2	CAZ-AVI dose CrCL ≥30 to <50 mL/min/1.73 m^2
1[a]	12 years to <18 years	≥40 kg	2000 mg CAZ 500 mg AVI	1000 mg CAZ 250 mg AVI
1[a]	12 years to <18 years	<40 kg	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
2[a]	6 years to <12 years	≥40 kg	2000 mg CAZ 500 mg AVI	1000 mg CAZ 250 mg AVI
2[a]	6 years to <12 years	<40 kg	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
3[a]	2 years to <6 years	All	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
4[b]	1 year to <2 years	All	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
4[b]	6 months to <1 year	All	50 mg/kg CAZ 12.5 mg/kg AVI	25 mg/kg CAZ 6.25 mg/kg AVI
4[b]	3 months to <6 months	All	40 mg/kg CAZ 10 mg/kg AVI	20 mg/kg CAZ 5.0 mg/kg AVI

a. Subjects considered for entry into the study will be within the body mass index (BMI) range between the 5th percentile and ≤95th percentile according to height, weight, and age.
b. BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

5.6. Investigational Product Storage

The Investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the Investigational Product Manual for storage conditions of the product once reconstituted and/or diluted.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.7. Investigational Product Accountability

The Investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the Investigator site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

Prescribed antibiotics used to treat the subject's infection should be continued or modified according to the Investigator's decision.

All prescription and over-the-counter medications being taken by the subject for 5 days prior to study entry (considered prior treatment) and from enrollment through Day 2 and Day 3 (follow-up period) (considered concomitant treatments) must be documented on the appropriate pages of the CRF. For Cohort 3 and 4 subjects who are being breast fed, record all medications taken by the lactating mother for 3 days before the CAZ-AVI infusion through Day 3.

Other medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF. Subjects who have completed study dose of CAZ-AVI infusion and are in the follow-up period should remain in the study as they are not actively on study dose of CAZ-AVI, but being followed for outcomes.

Treatment with probenecid within 48 hours of CAZ-AVI administration is not permitted as this could interfere with the CAZ-AVI PK assessment. In vitro, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake from the blood compartment, and thereby its excretion. As a potent OAT inhibitor, probenecid inhibits OAT uptake of avibactam by 56% to 70% in vitro and, therefore, has the potential to decrease the elimination of avibactam when co-administered.

Treatment with ceftazidime within 12 hours of CAZ-AVI administration, or treatment with ceftazidime within 24 hours of CAZ-AVI administration in subjects with renal impairment (CrCL ≤50 mL/min/1.73 m^2) is not permitted.

6. STUDY PROCEDURES

Study periods are defined in Figure 1. Details of the study plan and procedures are provided in the Schedule of Activities and are described in detail by visit in the following sections.

6.1. Screening and Enrollment

Prior to any study-specific procedures, the subject's parent or parents (depending on local requirements) or legally acceptable representative must provide written informed consent and the subject must provide informed assent as appropriate per local requirements. Either written assent or documented verbal assent may be obtained according to local requirements. During the screening period, subjects will be assessed regarding eligibility criteria. Subjects who do not meet all of these criteria must not be enrolled in the study.

6.1.1. Visit 1: Eligibility/Screening Procedures (Day -1 to 1)

Each subject will undergo Screening assessment procedures on the day of or one day prior to the dose of CAZ-AVI. These will serve as the baseline assessments and can be completed on the same calendar day as Day 1, prior to CAZ-AVI infusion, but must be completed no earlier than the day before the start of CAZ-AVI infusion. When screening assessment procedures are performed the day prior to the dose of CAZ-AVI, weight is also to be collected at day of dose administration. The weight collected on the date of dose administration will be used to properly calculate the dose of CAZ-AVI to be administered.

If additional assessments are conducted per standard of care prior to the first infusion of CAZ-AVI the assessments closest to the infusion will be considered baseline.

Potential subjects who do not meet enrollment criteria may, as appropriate, repeat screening evaluations at a later time for possible enrollment into the study.

6.1.1.1. Clinical Assessments

1. Obtain informed consent and assent as appropriate. At selected sites, if subjects will undergo BAL as part of their clinical management, separate consent and assent as appropriate must be obtained for collection of BAL fluid for CAZ-AVI analysis.

2. Review inclusion and exclusion criteria.

3. Collect demographics.

4. Collect medical and surgical history.

5. Review prior and concomitant treatments.

6. Perform complete physical examination, including height and weight. Body mass index (kg/m2) will be calculated as the ratio of weight in kg/(height in cm/100)^2. The BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

7. Measure vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature (oral, rectal, or tympanic, as appropriate). Vital signs will be measured at the following time points: before infusion and 2, 4, 6, 12, 24 and 48 hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken as needed.

8. Record oxygen saturation, if available.

9. Monitor for AEs and SAEs.

10. Obtain results of chest x-ray (CXR), computerized tomography scan (CT scan), or other imaging tests (eg, MRI, ultrasound) if performed diagnostically as part of the subject's regular medical care for the current diagnosis of pneumonia up to before screening.

11. For subjects who the Investigator determines are of childbearing potential and are sexually active confirm that highly effective contraception is being used.

6.1.1.2. Laboratory Assessments

1. Obtain a blood sample for clinical chemistry and hematology assessments (see Table 6 for details of laboratory assessments).

2. Obtain a urine sample for routine analysis.

3. Creatinine clearance will be determined using the Bedside Schwartz equation [eGFR (ml/min/1.73 m^2) = 0.413 * (length (cm)/serum creatinine (mg/dL)], Schwartz, Munoz, et al., 2009.[3]

4. Obtain a blood or urine pregnancy test with a sensitivity of at least 25 mIU/mL for β-hCG for females who have achieved menarche. If the test is positive, the subject must be excluded.

6.2. Study Period

6.2.1. Visit 2, Study Day 1

Study Day 1 is the day of CAZ-AVI infusion and PK assessment. Screening and Baseline activities may be combined if entry requirements can be completed jointly on the same calendar day.

6.2.1.1. Clinical Assessments

1. Review prior and concomitant treatments.

2. Measure vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be measured at the following time points: before infusion and 2, 4, 6, 12, 24, and 48 hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken prn.

3. Collect weight.

4. Record oxygen saturation, if available.

5. Record adjunctive therapeutic procedures (eg, endotracheal aspiration, bronchoscopy), if performed.

6. Obtain results of CXR, CT scan, or other imaging tests (eg, MRI, ultrasound) if performed as part of the subject's regular medical care.

7. For subjects who the Investigator determines are of childbearing potential and are sexually active confirm that highly effective contraception is being used.

8. Monitor for AEs and SAEs.

6.2.1.2. Laboratory Assessments

1. Obtain PK blood samples according to the detailed schedule in Section 7.2.1, Table 3, Table 4, or Table 5.

2. For those who have provided consent, obtain blood sample (0.5 mL) for plasma urea concentration in comparison to the BALF urea concentration for any subject undergoing BAL as part of their clinical management during the blood PK sampling interval.

3. For those who have provided consent, BAL fluid collection to be performed at selected sites only for subjects undergoing bronchoscopy as part of their clinical management during the time window for collection of PK blood samples after CAZ-AVI infusion. A matching blood sample to replace one of the PK blood samples is to be collected at the same time as the BAL, along with a blood sample for blood urea analysis.

6.2.1.3. Study Therapy Administration

1. Infusion of CAZ-AVI IV over a 120 minute (±10 min) period, according to the cohort as indicated in Table 2. The 120 minute infusion should be followed by an IV flush of the line. Details regarding drug administration will be provided in the IP Manual. The dose should be calculated based on the subject's weight at Baseline (Day 1). To support the use of population PK modeling the actual dose amount of CAZ-AVI administered, the accurate date and time of start and end of the IV infusion, end time of IV flush, and the actual blood sample times are required.

6.2.2. Visit 3, Study Day 2, 24 Hour Follow-Up Assessment

6.2.2.1. Clinical Assessments

1. Review concomitant treatments.

2. Measure vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be measured at the following time points: pre-infusion and 2, 4, 6, 12, 24 and 48 hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken prn.

3. Record oxygen saturation, if available.

4. Record adjunctive therapeutic procedures (eg, endotracheal aspiration, bronchoscopy), if performed.

5. Obtain results of CXR, CT scan, or other imaging tests (eg, MRI, ultrasound) if performed as part of the subject's regular medical care.

6. For subjects who the Investigator determines are of childbearing potential and are sexually active confirm that highly effective contraception is being used.

7. Monitor for AEs and SAEs.

6.2.3. Visit 4, Study Day 3, 48 Hour Follow-Up Assessment

6.2.3.1. Clinical Assessments

1. Review concomitant treatments.

2. Perform complete physical examination, including weight.

3. Measure vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be measured at the following time points: pre-infusion and 2, 4, 6, 12, 24 and 48 hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken prn.

4. Record oxygen saturation, if available.

5. Record adjunctive therapeutic procedures (eg, endotracheal aspiration, bronchoscopy), if performed.

6. Obtain results of CXR, CT scan, or other imaging tests (eg, MRI, ultrasound) if performed as part of the subject's regular medical care.

7. For subjects who the Investigator determines are of childbearing potential and are sexually active confirm that highly effective contraception is being used.

8. Monitor for AEs and SAEs.

6.2.3.2. Laboratory Assessments

1. Obtain a blood sample for clinical chemistry and hematology assessments (see Table 6 for details of laboratory assessments).

2. Obtain a urine sample for routine analysis.

3. Creatinine clearance will be determined using the Bedside Schwartz equation [eGFR (ml/min/1.73 m^2) = 0.413 * (length (cm)/serum creatinine (mg/dL)], Schwartz, Munoz, et al., 2009.[3]

4. Obtain a blood or urine pregnancy test with a sensitivity of at least 25 mIU/mL for β-hCG for females who have achieved menarche.

6.2.4. Late Follow-up (LFU)

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

6.3. Subject Withdrawal

In this single-dose study, the study drug infusion should not be discontinued before the 120 minute administration is complete unless the following events occur:

- Subject decision. The subject or the subject's parent(s) or other legally acceptable representative(s) is at any time free to discontinue treatment infusion, without prejudice to further treatment;

- Clinically significant AE, as judged by the Investigator;
- Investigator evaluation and decision.

Subjects are at any time free to withdraw from the study (CAZ-AVI and assessments), without prejudice to further treatment (withdrawal of consent). The subject or parent(s), or other legally acceptable representative(s), will always be asked about the reason(s) and the presence of any AEs. If possible, the subject will be seen and assessed by an Investigator at the time of withdrawal. Adverse events and serious adverse events (SAEs) will be followed up.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the Investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the Investigator should be reported and documented in the subject's medical records.

Subjects 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 (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject 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.

Subjects who withdraw from the study may be replaced at the discretion of the Investigator upon consultation with the Sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the Investigator site prior to initiation of the study.

7.1. Pregnancy Testing

For female subjects of childbearing potential, as determined by the Investigator, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL for β-hCG, will be performed locally at the screening visit, Visit 1, and the 48 hour assessment, Visit 4. A negative pregnancy test result is required before the subject may receive CAZ-AVI. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL for β-hCG and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

7.2. Pharmacokinetics

Sparse PK sampling, especially for pediatric patients younger than 12 years of age, has been employed to minimize blood sampling requirements. The use of analgesic creams to minimize discomfort is permitted as per standard of care. An indwelling catheter may be used for the repeated PK sampling, to minimize the discomfort; this catheter/port will not be used for administration of any medication. Prior to obtaining each sample the saline used to flush the catheter will be discarded.

7.2.1. Pharmacokinetic (PK) Blood Sample Collection

Samples may be obtained by venipuncture, through a saline/heparin lock, peripherally inserted central catheter, or through a central line. A site other than the infusion site is preferred; however, samples may be drawn from the same site as the infusion site, by use of a multi-lumen catheter, with the exception of the blood drawn immediately after the infusion which must not be drawn from any lumen of a catheter used for drug delivery. In cases where a multi-lumen catheter is used for drug delivery and blood draws, the PK blood samples, other than the first PK sample collection performed at the end of CAZ-AVI infusion/flush, must be taken from a lumen that was NOT used for drug delivery. Detailed instructions for PK sample collection will be provided in the Laboratory Manual.

Venous blood samples for the determination of CAZ-AVI PK for each cohort are presented in Table 3, Table 4, and Table 5 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively. The actual date and time of collection of each sample will be recorded in the CRF.

Detailed instructions for the collection, labeling, storage, and shipment of samples will be provided in the Laboratory Manual.

For total blood volume collection see Section 7.4.

Leftover plasma could be used to assess concentrations of endogenous biomarkers for drug transporters and/or drug metabolizing enzymes. Any results from such analyses may be reported separately from the CSR.

Table 3. Cohort 1 - Schedule for PK Assessments

Nominal time	Nominal Time Post-Dose (TPD)	Blood volume
End of CAZ-AVI infusion/flush +0 to 5 minutes	2 hours	0.5 mL
30 minutes after the end of the CAZ-AVI infusion/flush ±5 minutes	2 hours, 30 minutes	0.5 mL
1.5 hours after the end of the CAZ-AVI infusion/flush ±15 minutes	3 hours, 30 minutes	0.5 mL
3 hours after the end of the CAZ-AVI infusion/flush ±30minutes	5 hours	0.5 mL
6 hours after the end of the CAZ-AVI infusion/flush ±30 minutes	8 hours	0.5 mL
10 hours after the end of the CAZ-AVI infusion/flush ±30 minutes	12 hours	0.5 mL
22 hours after the end of the CAZ-AVI infusion/flush ±30 minutes	24 hours	0.5 mL

Table 4. Cohort 2 - Schedule for PK Assessments

Nominal time	Nominal Time Post-Dose (TPD)	Blood volume
End of CAZ-AVI infusion/flush +0 to 5 minutes	2 hours	0.5 mL
15 to 45 minutes after the end of the CAZ-AVI infusion/flush	2 hours, 15 minutes	0.5 mL
1 to 2 hours after the end of the CAZ-AVI infusion/flush	3 hours	0.5 mL
2 to 3 hours after the end of the CAZ-AVI infusion/flush	4 hours	0.5 mL
4 to 6 hours after the end of the CAZ-AVI infusion/flush	6 hours	0.5 mL
11 to 13 hours after the end of the CAZ-AVI infusion/flush	13 hours	0.5 mL

Table 5. Cohorts 3 and 4 - Schedule for PK Assessments

Nominal time	Nominal Time Post-Dose (TPD)	Blood volume
End of CAZ-AVI infusion/flush + 0 to 5 minutes	2 hours	0.5 mL
15 to 45 minutes after the end of the CAZ-AVI infusion/flush	2 hours, 15 minutes	0.5 mL
2 to 3 hours after the end of the CAZ-AVI infusion/flush	4 hours	0.5 mL
4 to 6 hours after the end of the CAZ-AVI infusion/flush	6 hours	0.5 mL

7.2.2. Collection of BAL Fluid Samples

At selected sites, subjects who are undergoing bronchoscopy with BAL as part of their clinical management any time during the blood PK sampling interval, should have a portion of the BAL fluid which is not required for the subject's medical care retained for PK analysis. For these subjects a blood PK sample should be obtained at the same time as the BAL fluid collection, to replace one of the designated blood PK samples. Additionally, a 0.5 mL blood sample should be obtained for plasma urea concentration in comparison to the BALF urea concentration.

Sites performing BAL will follow their standard local procedures for the lavage, recording the location of the lavage and volumes instilled. Immediately after completion of the lavage, BAL aspirates should be pooled and the volume recorded. After removing aliquots for local culture, cell count, and differential as per standard practice, the remaining pooled BALF should be placed on ice and centrifuged at 400 x g for 5 minutes. BALF supernatant will be collected without disturbing the pellet and one 3 mL aliquot of BALF supernatant will be prepared in a separate tube for bioanalysis of avibactam and ceftazidime, and one 3 mL aliquot of BALF supernatant for analysis of urea. Detailed instructions for the collection, labeling, storage, and shipment of BALF samples will be provided in the Laboratory Manual.

7.3. Safety Assessments

Subjects must be evaluated by a physician or an appropriately trained health care professional at every visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

7.3.1. Laboratory Safety Assessments

Blood samples and urine samples will be collected at baseline and the 48 hour assessment (Visit 4). Samples may also be collected at any time during study participation if clinically indicated.

The following laboratory tests will be measured:

Table 6. Laboratory Safety Tests

Chemistry panel	*Hematology panel*	*Urinalysis*
Sodium	Hematocrit[a]	Appearance (color, clarity)
Potassium	Hemoglobin	Bilirubin
Chloride	Red Blood Cell count	Glucose
Bicarbonate	White Blood Cell count	Ketones
Creatinine	Neutrophils	Leukocyte esterase
BUN	Lymphocytes	Nitrite
Glucose, nonfasting	Monocytes	pH
Calcium	Eosinophils	Protein
Phosphorus	Basophils	Specific gravity
Magnesium	Neutrophils, immature	Urobilinogen
Alkaline phosphatase	Platelets	Microscopic
GGT	Mean cell volume	Red blood cells
AST	Mean cell hemoglobin	White blood cells
ALT	β-hCG Pregnancy Test	Casts
Creatine kinase	(blood or urine) for females[b]	Crystals
LDH		Bacteria, yeast, parasites
Total bilirubin		
Indirect bilirubin		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma glutamyltransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time.

a. If a subject's hemoglobin or hematocrit decreases significantly (in the Investigator's judgement) after administration of the CAZ-AVI infusion, a workup for hemolytic anemia should be performed per standard of care.

b. Required for females of childbearing potential, as determined by the Investigator. Either a serum or urine pregnancy test is acceptable with a sensitivity of at least 25 mIU/mL for β-hCG.

7.4. Blood Volume

Table 7 shows the total volume of blood that will be drawn from each subject for the purposes of the study, apart from blood that is taken as part of subject's normal standard of care. This protocol complies with European Union's recommendations for blood loss associated with pediatric research (Anonymous, 2017)[11] and the World Health Organization guidelines "Blood Sample Volumes in Child Health Research: Review of Safe Limits" (Howie, 2011).[12]

Table 7. Volume of Blood to be Drawn from Each Subject

Assessment		Sample volume (mL) All Cohorts	Number of samples	Total volume (mL)
Safety	Clinical Chemistry	2[a]	2	4[a]
	Hematology	2	2	4
Pharmacokinetics	Cohort 1 (≥12 to <18 years)	0.5	7	3.5
	Cohort 2 (≥6 to <12 years)	0.5	6	3
	Cohort 3 (≥2 to <6 years)	0.5	4	2
	Cohort 4 (≥3 months to <2 years)	0.5	4	2
Total Cohort 1				11.5[a,b]
Total Cohort 2				11[a,b]
Total Cohort 3				10[a]
Total Cohort 4				10[a]

a. Subjects undergoing BAL will have one addition 0.5 mL blood sample obtained for plasma urea concentration at the time of the BAL.
b. Female subjects of childbearing potential will have either a serum or urine pregnancy test performed at the screening visit (Visit 1), and the 48 hour assessment (Visit 4); each serum pregnancy test requires an additional 2 mL blood sample.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the Investigator **are to be reported regardless of whether the event is determined by the Investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the Investigator does not become immediately aware of the occurrence of an event, the Investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the Investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the Investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The Investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the Investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts

(evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the Investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the Investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the Sponsor.

The subject should return to the Investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an

anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of Investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

- If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the Investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the Investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

- Additional information regarding the EDP may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the Investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the Investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the Investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the Sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary objective of this study is to evaluate the pharmacokinetics, safety, and tolerability of a single dose of CAZ-AVI in children with HAP/VAP. The study is not powered for inferential statistical analysis. The sample size of 32 subjects is considered adequate to evaluate the pharmacokinetics of CAZ-AVI in this population.

9.2. Efficacy Analysis

There is no assessment of efficacy in this single dose study.

9.3. Pharmacokinetic Analysis (Primary Endpoint)

The PK analysis set will consist of all subjects who received a complete IV study dose of CAZ-AVI and have at least 1 ceftazidime and/or avibactam plasma measurement available. The definition of an evaluable subject from Section 3 (one who has received the complete single IV dose of CAZ-AVI and provided PK blood samples at ≥50% of the sampling time points) is used for enrollment purposes only, and it does not impact the definition of the PK analysis set.

Plasma concentrations of CAZ and AVI will be listed, and summarized by nominal time using appropriate descriptive statistics such as number, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and coefficient of variation.

Individual plasma concentration profiles, using the PK analysis set for Cohorts 1 to 4, will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all patients on a single plot for each cohort and analyte. Median concentration-time profiles will be presented on both linear and semilogarithmic scales using nominal time for both ceftazidime and avibactam. Additional graphical presentations of PK data may be included at the discretion of the clinical pharmacologist.

In addition, PK parameters of ceftazidime and avibactam will be calculated by non-compartmental analysis (NCA) using actual PK sampling times following single dose administration of CAZ-AVI for Cohorts 1 and 2 as follows:

Parameter	Definition	Method of Determination
AUC_{0-8}	Area under the plasma concentration-time profile from time 0 to 8 hours.	Linear/Log trapezoidal rule.
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 to infinity.	Linear/Log trapezoidal rule. $AUC_{inf} = AUC_{last} + (C_{last}*/ k_{el})$, where $C_{last}*$ is the estimated concentration at the time of the last quantifiable concentration and k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the last quantifiable concentration.	Linear/Log trapezoidal rule.
C_{max}	Maximum plasma concentration.	Observed directly from data.
T_{last}	Time of last quantifiable plasma concentration.	Observed directly from data.
T_{max}	Time for $C_{max.}$	Observed directly from data.
$t_{½}$[a]	Terminal elimination half-life.	$Log_e(2)/k_{el.}$
CL[a]	Clearance.	$Dose/AUC_{inf.}$
V_{ss}[a]	Volume of distribution at steady-state.	Volume of distribution at steady state is calculated as: $V_{ss} = CL \times MRT$. Mean residence time (MRT) is calculated as: $MRT = AUMC_{inf}/AUC_{inf}$ - (infusion time/2). Area under the first moment curve from 0 time to infinity ($AUMC_{inf}$) is calculated as: $AUMC_{inf} = AUMC_{last} + ((t \times C_{est}^{1}*)/k_{el}) + (C_{est}^{1}*/k_{el}^{2})$ $^{1}C_{est} = e^{(-KEL \times Tlast)} \times KELC_0$, where C_0 is the back-extrapolated concentration at time zero.
V_z[a]	Volume of distribution during terminal phase.	$Dose/(AUC_{inf} \times k_{el})$.

a. If data permit.

These NCA PK parameters will be summarized for Cohorts 1 and 2 using descriptive statistics.

Further, the avibactam and ceftazidime concentration, pediatric patient demographics, and disease status data from Cohorts 1 to 4 will be combined with the data from appropriate previous clinical studies in pediatric patients and/or adults for a population PK analysis. The actual dosing and plasma sampling times will be used for the analysis. Individual compartmental PK parameters for pediatric patients in Cohorts 1 and 2 with available avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual non-compartmental PK parameters such as C_{max}, minimum concentration (C_{min}), area under the plasma concentration-time curves at steady-state (AUC_{ss}), and t½, will be derived from the determined avibactam and ceftazidime concentration time courses.

A stand-alone population PK modelling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report outside of the clinical study report.

9.3.1. BAL Analysis (Exploratory Endpoint)

Ceftazidime and avibactam ELF:plasma concentration ratios (for available matching ELF and plasma samples) will be provided. It is anticipated that interpretation of these ELF concentration results will be problematic due to the variability of BAL sampling (no standard timing of sample collection in relation to dosing) and the small sample size. As a result, ELF drug concentration data will not be used for decision-making purposes and will be considered exploratory only.

9.4. Safety Analysis (Secondary Endpoint)

The safety analysis set will consist of all subjects who received any amount of IV study dose of CAZ-AVI. No inferential statistical tests will be performed for any safety analyses. For each safety parameter, the last assessment made before the first dose of study therapy will be used as the baseline for all analyses. Summaries of demographics and other baseline characteristics will be provided. The incidence of AEs, SAEs, deaths, and discontinuations due to AEs will be summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to study therapy, and by severity. All recorded AEs will be listed and tabulated by system organ class, preferred term and for each cohort. Adverse events occurring from the start of study dose of CAZ-AVI infusion up to 48 hours after the end of infusion, and up to the end of the study (LFU) will be summarized by preferred term and system organ class using the MedDRA vocabulary (Version 14.0 or higher) by cohort. Descriptive statistics of observed results and the change from baseline to selected post baseline time points will be presented for clinical laboratory results and vital signs. Tabulations and listings of data for vital signs, physical examinations, and clinical laboratory tests will be presented with abnormal or out-of-range values flagged. Potentially clinically significant laboratory results will be summarized.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the Sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.6. Data Monitoring Committee

This study will not have an external data monitoring committee (E-DMC).

9.7. Safety Review Committee

This study will use an Internal Safety Review Committee which will be known as the Safety Review Committee (SRC). The SRC will consist of the study team physician, international coordinating Investigator or delegate, global safety/risk lead or delegate, therapeutic area director or delegate and the clinical pharmacologist/pharmacometrician or delegate. The SRC will assess safety and tolerability after the first 4 subjects in each cohort are enrolled. With the exception of the international coordinating Investigator or delegate, all members of the SRC will be members of the Sponsor organization. Other team members may be asked to join as needed.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the Investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The Investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with Pfizer or its agents to prepare the Investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The Investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the Investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/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 subject. 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[/Data Collection Tools (DCTs)] 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.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the Investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. 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 subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the Investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, 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 an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

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

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, subject 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, subject-specific code.

The Investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The Investigator must ensure that each study subject's parent(s), legal guardian, or legally acceptable representative is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject's parent(s), legal guardian, or legally acceptable representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the Investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the Investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original of each subject's signed consent/assent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

The end of the study is defined as the last visit of the last patient undergoing the study, or the date of study closure in the case of early study termination, whichever date is later.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of ceftazidime-avibactam at any time.

If a study is prematurely terminated, Pfizer will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the Principal Investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The Investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the Investigator agrees that the first publication is to be a joint publication covering all Investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration time profile from time 0 to 24 hours
AUC_{0-8}	area under the plasma concentration time profile from time 0 to 8 hours
AUC_{inf}	area under the plasma concentration time profile from time 0 to infinity
AUC_{last}	Area under the plasma concentration time profile from time 0 to the last quantifiable concentration
AUC_{ss}	area under the plasma concentration-time curves at steady-state
AVI	avibactam
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BMI	body mass index
CAZ	ceftazidime
CAZ-AVI	ceftazidime-avibactam
CBC	complete blood count
cIAI	complicated intra-abdominal infection
CK	creatine kinase
CL	systemic plasma clearance
C_{max}	maximum (or peak) plasma concentration
C_{min}	minimum (or trough) plasma concentration
CrCL	creatinine clearance
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
cSSTI	complicated skin and soft tissue infection
CT	clinical trial
CTA	clinical trial application
CT scan	computerized tomography scan
cUTI	complicated urinary tract infection
CXR	chest x-ray
DCT	data collection tool
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
E-DMC	external data monitoring committee

Abbreviation	Term
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rete
ESBL	extended spectrum β-lactamase
EU	European Union
EudraCT	European Clinical Trials Database
ELF	epithelial lining fluid
FDA	Food and Drug Administration
GA	gestational age
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HAP	hospital acquired pneumonia
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ID	identification code
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IV	intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KPCs	*Klebsiella pneumoniae* carbapenemases
LFT	liver function test
LFU	late follow-up
LSLV	last subject last visit
MedDRA	medical dictionary for regulatory activities
MIC	Minimal inhibitory concentration (lowest drug concentration that prevents visible microorganism growth)
MRI	magnetic resonance image
N/A	not applicable
NCA	non-compartmental analysis
NP	nosocomial pneumonia
OAT	organic anion transporters
PCD	primary completion date
PD	Pharmacodynamics(s)
PI	Principal Investigator
PIP	Pediatric Investigation Plan
PK	pharmacokinetic
PT	prothrombin time

Abbreviation	Term
PTA	probability of target attainment
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SmPC	summary of product characteristics
SRC	safety review committee
SRSD	single reference safety document
TBili	total bilirubin
TPD	Time post-dose
$t_{½}$	terminal plasma half-life
T_{last}	time of last quantifiable plasma concentration
T_{max}	time of maximum plasma concentration
ULN	upper limit of normal
US	United States
USPI	United States package insert
VAP	ventilator associated pneumonia
V_{ss}	volume of distribution at steady state
V_z	volume of distribution at the terminal phase
WBC	white blood cell

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