AN OPEN-LABEL, PARALLEL-GROUP, PHARMACOKINETIC STUDY OF MULTIPLE INTRAVENOUS DOSES OF AZTREONAM AND AVIBACTAM IN SUBJECTS WITH SEVERE RENAL IMPAIRMENT AND NORMAL RENAL FUNCTION

Investigational Product Number:	PF-06947387
Investigational Product Name:	Aztreonam-Avibactam
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3601006
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	14 July 2021	Addition of an exploratory objective: To determine concordance/comparability of capillary microsample plasma concentrations with venous plasma concentrations for aztreonam and avibactam in healthy subjects with normal renal function (Cohort 1). Rationale: To facilitate collection of lower blood volumes for PK samples in planned ATM-AVI pediatric protocols, a capillary microsampling technique will be evaluated for feasibility and performance in the healthy volunteer cohort with normal renal function. Added "temporally" as a method for measuring temperature, and changed the source of pregnancy tests kits from "provided by the central laboratory" to "provided by the investigator site", changes communicated to the investigator site in a PACL dated 07 August 2020.
Original protocol	13 June 2018	N/A

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APPENDICES

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 in the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	Screening[a]		Day -2	Day -1	Day 1				Day 2	Day 3					Day 4		Follow-up[l]
	S1	S2															
Hours post dose					0	0.5	6.5	8.5		0	3	4	6-8	12-16	24	EOT	
Informed consent	X																
CRU confinement			X														
Inclusion/exclusion criteria	X		X														
Medical history	X		X														
Demography	X																
Physical examination[o]	X		X[m]													X[i]	
Height[b] and weight	X		X														
Review illegal drug/alcohol/tobacco use	X		X														
Medication history	X		X														
Safety laboratory	X		X						X	X						X	
Pregnancy test	X		X														
Contraception check	X		X														X
Serum FSH[c]	X																
Serologic tests: HIV, HBsAg, and HCVAb testing	X																
Urine drug testing	X		X														
eGFR assessment[d]	X	X	X														
Supine 12-lead ECG	X				X[e]	X				X[e]	X					X	
Single supine blood pressure, pulse rate and temperature	X				X[e]	X[f]			X[e,f]	X[e,f]	X[f]					X	
CCI																	
ATM-AVI loading dose (30 min infusion)[k]					X												
ATM-AVI extended loading dose (3 hour infusion)[k]						X[k]											
ATM-AVI maintenance dose (3 hour infusion) q6h							X	→	→	X							

Visit Identifier	Screening[a]		Day -2	Day -1	Day 1				Day 2	Day 3					Day 4		Follow-up[l]
	S1	S2															
Hours post dose					0	0.5	6.5	8.5		0	3	4	6-8	12-16	24	EOT	
Cohort 1 – normal renal function																	
ATM-AVI maintenance dose (3 hour infusion) q8h Cohort 2 – severe renal impairment								X	→	X							
Urine sampling for ATM-AVI PK[g,h](see PK sampling schema below)										X[g]	→	→	X				
Blood sampling for ATM-AVI PK[p] (see PK sampling schema below)					X	→	→	→	→	→	→	→	→	→	X		
Serious and non-serious adverse event monitoring	X	X	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Prior/Concomitant treatments				X	→	→	→	→	→	→	→	→	→	→	→	X	
Standardized meals[j]			X	→	→	→	→	→	→	→	→	→	→	→	→	X	
Discharge from clinic																X	

Abbreviations: → = ongoing/continuous event; ATM = aztreonam; AVI = avibactam; BSA = body surface area; CRU = clinical research unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = end of trial; FSH = follicle-stimulating hormone; HCVAb = hepatitis C core antibody; HepBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MDRD = Modification of Diet in Renal Disease; PK = pharmacokinetic(s); S = Screening Visit.

a. Subject will be screened within 28 days prior to administration of the investigational product.

b. Height measurement only at Screening when full physical examination is performed.

c. To be conducted for females who have achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause.

d. To confirm eligibility, subjects must have stable renal function defined as ≤25% difference between 2 measurements of eGFR obtained, from the same laboratory, on 2 separate occasions during the Screening period that are at least 72 hours but no more than 14 days apart. Additionally, difference between eGFR Screening 1 value and Day -2 value should be ≤25%. The Day -2 eGFR values will be used for group placement. The eGFR determination will utilize the MDRD formula adjusting for BSA (See Section 3.1).

e. Pre-dose.

f. Temperature does not need to be collected at this timepoint.

g. Instruct subject to void prior to administration of study treatment (pre-dose collection). Instruct subject to void into the collection container at the end of each collection period.

h. Urine will be collected pre-dose on Day 3, and then during collection periods of 0-2, 2-4, 4-6, and 6-8 (Cohort 2 only) hours after dosing.

i. Limited physical examination.

j. See Section 4.3.1 for more details.

Visit Identifier	Screening[a]		Day -2	Day -1	Day 1				Day 2	Day 3					Day 4		Follow-up[l]
	S1	S2															
Hours post dose					0	0.5	6.5	8.5		0	3	4	6-8	12-16	24	EOT	

k. Loading dose and extended loading dose will be prepared in one infusion bag with an infusion rate change after the first 30 minutes.

l. A follow-up contact with each subject must occur at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to monitor for any AEs/SAEs and to verify contraception use. Contact with the subject may be done via a phone call.

m. Full physical examination, if deferred from the screening visit.

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o. After the full complete physical examination (Screening or Day -2), further examinations will be performed at the discretion of the investigator.

p. PK blood sample may be collected for the subjects who discontinue the study early for final safety assessments.

Pharmacokinetic Sampling Schema

Visit Identifier																			
Study Day	**1**					**2**	**3**												**4**
Hours Before/After Dose	**0**	**0.5**	**3.5**	**6.5**	**8.5**		**0**	**2**	**3**	**3.25**	**3.5**	**3.75**	**4**	**5**	**6**	**8**	**12**	**16**	**24**
ATM-AVI loading dose (30 min infusion)[i]	X																		
ATM-AVI extended loading dose (3 hour infusion)[i]		X[i]																	
ATM-AVI maintenance dose (3 hour infusion) q6h Cohort 1 – normal renal function				X	→	→	X												
ATM-AVI maintenance dose (3 hour infusion) q8h Cohort 2 – severe renal impairment					X	→	X												
Blood sampling for ATM-AVI PK[k]	X[a]	X[b]	X[c]				X[a]	X	X[j]	X	X	X	X	X	X	X	X	X	X
Capillary sampling for ATM-AVI PK[l] ***Cohort 1 – normal renal function***		X	X	X					X				X	X	X				
Trough blood sampling for ATM-AVI PK ***Cohort 1 – normal renal function***				X[d]	→	→	X[e]												
Trough blood sampling for ATM-AVI PK ***Cohort 2 – severe renal impairment***					X[d]	→	X[e]												
Urine sampling for ATM-AVI PK[f,h] ***Cohort 1 – normal renal function***							X[f]	→	→	→	→	→	→	→	X				
Urine sampling for ATM-AVI PK[g,h] ***Cohort 2 – severe renal impairment***							X[g]	→	→	→	→	→	→	→	→	X			

Abbreviations: ATM = aztreonam; AVI = avibactam; IV = intravenous; PK = pharmacokinetic.

a. Predose sample collection.

b. Collect PK blood sample within 5 min before the end of the loading dose IV infusion.

c. Collect PK blood sample within 15 min before the end of extended loadng IV infusion.

d. Collect maintenance pre-dose PK blood sample within 10 min before start of each maintenance dose infusion.

e. Trough sample does not need to be collected for final maintenance dose on Day 3 as pre-dose sample will already be collected as part of intensive PK sampling collection.

Visit Identifier																			
Study Day	**1**					**2**	**3**												**4**
Hours Before/After Dose	**0**	**0.5**	**3.5**	**6.5**	**8.5**		**0**	**2**	**3**	**3.25**	**3.5**	**3.75**	**4**	**5**	**6**	**8**	**12**	**16**	**24**

f. Urine will be collected pre dose on Day 3, and then during collection periods of 0-2, 2-4, and 4-6 hours after dosing.

g. Urine will be collected pre dose on Day 3, and then during collection periods of 0-2, 2-4, 4-6, and 6-8 hours after dosing.

h. Instruct subject to void prior to administration of study treatment (pre-dose collection). Instruct subject to void into the collection container at the end of each collection period.

i. Loading dose and extended loading dose will be prepared in one infusion bag with an infusion rate change after the first 30 minutes.

j. Collect PK blood sample within 15 min before IV infusion stop.

k. PK blood sample may be collected for the subjects who discontinue the study early for final safety assessments.

l. Collect finger-prick capillary PK blood sample time-matched to venous PK blood sample for subjects in ***Cohort 1 – normal renal function***.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Aztreonam-avibactam (ATM-AVI) is a combination product that contains the β-lactam antibiotic aztreonam (ATM) and the non-β-lactam β-lactamase inhibitor avibactam (AVI). ATM-AVI is being developed to treat infections caused by resistant Gram-negative pathogens, including those with metallo-β lactamase (MBL)-mediated drug resistance.

1.2. Background

The prevalence of multi-drug resistant (MDR) bacteria is increasing worldwide. This has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by MDR bacteria.[1,2] In particular, ongoing surveillance studies have demonstrated an increasing frequency of antibiotic resistance among MDR Gram-negative bacteria. New antibiotics or combinations of existing antibiotics with resistance enzyme inhibitors are urgently needed to provide treatment options for patients with infections known or suspected to be caused by MDR Gram-negative pathogens.[3,4]

Aztreonam is an established injectable antibiotic indicated for the treatment of various infections caused by susceptible Gram-negative bacteria. It has a unique monocyclic β-lactam nucleus that makes it structurally different from other β-lactam antibiotics, as well as several chemical side groups that interfere with degradation by MBLs. In this way, activity against MBL (Class B) producing pathogens is possible, although potential inactivation by Class A, C, or D β-lactamases remains problematic.

Avibactam is a novel, non β-lactam, β-lactamase inhibitor of a broad spectrum of enzymes, including Ambler Class A extended-spectrum β-lactamases (ESBLs), Class A *Klebsiella pneumoniae* carbapenemase (KPC), and Class C (AmpC) enzymes, and some Class D enzymes. Its beneficial effect in combination with aztreonam occurs by inhibiting the enzymes that inactivate aztreonam.

Together, aztreonam and avibactam have the potential to address the unmet need for safe and effective agents to combat MBLs and other problematic β-lactamases, such as ESBLs and KPCs, which may be co-expressed with MBLs and contribute to MDR.

Aztreonam has been marketed as a stand-alone product under the tradename AZACTAM® for over 25 years while avibactam was approved in 2015 (US)/2016 (EU) as part of a combination product with ceftazdime (AVYCAZ™/ZAVICEFTA®).

The serum half-life of aztreonam averaged 1.7 hours (1.5 to 2.0 hours) in subjects with normal renal function, independent of the dose. In healthy subjects, based on a 70 kg person, the serum clearance (CL) was 91 mL/min and renal clearance (CL_r) was 56 mL/min; the apparent mean volume of distribution at steady-state (V_{ss}) averaged 12.6 L, approximately equivalent to extracellular fluid volume. Intravenous (IV) administration of a single 500 mg or 1000 mg dose of aztreonam q8h for 7 days to healthy subjects produced no apparent

accumulation of aztreonam or modification of its disposition characteristics; serum protein binding averaged 56% and was independent of dose.[5]

Avibactam demonstrated approximately linear pharmacokinetics (PK) across the dose range studied for single IV administration with a 30-min infusion time (50 to 2000 mg avibactam alone) and time-invariant PK across the dose range studied for multiple IV doses with a 30 min infusion time (500 to 1000 mg avibactam). Following IV administration, the maximum observed concentration (C_{max}) of avibactam is achieved at the end of infusion, after which plasma concentrations decline in a multi-exponential manner. The half-life of avibactam ranged from 1.4 to 3 hours and resulted in little or no accumulation upon repeated administration.

The carbon-14 [^{14}C] avibactam absorption, distribution, metabolism, and excretion (ADME) study showed that an average of 97% (range, 95% to 98%) of administered radioactivity was recovered from the urine, over 95% within 12 hours of dosing. Avibactam is predominantly renally cleared and metabolism has little contribution to its excretion. An average of 85% (range, 67% to 101%) of administered avibactam was recovered from the urine during the study, with >50% being recovered within 2 hours of the start of the infusion. CL_r was 158 mL/min suggesting active tubular secretion.

The PK of avibactam (100 mg, single 50-mL IV infusion over 30 minutes) in renally impaired patients was assessed in the ceftazidime-avibactam (CAZ-AVI) program. Avibactam exposure, expressed by area under the curve ($AUC_{0-\infty}$), increased with increasing level of renal impairment by approximately 2.7-, 3.9-, 7.7-, and 21.3-fold for patients with mild, moderate, severe renal impairment, and end-stage renal disease (ESRD), respectively. This was associated with a decrease in avibactam clearance with increasing severity of renal impairment, which is consistent with CL_r being the dominant elimination route. The relationship between avibactam renal clearance and calculated creatinine clearance (CrCL) was found to be linear. The impact on clearance resulted in the increasing half-life from less than 2 hours in subjects with normal renal function up to about 8 hours for patients with severe renal disease and 22 hours in patients with end-stage renal failure. Mean C_{max} also increased with the degree of renal impairment. The inter-individual variability (expressed by the coefficient of variation [CV%]) of C_{max} and area under the curve at steady-state (AUC_{ss}) was also markedly higher in patients with renal impairment than in healthy subjects. Time to reach C_{max} (T_{max}) remained consistent at the end of infusion at 30 minutes, and V_{ss} also remained roughly comparable across the groups.

The PK of aztreonam has been studied in patients with renal impairment where all subjects received a single 1000 mg aztreonam IV bolus dose or as a 2-min IV infusion, with frequent blood sampling for at least 24 h post-dose for drug concentration and PK analysis.[6,7] Both studies included a healthy control group (n=6 per study) with creatine clearance (CrCL) ≥80 mL/min.

One study[6] included patients with various degrees of chronic renal failure (n=12; mean ±SD CrCL 17.8 ±13.5 mL/min; range 4.8-49.9 mL/min). In this study the half-life (mean ±SD) was significantly increased ($p<0.001$) from 1.8 ±0.14 hours in subjects with normal renal function to 4.9 ±1.06 hours in patients with chronic renal failure. The corresponding statistically significant decreases ($p<0.001$) in aztreonam CL were 84.2 ±7.8 mL/h/kg in subjects with normal renal function to 30.2 ±9.2 mL/h/kg in patients with chronic renal failure.

The other study[7] included 4 groups (n=6/group) with CrCL of >80, mL/min, 30-79 mL/min, 10-29 mL/min, and <10 mL/min, respectively. The half-life (mean ±SD) increased ($p<0.001$) with decreasing renal function, from 1.98 ±0.12 h (normal renal function), to 3.42 ±0.80 h, 4.76 ±0.85 h, and 6.02 ±1.53 h, respectively. Aztreonam CL decreased from 107 mL/min in subjects with normal renal function to 29 mL/min for functionally anephric patients. Urinary excretion (urine collected in intervals up to 48 hours post dose) of aztreonam was also determined in this study. Urinary recovery of aztreonam ranged from 58% of the administered dose in normal subjects to 1.4% in uremic patients.

Both avibactam and aztreonam were shown to be a substrates of the human organic anion transporter (OAT) proteins OAT1 and OAT3.

In various Phase 1/2a studies, it has been shown that there are no PK interactions between ceftazdime (CAZ) and AVI, CAZ-AVI and metronidazole, ceftaroline and avibactam, or aztreonam and avibactam, which validates the use of data from these individual components to support the ATM-AVI program.

At steady state (Day 10 of dosing q6h) statistical comparison (analysis of variance [ANOVA]) showed a difference in PK of avibactam when it was co-administered with aztreonam in elderly versus young subjects (aztreonam AUC_{ss} increased by 22.6%; $C_{ss,max}$ increased by 15.8% and $C_{ss,min}$ was increased by 54.4% in elderly subjects). Corresponding changes were observed for avibactam where AUC_{ss} increased by 32.7%; $C_{ss,max}$ increased 31.1% and $C_{ss,min}$ was increased by 74.2% in elderly compared to young subjects. Post-hoc modelling suggested this may be related to difference in renal function in these patients.

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

A dual-analyte bioanalytical assay has been developed and validated for simultaneous analysis of aztreonam and avibactam plasma concentrations from a single microvolume plasma sample (minimum 5 µL of plasma) to support planned pediatric clinical trials in the ATM-AVI development program. This assay enables collection of much lower blood sample volumes for evaluation of PK in children, including a blood microsample (≤50 µL) that may be collected via capillary sampling.

1.3. Rationale

1.3.1. Study Rationale

Dose adjustment for aztreonam and avibactam are warranted in renal impairment given that both are eliminated primarily as unchanged substances by the kidney. This study is therefore being conducted to evaluate the effect of severe renal impairment on the PK, safety and tolerability of ATM-AVI. Results from this study along with previous renal impairment PK data from each of the ATM-AVI components will be used to confirm proposed ATM-AVI dosing in severe renal impairment which was based on modelling/simulation.

Capillary blood microsamples will be collected from subjects in Cohort 1 (normal renal function) at specified time points matched to standard venous blood sample collection to evaluate the correlation/concordance of plasma concentrations for aztreonam and avibactam from microsampled capillary and venous blood collections. Results from this sub-study will be used to confirm the microsampling technique prior to inclusion in pediatric protocols.

CCI

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1.3.2. Dose Rationale

The intention for ATM-AVI is that it will be active against clinically isolated Gram-negative bacteria for which there are limited or no treatment options when dosed in a fixed 3:1 ratio. The ATM-AVI doses for this Phase 1 study (and proposed for Phase 3) have been selected based on pre-clinical and clinical data on ATM-AVI, using PK data for ATM, AVI and ATM-AVI and including covariate information collected in healthy volunteers and patients to construct a robust population PK model. Furthermore, AVI PK and safety data together with PK/pharmacodynamic (PD) modelling results obtained during development of the new CAZ-AVI combination product Avycaz™ in the US (Zavicefta® in Europe) have been taken into account.[8,9]

Dose selection (ATM-AVI) for patients with normal renal function

In this Phase 1 study, the dosing regimen is the same as that administered in Cohorts 2 and 3 of the Phase 2a study and what is being evaluated in Phase 3. The loading dose for patients with normal renal function or mild renal impairment (CrCL or GFR >50 mL/min) is 500 mg

ATM plus 167 mg AVI infused over a 30 minute period, immediately followed by an extended loading dose of 1500 mg ATM plus 500 mg AVI over a three hour period. Three (3) hours after the extended loading dose is completed, a maintenance dose of 1500 mg ATM and 500 mg AVI is infused over 3 hours and administered every 6 hours (q6h). The targeted total daily dose on Day 1 is 6500 mg ATM/2167 mg AVI. From Day 2 onwards, the maximum daily dose will be 6000 mg ATM/2000 mg AVI.

For patients with serious bacterial infections where there are limited or no treatment options, it is recommended for β-lactams to rapidly achieve target attainment and steady state concentrations while prolonging time above the minimum inhibitory concentration (MIC) with extended infusion time and shorter dosing intervals. The rationale for the selected dose regimen is based on the objective of obtaining optimal exposure to achieve a >90% probability of target attainment (PTA) against PK/PD targets for both ATM and AVI which have been identified from non-clinical data. The PK/PD targets are:

- Maintain unbound ATM concentrations above an MIC for 60% of the dosing interval;
- Maintain unbound AVI concentrations above a threshold concentration (C_T) of 2.5 mg/L for 50% of the dosing interval.

The dose has been selected to achieve >90% PTA at an ATM-AVI MIC of 8 mg/L.

Population PK models have been constructed using the following data: ATM PK data from the literature, ATM and AVI PK data from the Phase 1 study (C3601005) of the ATM-AVI development program, and AVI PK data from the Zavicefta development program (AVI in combination with CAZ) which included a substantial amount of PK data in patients. Most recently, the PK model was updated using PK and covariate data from patients with complicated intra-abdominal infections (cIAI) in the Phase 2a study. The PK models were used in Monte Carlo simulations of 5000 patients to select a dosing regimen which achieved a >90% joint PTA for ATM and AVI based on PK/PD targets:

In Cohort 1 of the Phase 2a study in patients with cIAI (and CrCL >50 mL/min) the dosing regimen was selected based on the Phase 1 safety data and PK/PD modeling above, ie, a loading dose (500 mg ATM plus 137 mg AVI by IV infusion) over a 30 minute period, was immediately followed by a maintenance infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period [q6h]).

The safety and PK data from 10 patients in Cohort 1 (who completed all safety and PK assessments) was reviewed by a Scientific Advisory Committee (SAC). Based on assessment of the safety and PK data in Cohort 1, Cohort 2 was subsequently initiated using a higher AVI dose (a loading dose of 500 mg ATM plus 167 mg AVI by IV infusion over a 30 minute period, immediately followed by a dose of 1500 mg ATM plus 500 mg AVI by IV infusion over a 3 hour period q6h [maintenance infusion]). Following the review of PK and safety data from 10 patients in Cohort 2 by the SAC, the higher AVI dose was continued in Cohort 3. The higher AVI dose was selected as it provides a higher PTA for AVI using the PK/PD targets as described above compared to the lower AVI dose.

Dose selection (ATM-AVI) for patients with severe renal impairment (GFR >15 to ≤30 mL/min)

In this Phase 1 study, the dose for patients with severe renal impairment (GFR >15 to ≤30 mL/min) is a loading dose of 675 mg ATM plus 225 mg AVI by IV infusion over a 30 minute period, immediately followed by an extended loading dose of 675 mg ATM plus 225 mg AVI by IV infusion over a 3 hour period, then following a 5 hour gap, maintenance dose of 675 mg ATM plus 225 mg AVI by IV infusion over 3 hours q8h.

Doses for patients with impaired renal function are based on PK modeling and simulation. The population PK models for both ATM and AVI included data from patients with renal impairment which allowed the use of modeling and simulation for dose selection in Phase 2a and 3. The dose selection for patients with severe renal impairment was based on the following criteria: matching the predicted ATM steady state area under the curve between time 0 and 24 hours after dose ($AUC_{(0-24,ss)}$) in patients with severe renal impairment, to the predicted $AUC_{(0-24,ss)}$ in patients with normal renal function (CrCL >80 mL/min) receiving ATM 1500 mg/AVI 500 mg; maintaining the same 3:1 dosing ratio between ATM and AVI; and maintaining >90% joint PTA. Furthermore, since the dosing ratio between ATM and AVI is fixed, and given the differential impact of renal impairment on the clearance of ATM and AVI, it was accepted that matching an area under the plasma concentration versus time curve (AUC) target for ATM would result in exceeding the exposure targets for AVI in patients with normal renal function, but should not appreciably exceed the exposure in patients with mild renal impairment with the standard dose.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the pharmacokinetics of the co-administration of aztreonam and avibactam following multiple doses via IV infusion in subjects with severe renal impairment and in healthy subjects with normal renal function.	• Total daily area under the plasma concentration time profile from time 0 to 24 hours at steady-state ($AUC_{0-24,ss}$) and C_{max}.
	Secondary Endpoint(s):
	• Area under the plasma concentration-time profile from time 0 to to the time of the end of the dosing interval (τ) ($AUC_{0-\tau}$), T_{max}, observed concentration at the end of the dosing interval (τ) (C_τ), terminal elimination half-life ($t_{½}$), clearance (CL), renal clearance (CL_r), apparent volume of distribution during terminal phase (V_z), apparent volume of distribution at steady-state (V_{ss}), amount of unchanged drug excreted into urine over dosing interval ($Ae_{0-\tau}$), $Ae_{0-\tau}$ expressed as percent of dose ($Ae_{0-\tau}$%).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of multiple doses of aztreonam and avibactam in subjects with severe renal impairment and in healthy subjects with normal renal function.	• Safety will be assessed by physical examinations, adverse event (AE) monitoring, 12-lead electrocardiograms (ECGs), supine blood pressure and pulse rate, and clinical laboratory tests.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**

C C I [redacted]	C C I [redacted]
• To determine concordance/comparability of capillary microsample plasma concentrations with venous plasma concentrations for aztreonam and avibactam in healthy subjects with normal renal function.	• Comparison of concentrations (capillary microsamples collected at specified time points matched to venous plasma concentrations) assessed by X-Y and Bland-Altman (B-A) scatter plots with limits of agreement (LoA) for a precision assessment.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open-label, parallel-group study where an IV loading dose (30 min infusion) followed by multiple IV doses (3 hr infusion) of ATM-AVI will be administered to subjects with severe renal impairment (not on dialysis) and to healthy subjects with normal renal function. Subjects with the following levels of renal function will be enrolled:

Cohort	Renal Impairment	Number of Subjects	eGFR[a](mL/min)
1	None (Normal)	6	≥80
2	Severe (Not on dialysis)	5-6	>15 - ≤30

Abbreviations: BSA = body surface area; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

a. Estimate of eGFR based on the MDRD formula adjusting for BSA. The Day -2 eGFR values will be used for group placement.
   - Step 1: eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr, std})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay.
   - Step 2: Convert the MDRD-derived, BSA-adjusted eGFR obtained above to absolute eGFR (mL/min) for eligibility assessment using the following equation:
     - eGFR (mL/min) = eGFR (mL/min/1.73 m^2) × subject's BSA where BSA is calculated as BSA = $(Weight^{0.425} \times Height^{0.725}) \times 0.007184$.

Approximately 6 subjects will be enrolled into Cohorts 1 and 2. Due to the potential difficulty in recruiting subjects with eGFR ≤30 mL/min, the number of subjects to be enrolled in this group will be approximately 5-6 in order to have at least 5 evaluable subjects.

The following equation from the MDRD study will be used to calculate eGFR ($S_{cr, std}$ denotes serum creatinine measured with a standardized assay for serum creatinine):

$$\textbf{eGFR (mL/min/1.73 } \textbf{m}^2\textbf{) = 175 × } (S_{cr, std})^{-1.154} \textbf{ × (Age)}^{-0.203} \textbf{ × (0.742 if female) × (1.212 if African-American)}$$

Note that the value of eGFR, which is directly obtained from the lab or calculated using the equation above, is generally normalized to an average body size of 1.73 m^2 for diagnosis, prognosis and treatment of renal disease. In terms of clearance of renally filtrated drugs (including secreted drugs), renal elimination capacity is related to absolute glomerular filtration rate (GFR) in mL/min. To use the MDRD-derived, body surface area (BSA)-adjusted value of eGFR to obtain absolute GFR (mL/min) for renal disease

classification/cohort assignment, this value should be multiplied by the individual subject's BSA (ie, measured BSA/1.73 m^2). The BSA of an individual can be calculated by the following formula as described below:

1. $BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$

In summary, GFR in mL/min calculated as below will be used for group placement:

- Step 1: Obtain the MDRD-derived eGFR:
  - eGFR (mL/min/1.73 m^2) = $175 \times (S_{cr, std})^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if female) × (1.212 if African-American) where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay
- Step 2: Convert the MDRD-derived, BSA-adjusted eGFR obtained above to absolute GFR (mL/min) for eligibility assessment using the following equation:
  - **eGFR (mL/min)** = eGFR (mL/min/1.73 m^2) ×subject's BSA where BSA is calculated as BSA = $(Weight^{0.425} \times Height^{0.725}) \times 0.007184$

CrCL will also be estimated from a spot serum creatinine measurement using the following Cockcroft-Gault (C-G) equation:

2. $CrCL\ (mL/min) = \frac{[140 - age\ (years)] \times total\ body\ weight\ (kg) \times (0.85\ for\ females)}{72 \times serum\ creatinine\ (mg/dL)}$

Note that eGFR calculated by the MDRD equation will be used for group placement. Nevertheless, renal function will be estimated using both C-G and MDRD equations in this study.

All subjects must have stable renal function to enter the study. Stable renal function is defined as ≤25% difference between 2 measurements of eGFR obtained, from the same laboratory, on 2 separate occasions during the screening period that are at least 72 hours but no more than 14 days apart. Additionally, difference between eGFR Screening 1 value and Day -2 value should be ≤25%. The Day -2 eGFR value will be used for group placement. The CrCL value will be recorded at the same time eGFR is determined.

All screening evaluations will occur within 28 days prior to administration of the investigational product. All subjects will provide informed consent and undergo screening evaluations to determine their eligibility. Eligible subjects will check into the Clinical Research Unit (CRU) on Day -2. Subjects will receive a loading/extended loading dose followed by multiple doses of IV ATM-AVI according to Table 2 (see Section 5.4).

Serial blood samples and urine at specified intervals will be collected pre-dose and for 24 hours following the final maintenance dose administered on the morning of Day 3 for PK assessments. PK samples will also be collected 0.5 and 3.5 hours after start of loading dose on Day 1 as well as trough samples collected just prior to administration of maintenance

doses over the course of the study. Subjects from Cohort 2 (severe renal impairment) will be recruited first. The healthy subjects will then be recruited. An attempt will be made to choose such that each subject's age is within ±10 years and weight is within ±15 kg of the mean demographics for the severe renal impairment cohort, and maintain a similar male/female ratio (±2 subjects per gender).

The total participation time for each subject in this study will be approximately 6 days (excluding Screening).

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.

4.1. Inclusion Criteria

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

1. Female subjects and/or male subjects who, at the time of Screening, are between the ages of 18 and 75 years, inclusive.

   - Male and female subjects of childbearing potential must agree to use highly effective method(s) of contraception (refer to Section 4.3.4). A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

   - Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

     a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

     b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

     c. Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

2. Body mass index (BMI) of 17.5 to 40.5 kg/m^2; and a total body weight >50 kg (110 lb).

3. Stable renal function defined as ≤25% difference between 2 measurements of eGFR obtained, from the same laboratory, on 2 separate occasions during the screening period that are at least 72 hours but no more than 14 days apart. Additionally, difference between eGFR Screening 1 value and Day -2 value should be ≤25%. The Day -2 eGFR value will be used for group placement.

4. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.1.1. Specific Requirements for Healthy Subjects with Normal Renal Function

1. Healthy as defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate (PR) measurement, 12-lead ECG, or clinical laboratory tests.

2. Normal renal function (eGFR ≥80 mL/min) at Screening based on the Day -2 value, using the MDRD formula adjusting for BSA (See Section 3.1).

3. An attempt will be made to enroll demographically comparable to the group of subjects with severe impaired renal function.

    - Body weight within ±15 kg of the mean body weight of the group of subjects with severe renal impairment.

    - Age within ±10 years of the mean age of the group of subjects with severe renal impairment.

    - Gender ratio for the group similar (±2 subjects per gender) to the group of subjects with severe renal impairment.

4.1.2. Specific Requirements for Subjects with Severe Renal Impairment

1. Good general health commensurate with the population with chronic kidney disease (renal impairment).

2. Documented severe renal impairment indicated by a eGFR >15 - ≤30 mL/min but not requiring hemodialysis, based on the Day -2 value, using the MDRD formula adjusting for BSA (See Section 3.1).

4.2. Exclusion Criteria

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

Exclusion Criteria: All Subjects

1. A positive urine drug test.

2. Urinary incontinence without catheterization.

3. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before Screening.

4. Treatment with an investigational product within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).

5. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level >1.0 × upper limit of normal (ULN);

   - Total bilirubin level >1.0 × ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured if total bilirubin level >1.0 × ULN and would be eligible for this study provided the direct bilirubin level is ≤ ULN;

   - Activated partial thromboplastin time (aPTT), prothrombin time (PT) and/or international normalized ratio (INR) >1.0 × ULN.

6. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol (Section 4.3.4) for the duration of the study and for at least 28 days after the last dose of investigational product.

7. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

For subjects with severe renal impairment, concomitant medications may be given if they are considered necessary for the welfare of study subjects (eg, standard therapy for underlying diseases), are not contraindicated with the study drug, and are unlikely to interfere with the PK/PD response of the study drug. Subjects must be receiving stable doses of these concomitant medications for at least 28 days before Screening. If concomitant medications are likely to interfere with the PK/PD response of the study drug, they may be substituted with agents that have similar pharmacological effects.

Use of oral anticoagulants and potent inhibitors of OAT1 and/or OAT3 (eg, probenecid) are prohibited in this study for all subjects.

8. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

9. History of sensitivity to heparin or heparin-induced thrombocytopenia.

10. History of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to aztreonam, carbapenem, monobactam or other β-lactam antibiotics, avibactam, or any of the excipients of the respective (investigational) medicinal products to be administered during the study.

11. History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HepBsAg), or hepatitis C antibody (HCVAb).

12. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.

13. Subjects who are 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.

14. 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.

15. Subject has past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood.

Exclusion Criteria: Subjects with Severe Renal Impairment

1. Subjects with any significant hepatic, cardiac, or pulmonary disease.

2. Renal allograft recipients or subjects who are clinically nephrotic.

3. Screening supine 12-lead ECG demonstrating QT interval corrected by Fridericia's formula (QTcF) >470 msec or a QRS interval >120 msec. If initial QTcF exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the subject's eligibility.

4. Screening supine BP ≥180 millimeters of mercury (mm Hg) (systolic) or ≥110 mm Hg (diastolic), on a single measurement (confirmed by a single repeat, if necessary) following at least 5 minutes of rest. If BP is ≥180 mm Hg (systolic) or ≥110 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.

5. Subjects requiring dialysis.

Exclusion Criteria: Healthy Subjects with Normal Renal Function

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including clinically relevant and significant drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

2. Screening supine 12-lead ECG demonstrating QTcF >450 msec or a QRS interval >120 msec. If initial QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the subject's eligibility.

3. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.

4.3. Lifestyle Requirements

The following guidelines are provided:

4.3.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and at least 1 hour prior to ECG evaluations.

- Breakfast will be provided approximately 1 hour after dosing on Day 1 (loading dose). On Day 3, breakfast will be provided prior to administration of the final

maintenance dose but after the pre-dose safety laboratory tests, ECG, BP and PR procedures have been completed. Breakfast can be given at any time on all other days.

- Lunch will be provided approximately 4-5 hours after dosing on Day 1 (loading dose) and Day 3 (final dose). Lunch can be given at any time on all other days.

- Dinner will be provided approximately 9 to 10 hours after dosing on Day 1 (loading dose) and Day 3 (final dose). Dinner can be given at any time on all other days.

- An evening snack may be permitted.

- The continuation of a renal diet is permitted.

- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of investigational product until collection of the final PK blood sample.

- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.3.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period, and at least 3 hours prior to ECG evaluations.

- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

4.3.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.3.4. 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 last dose of

investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform 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 (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). 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 or male subject's female partner 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.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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.

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 first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.4. 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 team SharePoint site.

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. For sites other than a Pfizer CRU, 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(s) are Azreonam and Avibactam.

5.1. Allocation to Treatment

The investigator will assign subject numbers to the subjects as they are screened for the study. This identifying number will be retained throughout the study. All subjects enrolled will receive 3 days of IV ATM-AVI according to the dose/schedule provided in the Section 5.4.

5.2. Subject Compliance

Investigational product will be administered under the supervision of investigator site personnel.

5.3. Investigational Product Supplies

5.3.1. Dosage Form and Packaging

Aztreonam and avibactam will be provided as separate vials for reconstitution and mixed together in a saline bag for co-administration at the appropriate concentration for IV infusion

using a standard aseptic IV infusion technique (see Investigational Product Manual [IP Manual]).

The identity of the investigational product is provided in Table 1.

Table 1. Identity of Investigational Product

Investigational Products[a]	Dosage form and Strength
Aztreonam	Aztreonam for injection, powder for solution for infusion 2000 mg
Avibactam	Avibactam lyophilisate 600 mg/vial Concentrate for solution for infusion

a. Aztreonam and Avibactam will be supplied by Pfizer Global R&D as separate vials for reconsititution and mixed together in a saline bag for co-administration at the appropriate concentration for intravenous infusion.

5.3.2. Preparation and Dispensing

See the IP manual for instructions on how to prepare the investigational product for administration. Both aztreonam and avibactam vials are for single-use. 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.

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

5.4. Administration

Subjects will receive the loading dose of the investigational product at approximately 7:30 AM (plus or minus 2 hours) on Day 1. No fasting is required in respect to dosing as ATM-AVI is administed intravenously. Fasting will only be required prior to safety laboratory and ECG assessments (see Section 4.3).

On Day 1, the loading dose and extended loading dose will be prepared in 1 infusion bag. The infusion pump will be programmed to administer the loading dose of ATM-AVI over 30 minutes followed by a rate change to administer the extended loading dose over 3 hours. This is followed by maintenance infusions dosed q6h (normal renal function) or q8h (severe renal impairment) according to the treatment schedule described in Table 2. The infusion line will be flushed according to local site procedure to ensure complete delivery of the dosing solution. The details of the IV infusion will be described in the IP manual. The start and stop time of each infusion will be recorded in the case report form (CRF).

Table 2. Treatment Schema

Day	Administration Start Time (±2 hrs)	Cohort 1 (Normal Renal Function)	Cohort 2 (Severe Renal Impairment)
1	7:30 AM[1]	30 min IV loading dose infusion (500/167 mg ATM/AVI)[1]	30 min IV loading dose infusion (675/225 mg ATM/AVI)[1]
	8:00 AM[1]	3 hr IV extended loading (1500/500 mg ATM/AVI)[1]	3 hr IV extended loading (675/225 mg ATM/AVI)[1]
	2:00 PM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	
	4:00 PM		3 hr IV maintenance infusion q8h (675/225 mg ATM/AVI)
	8:00 PM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	
2	12:00 AM		3 hr IV maintenance infusion q8h (675/225 mg ATM/AVI)
	2:00 AM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	
	8:00 AM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	3 hr IV maintenance infusion q8h (675/225 mg ATM/AVI)
	2:00 PM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	
	4:00 PM		3 hr IV maintenance infusion q8h (675/225 mg ATM/AVI)
	8:00 PM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	
3	12:00 AM		3 hr IV maintenance infusion q8h (675/225 mg ATM/AVI)
	2:00 AM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	
	8:00 AM	3 hr IV maintenance infusion q6h (1500/500 mg ATM/AVI)	3 hr IV maintenance infusion q8h (675/225 mg ATM/AVI)

Abbreviations: ATM/AVI = aztreonam/avibactam; hr(s) = hour(s); IV = intravenous; q6h = every 6 hrs; q8h = every 8 hrs.

1. Loading dose and extended loading dose will be prepared in one infusion bag with an infusion rate change after the first 30 minutes.

5.5. 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 IP manual for storage conditions of the product once reconstituted for ATM-AVI.

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.

5.6. 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.

5.6.1. 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.

5.7. Concomitant Treatment(s)

Healthy subjects with normal renal function will abstain from all concomitant treatments (prescription or over the counter [OTC]) and herbal/dietary supplements during the study, except for acetaminophen ≤1 g/dayand the treatment of AEs. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

For subjects with severe renal impairment, concomitant medications may be given if they are considered necessary for the welfare of study subjects (eg, standard therapy for underlying

diseases), are not contraindicated with the study drug, and are unlikely to interfere with the PK/PD response of the study drug. Subjects must be receiving stable doses of these concomitant medications for at least 28 days before Screening. If concomitant medications are likely to interfere with the PK/PD response of the study drug, they may be substituted with agents that have similar pharmacological effects.

Use of oral anticoagulants and potent inhibitors of OAT1 and/or OAT3 (eg, probenecid) are prohibited in this study for all subjects.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 28 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require rescreening if the Day -2 laboratory results meet the eligibility criteria.

Two (2) screening visits that are at least 72 hours but no more than 14 days apart are required for this study.

The following procedures will be completed for Screening Visit 1:

- Obtain written informed consent.
- Confirm and document that the subject meets the inclusion/exclusion criteria.
- Collect demography.
- Collect height and weight.
- Obtain medical history, including history of illegal drug, alcohol, and tobacco use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.
- Obtain single supine BP, PR and temperature.

- Conduct full physical examination.
- Collect single 12-lead ECG.
- Following at least a 4-hour fast, collect blood and urine specimens for the following:
  - Safety laboratory tests;
  - Urine drug test;
  - Serum FSH concentration for any female subject who has been amenorrheic for at least 12 consecutive months;
  - HIV, HepBsAg, and HCVAb testing;
  - Serum or urine beta-human chorionic gonadotropin (β-hCG) level for all female subjects of childbearing potential;
  - Confirm highly effective contraception is being used;
  - eGFR assessment. To confirm eligibility, subjects must have stable renal function defined as ≤25% difference between 2 measurements of eGFR obtained, from the same laboratory, on 2 separate occasions during the Screening period that are at least 72 hours but no more than 14 days apart. Additionally, difference between eGFR Screening 1 value and Day -2 value should be ≤25%. The Day -2 eGFR value will be used for group placement. The eGFR determination will utilize the MDRD formula adjusting for BSA (See Section 3.1). The CrCL value will be recorded at the same time eGFR is determined.
  - Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

The following procedures will be completed for Screening Visit 2:

- Following at least a 4-hour fast, collect blood sample for eGFR assessment.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

To prepare for study participation, subjects will be instructed on the information in the Lifestyle Requirements and Concomitant Treatment(s) sections of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital sign measurements and as close as possible to the scheduled time, but prior to blood specimen collection;
- BP/PR: obtain as close as possible to the scheduled time, but prior to blood specimen collection;
- PK blood specimens: obtain at the scheduled time;
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

When an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR, BP, and temperature) should be collected prior to the insertion of the catheter. **Blood obtained for PK samples should not be taken from the same IV line used to administer study drugs**.

6.2.1. Day -2

Subjects will be admitted to the CRU on Day -2. The following procedures will be completed following admission to the CRU:

- Review inclusion and exclusion criteria.
- Review changes in the subject's medical history including medication history, illegal drug, alcohol and tobacco use since Screening.
- Measure weight.
- Obtain blood and urine samples for safety laboratory tests. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1.
- Collect urine for drug testing.
- Collect serum or urine pregnancy test for female subjects of childbearing potential.
- Confirm highly effective contraception is being used.
- Conduct full physical examination, if deferred from the screening visit.
- Assess baseline symptoms/AEs.

- Assess eGFR: The Day -2 eGFR value will be used for group placement. To confirm eligibility, subjects must have stable renal function defined as ≤25% difference between 2 measurements of eGFR obtained, from the same laboratory, on 2 separate occasions during the Screening period that are at least 72 hours but no more than 14 days apart. Additionally, difference between eGFR Screening 1 value and Day -2 value should be ≤25%. The eGFR determination will utilize the MDRD formula adjusting for BSA (See Section 3.1). The CrCL value will be recorded at the same time eGFR is determined.

- Standardized meals will be provided as described in Section 4.3.

- CCI [redacted]

6.2.2. Day -1

The following procedures will be completed on Day -1:

- Assess baseline symptoms/AEs.

- Commence prior treatment monitoring.

- Standardized meals will be provided as described in Section 4.3.1.

Subjects will begin fasting at least 4 hours prior to dosing on Day 1.

6.2.3. Day 1

Prior to dosing, the following procedures will be completed:

- Assess baseline symptoms/AEs.

- Collect single 12-lead ECG measurements prior to insertion of the IV catheter.

- Collect single supine BP and PR and temperature prior to insertion of the IV catheter.

- Collect pre-dose blood sample for PK analysis (within 1hour before start of loading dose infusion).

- Monitor prior treatment.

- After all predose procedures have been completed, administer the ATM-AVI 30 min loading dose infusion immediately followed by the 3 hour extended loading dose. Loading dose and extended loading dose will be prepared in one infusion bag with an infusion rate change after the first 30 min (see Section 5 and Section 5.4).

- Standardized meals will be provided as described in Section 4.3.1.

After dosing of loading dose infusion, the following procedures will be completed:

- Obtain single 12-lead ECG measurements at 0.5 hour after dosing. (Breakfast should not be given prior to this ECG assessment).
- Assess single supine BP and PR at 0.5 hour after dosing.
- Collect blood samples for PK analysis at 0.5 (within 5 min before the end of the loading dose IV infusion) and 3.5 (within 15 min before the end of extended load IV infusion) hours after start of loading dose on Day 1. Both a venous blood sample and a finger-prick capillary blood sample will be collected (time-matched) from subjects in Cohort 1 (normal renal function).
- Collect maintenance pre-dose (trough) blood sample for PK analysis (within 10 min before start of maintenance dose infusion). Both a venous blood sample and a finger-prick capillary blood sample will be collected (time-matched) from subjects in Cohort 1 (normal renal function).
- Monitor concomitant treatment.
- Administer the ATM-AVI maintenance dose infusion q6h (normal renal function) and q8h (severe renal impairment) (see Section 5 and Section 5.4).
- Standardized meals will be provided as described in Section 4.3.1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.4. Day 2

The following procedures will be completed:

- Following at least a 4-hour fast, collect blood and urine specimens for safety laboratory tests in the morning; obtain a fresh 6 mL urine sample for urinalysis.
- Assess single supine BP and PR in the morning prior to dosing of maintenance dose administered at approximately 8:00 AM.
- Collect maintenance pre-dose (trough) blood sample for PK analysis (within 10 min before start of each maintenance dose infusion).
- Administer the ATM-AVI maintenance dose infusion q6h (normal renal function) and q8h (severe renal impairment) (see Section 5 and Section 5.4).
- Monitor concomitant treatment.
- Standardized meals will be provided as described in Section 4.3.1.

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.5. Day 3

The following procedures will be completed:

- Collect maintenance pre-dose (trough) blood sample for PK analysis (within 10 min before start of each maintenance dose infusion).

Prior to dosing of final maintenance dose, the following procedures will be completed:

- Following at least a 4-hour fast, collect blood and urine specimens for safety laboratory tests; obtain a fresh 6 mL urine sample for urinalysis.
- Collect single 12-lead ECG measurements prior to insertion of the IV catheter (if catheter not already inserted).
- Collect single supine BP and PR prior to insertion of the IV catheter (if catheter not already inserted).
- Breakfast will be provided prior to administration of the final maintenance dose but after the above procedures (safety laboratory tests, ECG, BP and PR) have been completed.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”
- Collect maintenance pre-dose blood sample for PK analysis (within 10 min before start of each maintenance dose infusion).
- Each subject will empty his or her bladder just prior to dosing (Dose given just prior to intensive PK assessment).
- Monitor concomitant treatment.
- After all predose procedures have been completed, administer the ATM-AVI maintenance dose (see Section 5 and Section 5.4).

After dosing of final maintenance dose, the following procedures will be completed:

- Obtain single 12-lead ECG measurements at 3 hours after dosing.
- Assess single supine BP and PR at 3 hours after dosing.
- Collect venous blood samples for PK analysis at 2, 3 (within 15 min before IV infusion stop), 3.25, 3.5, 3.75, 4, 5, 6, 8, 12 and 16 hours after start of maintenance

dose infusion on Day 3. Also collect a finger-prick capillary blood sample (time-matched) from subjects in Cohort 1 (normal renal function) at the following times: 3 (within 15 min before IV infusion stop), 4, 5, and 6 hours after start of maintenance dose infusion. Trough sample does not need to be collected for final maintenance dose on Day 3 as pre-dose sample will already be collected as part of intensive PK sampling collection.

- Collect urine over the following intervals:
  - 0 to 2 hours after start of maintenance dose on Day 3;
  - 2 to 4 hours after start of maintenance dose on Day 3;
  - 4 to 6 hours after start of maintenance dose on Day 3;
  - 6 to 8 hours after start of maintenance dose on Day 3 (**Cohort 2 only**).
- Monitor concomitant medication.
- Standardized meals will be provided as described in Section 4.3.1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"

6.2.6. Day 4 (end of trial [EOT])

The following procedures will be completed:

- Conduct limited physical examination.
- Perform single 12-lead ECG.
- Obtain single supine BP and PR and temperature.
- Following at least a 4-hour fast, collect blood and urine specimens for safety laboratory tests; obtain a fresh 6 mL urine sample for urinalysis.
- Collect blood samples for PK analysis at 24 hours after start of last maintenance dose infusion on Day 3.
- Monitor concomitant treatment.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"
- Standardized meals will be provided as described in Section 4.3.1.

- Discharge from CRU confinement.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3. Follow-up

6.3.1. Follow-up Contact

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.

6.4. Subject Withdrawal

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 (see also the Subject Withdrawal 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. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or CRU staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. 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 AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. Assessments may include:

- Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit;

- Supine BP and PR measurements;
- 12-lead ECG;
- Blood and urine specimens for safety laboratory tests;
- Blood sample for PK analysis.

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 protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must 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 the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must 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. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests (Table 3) will be performed at times defined in Section 6 of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 3. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) aPTT PT INR	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	FSH Urine drug screening β-hCG[b] Hepatitis B surface antigen Hepatitis C core antibody Human immunodeficiency virus (HIV)
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. Serum or urine β-hCG for female subjects of childbearing potential.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

- Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive investigational product.

7.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at Screening and at admission on Day -2.

A negative pregnancy test result is required before the subject may receive the ATM-AVI. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). 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 and will be conducted with the test kit provided by the investigator site 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).

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Height measurement only at screening when full physical examination is performed.

7.1.4. Blood Pressure and Pulse Rate

BP and PR will be measured at times specified in Section 6 of this protocol. Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject’s arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. BP should not be taken from the arm with an IV infusion. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and PR is acceptable; however, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

7.1.5. Temperature

Temperature will be measured temporally or orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

7.1.6. Electrocardiogram

Twelve (12)-Lead ECGs should be collected at times specified in Section 6 of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

7.2. Pharmacokinetics

7.2.1. Plasma for Analysis of Aztreonam-Avibactam

During all study periods, venous blood samples (2 mL) to provide approximately 1.0 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing Sodium Fluoride/Potassium Oxalate (grey top) at times specified in Section 6 of the protocol.

On Day 1 and Day 3, capillary blood microsamples (approximately 65 µL) to provide 30-35 µL of plasma for PK analysis will be collected from a finger-prick into capillary tubes containing Sodium Fluoride/Potassium Oxalate at times specified in Section 6 of the protocol (subjects with normal renal function only). Capillary sampling will be from the second and third finger (ie, ring and middle finger) after proper preparation and puncture of the skin. Details of the procedure for capillary sampling are provided in the Laboratory Manual. After collection, capillary tubes will be placed into appropriately labeled holders for processing. Sample handling details for both venous and capillary blood are provided in the Laboratory Manual.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (DCT) (eg, case report form [CRF]).

Samples will be analyzed using a validated analytical method in compliance with Pfizer & vendor standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report (CSR).

7.2.2. Urine for Analysis of Aztreonam-Avibactam

Urine will be collected at times specified in Section 6 of the protocol. Each subject will empty his or her bladder just prior to the last maintenance dose being administered at approximately 8:00 AM on Day 3. Each subject will be instructed to void into the collection container at the end of each collection period.

Samples will be analyzed using a validated analytical method in compliance with Pfizer & vendor SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor.

On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, urine samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the CSR.

7.3. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 86 mL for subjects with normal renal function and 81 mL for subjects with severe renal impairment. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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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 Section 8.2.3). 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. In addition, each study subject 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. 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 live function test (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.

8.4.2. 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.

8.4.2.1. 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.

8.4.2.2. 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.

8.4.2.3. 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.

8.4.3. Medication Errors and Lack of Efficacy

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

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

8.4.3.1. 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**.

8.4.3.2. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

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

Approximately 6 subjects will be enrolled into each the normal renal function group and the severe renal impairment group as described in Section 3.1. The sample size is based on recommendations from the "food and drug administration (FDA) Guidance for Industry - Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling".[10] Subjects who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and Sponsor.

A total of 42 capillary microsamples (7 samples per subject) will be collected from subjects in the normal renal function group at pre-specified time points on Day 1 and Day 3 as described in Section 6.2. The sample size of capillary microsamples time-matched to venous samples is based on recommendations from the "Land O'Lakes Microsampling workshop organized by the American Association of Pharmaceutical Scientists (AAPS)".[11] Allowing for up to a 10% difference between capillary and venous plasma concentrations, between 30 to 40 data points at minimum are recommended where the intra-sample variability (%CV) is <20%. Precision (%CV) is ≤10% for concentrations spanning the calibration curve of the dual-analyte bioanalytical assay validated for simultaneous analysis of aztreonam and avibactam plasma concentrations from a single microvolume plasma sample.

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

The PK concentration population is defined as all subjects treated with study drug who have at least 1 ATM and AVI concentration measurement.

The PK parameter analysis population is defined as all subjects treated with study drug who have at least 1 of the PK parameters of interest.

Analysis of variance (ANOVA) will be used to compare the natural log transformed $AUC_{0\text{-}24,ss}$ and C_{max} between the normal renal function group and the severe renal impairment group. The geometric least squares mean point estimate and the associated 90% confidence intervals (CIs) for the difference of each comparison will be estimated.

Aztreonam and avibactam PK parameters $AUC_{0\text{-}24,ss}$, C_{max}, $AUC_{0\text{-}\tau}$, T_{max}, C_τ, $t_{½}$, CL, CL_r, V_Z, V_{ss}, $Ae_{0\text{-}\tau}$, $Ae_{0\text{-}\tau}$ % will be summarized descriptively by group.

Box plots of mean, median and individual subject parameters will be made across both groups for $AUC_{0\text{-}24,ss}$,C_{max} and C_τ. Concentrations will be listed and summarized descriptively by PK sampling time and group. Summary profiles (means and medians) of the concentration-time data will be plotted across different groups. Individual subject concentration-time profiles will be also presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used; for individual subject plots by time, the actual PK sampling time will be used.

Attainment of steady state will be evaluated by a graphical presentation of pre-infusion concentration (trough) values on Days 1-3.

9.3.1. Plasma

PK parameters of aztreonam and avibactam following multiple dose administration will be derived from the venous plasma concentration-time profiles as follows:

Parameter	Definition	Method of Determination
$AUC_{0\text{-}24,ss}$	Total daily area under the plasma concentration-time profile from time 0 to 24 hours at steady-state	Normal renal function (Cohort 1): $AUC_{0\text{-}\tau} \times 4$ (τ = 6 hours) Severe renal impairment (Cohort 2): $AUC_{0\text{-}\tau} \times 3$ (τ = 8 hours)
$AUC_{0\text{-}\tau}$	Area under the plasma concentration-time profile from time 0 to to the time of the end of the dosing interval (τ)[b]	Linear/Log trapezoidal rule
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
C_τ	Observed concentration at the end of the dosing interval (τ)[b]	Observed directly from data
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where 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

Parameter	Definition	Method of Determination
CL	Clearance	$Dose/AUC_{0-\tau}$
V_{ss}	Apparent 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: $MRT = AUMC_{0-\tau}/AUC_{0-\tau}$ - (infusion time/2) Area under the first moment curve from 0 time to τ ($AUMC_{0-\tau}$) is calculated as: $AUMC_{0-\tau} = ((t \times C_{est}^{1}*)/k_{el}) + (C_{est}^{1}*/k_{el}^{2})$ $^{1}C_{est} = e^{(-KEL \times Tlast)} \times KELC_0$
V_z	Apparent volume of distribution during terminal phase	$Dose/(AUC_{0-\tau} \times k_{el})$

a. If data permit.
b. τ = 6 hours for normal renal function (Cohort 1) and 8 hours for severe renal impairment (Cohort 2).

Actual PK sampling times and non-compartmental methods will be used in the derivation of PK parameters.

Capillary Plasma Microsamples

To determine concordance/comparability of capillary microsample plasma concentrations with venous plasma concentrations, X-Y and Bland-Altman (B-A) scatter plots with limits of agreement (LoA) for a precision assessment will be used.

The Bland-Altman scatterplot will include the difference of the 2 measurements divided by the mean (% difference) for each sample on the vertical axis and the average of the 2 measurements on the horizontal axis. Three horizontal reference lines will be superimposed on the scatterplot - one line at the average percent difference between the measurements and lines to mark the upper and lower limits of 95% CI. The same plot will be generated for difference of the 2 measurements (vertical axis) and the average of the 2 measurements on the horizontal axis.

If the 2 methods are comparable, then % differences/differences should be negligible, with the mean of the differences close to 0, and show no systematic variation with the mean of the 2 measurements.

Venous and capillary observed plasma concentrations, individual subject differences and % differences of concentrations will be listed and summarized descriptively by PK sampling time.

9.3.2. Urine

Urine PK parameters of aztreonam and avibactam following multiple dose administration of ATM-AVI will be derived as follows:

Parameter	Definition	Method of Determination
$Ae_{0-\tau}$	Total amount of unchanged drug excreted in the urine over the dosing interval (τ)[a]	Sum of amount excreted for each collection period.
$Ae_{0-\tau}$%	Total amount of unchanged drug excreted in the urine over the dosing interval (τ)[a], expressed as percent of dose	$100 \times (Ae_{0-\tau}/Dose)$
CL_r	Renal clearance	$Ae_{0-\tau}/AUC_{0-\tau}$

a. τ = 6 hours for normal renal function (Cohort 1) and 8 hours for severe renal impairment (Cohort 2).

9.4. Safety Analysis

AEs, ECGs, BP, PR, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

9.4.1. Electrocardiogram Analysis

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS interval will be summarized by treatment and time.

The number (%) of subjects with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

	Borderline (msec)	Prolonged (msec)
Absolute value	≥450 - ≤480	>480
Absolute change	30-≤60	>60

In addition, the number of subjects with corrected and uncorrected QT values >500 msec will be summarized.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

9.6. 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 dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, 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/DCTs 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.

For studies conducted at non-Pfizer investigator sites, 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/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF/DCT 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/DCT is required and should be completed for each included subject. The completed original CRFs/DCTs 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/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/DCTs 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/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs/DCTs are true. Any corrections to entries made in the CRFs/DCTs 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's chart. In these cases, data collected on the CRFs/DCTs must match those charts.

In some cases, the CRF/DCT 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/DCT, and for which the CRF/DCT 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/DCTs and hospital records), all original signed informed consent documents, copies of all CRFs/DCTs, safety reporting forms, source documents, 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 to 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 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.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

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 laws.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, 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 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 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 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, 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.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent 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

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

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 PF-06947387 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/DCTs 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 study 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 (CSR synopses in which any data that could be used to identify individual patients have 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

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

Abbreviation	Term
^{14}C	carbon-14
%CV	coefficient of variation as percentage
AAPS	American Association of Pharmaceutical Scientists
Abs	absolute
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
$Ae_{0-\tau}$	total amount of unchanged drug excreted in the urine over dosing interval
$Ae_{0-\tau}$%	Total amount of unchanged drug excreted in the urine over dosing interval, expressed as percent of dose
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATM	aztreonam
ATM-AVI	aztreonam-avibactam
AUC	area under the curve
$AUC_{0-24,ss}$	Total daily area under the plasma concentration time profile from time 0 to 24 hours at steady-state
$AUC_{0-\tau}$	area under the plasma concentration-time profile from time 0 to to the time of the end of the dosing interval (τ)
AUC_{ss}	area under the curve at steady-state
AVI	avibactam
B-A	Bland-Altman
BA	bioavailability
BE	bioequivalence
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
C-G	Cockcroft-Gault
CAZ	ceftazidime
CAZ-AVI	ceftazidime-avibactam
CI	confidence interval
cIAI	complicated intra-abdominal infections
CK	creatine kinase
CL	Clearance

Abbreviation	Term
CL_r	renal clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CO2	carbon dioxide (bicarbonate)
CrCL	creatinine clearance
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
C_τ	observed concentration at the end of the dosing interval (τ)
C_T	threshold concentration
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CTX-M	cefotaximase -M
CV%	coefficient of variation
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI [redacted]	[redacted]
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
ESBL	extended spectrum β-lactamase
ESRD	end-stage renal disease
EU	European Union
EudraCT	European Clinical Trials Database
FDA	food and drug administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
hCG	human chorionic gonadotropin
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
CCI [redacted]	[redacted]
IND	investigational new drug application

Abbreviation	Term
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
KPC	*Klebsiella pneumonia* carbapenemase
LFT	liver function test
CCI	[redacted]
LSLV	last subject last visit
MBL	metallo-β lactamase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multidrug resistant
MDRD	Modification of Diet in Renal Disease
MIC	minimum inhibitory concentration
N/A	not applicable
NDM	New Delhi Metallo-β-lactamase
OAT	organic anion transporter
OTC	over the counter
OXA	Oxacillinase
PCD	primary completion date
PD	pharmacodynamic(s)
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PR	pulse rate
PT	prothrombin time
PTA	probability of target attainment
q6h	every 6 hours
q8h	every 8 hours
QTc	corrected QT
QTcF	QT interval corrected by Fridericia's formula
qual	qualitative
RBC	red blood cell
CCI	[redacted]
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SCr	serum creatinine
SD	standard deviation
SOP	standard operating procedure
SRSD	single reference safety document
$t_{½}$	terminal elimination half life
TBili	total bilirubin
THC	tetrahydrocannabinol
T_{max}	Time for C_{max}
ULN	upper limit of normal
US	United States
VIM	Verona Integron encoded metallo-β-lactamase
V_{ss}	apparent volume of distribution at steady-state
V_z	apparent volume of distribution during terminal phase
WBC	white blood cell