A PHASE I, SINGLE CENTER, OPEN-LABEL STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF AZTREONAM-AVIBACTAM ADMINISTERED AS SINGLE AND REPEATED INTRAVENOUS DOSES IN HEALTHY CHINESE PARTICIPANTS

Investigational Product Number:	PF-06947387
Investigational Product Name:	Aztreonam-Avibactam
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3601007
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	December 31st, 2020	This amendment incorporates the investigator's comments, protocol template revisions and content in previous PACL (20200701). Added Section 1. Protocol Summary and modified the section number and section sub-title in the following section for consistency with the current protocol template, and modified related hyperlink(s). Changed "subjects" to "participants" consistency with current protocol template. Modified the abbreviation of "hepatitis B core Antibody" as "HBcAb", and the "hepatitis B surface antigen" as "HBsAg" for consistency with current protocol template. Modified the description of PK parameters for consistency with current Pfizer standard. Section 1: 1) Added Section 1.1 Synopsis and Section 1.2 Schema; 2) Schedule of activities: modified the "follow-up visit" date format to "Day 28+7" and added a footnote "l" to clarify protocol requirement; added a pregnancy test at Day 5/Early termination/discontinuation and pregnancy test method changed to serum or urine β-hCG test; added time window requirement for ECG test is ±15 minutes and for Vital signs test is ±10 minutes; modified some other details in footnote e, f, h, i, j to clarify protocol requirements; Added another column "Early termination/Discontinuation" and another footnote m for consistency with current protocol template; 3) Pharmacokinetic Sampling Schema: Added footnote b to clarify maintenance dose administration frequency; Added footnote i on the urine collection time points on Day 1 and Day 4 to avoid confusion; Added "and on Day 4, approximately 10 mL of pre-dose urine will be collected before the final dose administration." in footnote i; clarified the usage of pre-dose blood or urine PK sample as "evaluation of the matrix effect on the bioanalyticalmethod and validation" in footnote c and i. Section 2: 1) Added Section 2.1 study rationale; 2) Deleted the detailed version number of IB, and changed to "current

Document	Version Date	Summary of Changes and Rationale
		version" in Section 2.2 and Section 2.3.2 to align with IB updates; 3) Updated key conclusions of study Phase 2a study D4910C00009/C3601001in Section 2.3 according to current version IB, because this study has been completed; 4) Supplemented some study design rationale and dose selection rationale in Section 2.4; 5) Added Section 2.5 Benefit/Risk Assessment according to current version of IB for consistency with current protocol template. Section 3: Modified the wording in primary objective for clarity: "to investigate the PK profile of ATM and AVI after single and repeated IV infused doses of ATM-AVI" Section 4: 1) Modified subtitle and reference section information in Section 4.1 for consistency with current protocol template; 2) Added Section 4.4.1"End of study definition"; 3) Modified "Adverse Events" to "Occurrence of an AE or any other condition posing a risk to a participant or jeopardizing a safe continuation of the study treatment for the respective participant (as judged by the investigator, and/or the national coordinators, and/or the Medical Monitor and the Study Sponsor)." in stopping rules. Section 5.1, modified the inclusion criteria detailed requirements according to investigator's comments and current protocol template requirements: 1) Added the requirement for enrolled female and male participants number proportion in criteria 1; 2) Modified the healthy participants criteria, changed "full physical examination, including BP and PR" to "physical examination, vital signs". 3) Deleted the detail description in female childbearing potential in Section 5.1 and added "Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.". 4)Added requirement "(both not inclusive)" after "Body mass index (BMI) of 17.5 to 30.5 kg/m^2". 5) Modified the wording on criteria 5 related to signing an ICD for consistency with current protocol template. Section 5.2, modified the exclusion criteria detailed requirements according to investigator's comments and current protocol template requirements: 1) Modified criteria 5 related to alcohol abuse or bringe drinking. 2)

Document	Version Date	Summary of Changes and Rationale
		Deleted "including those that are known to cause PK drug interaction." in criteria 6 because the known cause PK drug interaction drug is already listed in criteria 18; 3) Separated exclusion criteria 10 into 2 items, one is the disease that affects ADME of ATM-AVI, and the other one is "Participant has known Clostridium difficile associated diarrhea.", for clarity. 4) Added a sentence"CL_{CR} will be calculated when the participants are selected according to exclusion criteria in the SoA. " in criteria 12 according to investigator's requirement. 5) Added more information related to baseline 12-lead ECG procedure in criteria 13 for consistency with current protocol template. 6) Deleted "liver function and coagulation tests after 48 hours. If the results still greater than 1.0×ULN," according to investigator's comments in criteria 14. 7) Modified the vital signs examination requirement in criteria 15 according to investigator's comments in criteria 15. 8) Added the "Hepatitis B vaccination is allowed." in criteria 23 per current protocol template. 9) Modified the description in criteria 26 for consistency with the current protocol template. 10)Added the definition of allergy/Hypersensitivity in exclusion criteria 2, and added the specific contents of dietary supplements in criteria 18 according to ethic committee comments. Section 5.3 and Section 5.4: 1) Deleted the time requirement for breakfast on Day 2, and lunch/dinner on Days 1, 2, and 4 according to investigator's requirement in Section 5.3.1. Because the infusion time is long and the food has limited impact on ATM-AVI, so this modification is convenient for site's operation. 2) Modified the specific description for meals to "the meals for all participants should be standardized meals provided by CRU" in Section 5.3.1. 3) Deleted the requirement for "Energy drinks containing taurine or glucuronolactone eg, Red Bull from 72 hours before follow-up." in previous Section 4.3.2 (currently in Section 5.3.2)for the final follow-up can be via phone call. 4) Modified the description in Section 5.3.4 and added Appendix 4 for contraception requirement for consistency with current protocol template. 5) Added Section 5.4 screen failures based on current protocol template. 6) Moved "Sponsor's Qualified Medical

Document	Version Date	Summary of Changes and Rationale
		Personnel" into Section 10.1.10 for consistency with current protocol template. Section 6: 1) Deleted the Investigational product manufacturer requirement in Table 1, because the actual manufacturer may be changed. 2) Modified the administration specific time requirement in Section 6.2 and Table 2. Added "The single dose administration on Day 1 as it needs to occur in the morning to allow 24 hours for sample collection prior to start of Day 2 dosing." to guarantee PK samples can be collected on time; added the infusion duration time window is "± 5 minutes" convenient for site's operation. 3) Integrated the Investigational product preparation, handling, storage and accountablility requirement in Section 6.3, added new requirement "A second staff member will verify the dispensing" according to current protocol template requirement. 4) Change the version of "Common Terminology Criteria for Adverse Events [CTCAE] v 4.03" to "v 5.0"; 5) Modified Sections 6, 6.4, 6.5, 6.6, 6.7 and 6.8 according to current protocol template. Section 7: Modified requirements related to "discontinuation of study intervention" in Section 7 according to current protocol template. And deleted the section "study procedure" because the information has been covered in Schedule of Activities and Section 8. Section 8, was modified for consistency with current protocol template: 1) Added some general requirement for study assessment and modified the total blood sampling volume according to PACL; Added some detail requirements: 2) Modified to "pregnancy test may be urine or serum tests" and added another pregnancy test at the end of the study; 3) Modified the physical examination test requirement for consistency with current protocol template; 4) Added "As much as possible, " before "The same arm (preferably the dominant arm) will be used throughout the study." according to investigator's comments; Added the requirement of "supine rest of 5 min" before BP test conduction; Added requirement of tympanic temperature measurement; 5) Changed the supine time before ECG test to 5 minutes; 6) Modified the time requirement to "Triplicate 12 lead ECGs will be obtained approximately

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		within 2 to 5 minutes"; 7) Modified requirements related to AE and SAE in Section 8.3 for consistency with current protocol template; 8) Add Section 8.4 "Treatment of Overdose"; 9) Clarified the usage of pre-dose blood and urine samples and added time window for urine PK sample collection is 10% of nominal time interval in Section 8.5.10) Modified Section 8.5 to Section 8.10 for consistency with current protocol template. Section 9: Modified data analysis and statistical method related requirements for consistency with current protocol template: 1) Added Section 9.1, Section 9.2 and Section 9.3; 2) Some other modifications in Sections 9.4 to 9.6, for consistency with current protocol template and standard of PK parameters.Section 10: 1) Added Section 10 according to current protocol template requirement; for Section 10.2 (Table 3), modified some detail requirements: 2)Added additional option "carbondioxide combining power (CO_2CP)" for total CO_2 in the Chemistry safety laboratory tests; 3) Modified some detail requirements according to site practice and new protocol template: the blood sample volume in footnote f of Table 3, "7 mL" for serology at screening; added Investigators must document their review of each laboratory safety report; some additional wording for consistency with new protocol template; 4) Modified and added new abbreviations in Section 10.7. Updated typographical and clerical errors.
Original protocol	30 August 2018	Not applicable (N/A)

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LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study to Assess the Pharmacokinetics, Safety and Tolerability of Aztreonam-Avibactam in Healthy Chinese Participants.

Rationale: The purpose of the study is to investigate the PK characteristics, safety and tolerability of aztreonam-avibactam administered as single and repeated IV infusion of doses in healthy Chinese participants. Results from this study will be used to support clinical development of ATM-AVI in China and to support China registration.

Objectives and Endpoints

Primary Objective(s):	**Primary Endpoint(s):**
• To investigate the PK profile of ATM and AVI after single and repeated IV infused doses of ATM-AVI.	• For plasma concentration data, the PK parameters C_{max}, AUC_6, AUC_{last}, AUC_{24}, AUC_{inf} for Day 1; C_{max}, AUC_{τ}, AUC_{last}, AUC_{24}, $AUC_{24,ss}$, AUC_{inf} for Day 4; • For urine concentration data, the PK parameter CLr.
	Secondary Endpoint(s):
	• For plasma concentration data, the PK parameters $t_{1/2}$, V_{ss}, V_z, CL, T_{max}, $R_{ac,Cmax}$, R_{ac}.
	Tertiary Endpoint(s):
	• For plasma concentration data, the PK parameters C_{min} for Day 2, Day 3, and Day 4; • For urine concentration data, the PK parameters Ae_t, Ae_t%.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To investigate the safety and tolerability of ATM-AVI as single and repeated intravenous (IV) infusions in healthy Chinese participants.	• Safety and tolerability as assessed by adverse events (AEs), physical examination, vital signs, ECGs, and laboratory assessments.

Overall Design

This is a Phase 1, single center, single arm, open-label study to assess the PK, safety and tolerability of ATM and AVI after single and repeated IV infusion of doses ATM-AVI in healthy Chinese participants.

Number of Participants

A maximum of approximately 12 healthy male and female Chinese participants will be enrolled to study intervention such that approximately 9 evaluable participants complete the study.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

All participants are scheduled to receive ATM-AVI single dose administration on Day 1 and repeated dose administration on Day 2 to Day 4 by IV infusion.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

All data analyses will be descriptive.

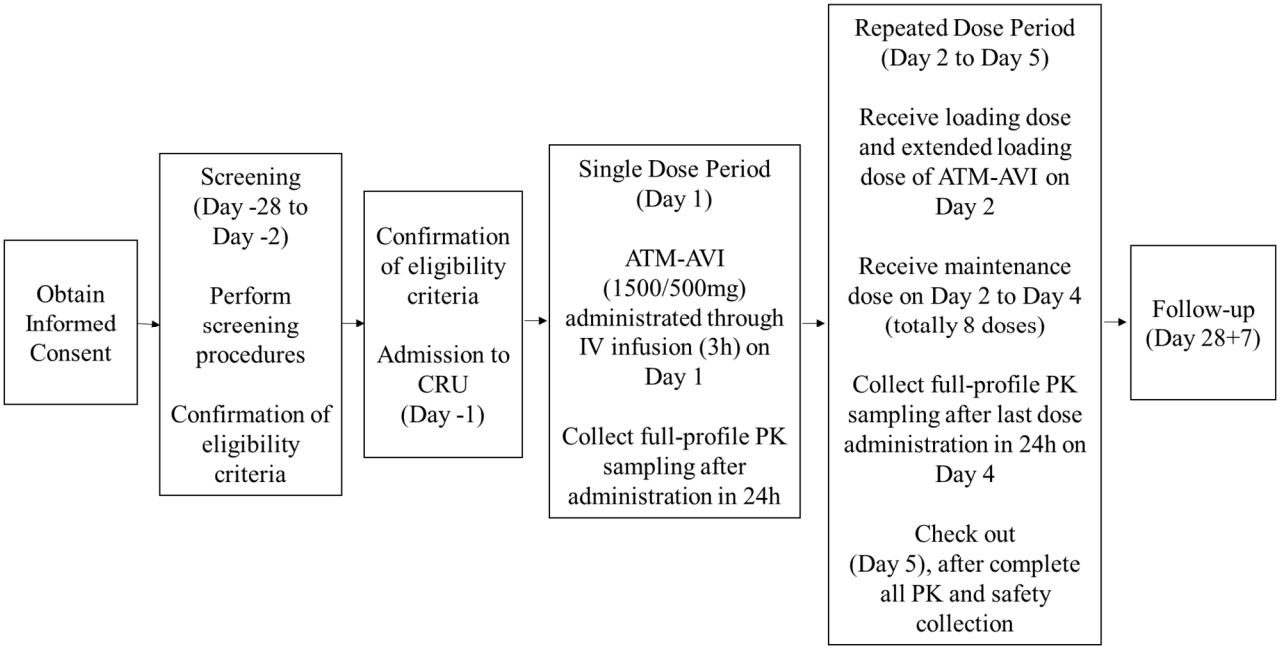
ATM and AVI PK parameters (C_{max}, AUC_6, AUC_{last}, $AUC_{24,}$ AUC_{inf} for Day 1, C_{max}, AUC_{τ}, $AUC_{24,}$ $AUC_{24,ss,}$ for Day 4, CLr, $t_{1/2}$, V_{ss}, V_z, CL, T_{max}, $R_{ac,Cmax}$, $R_{ac,}$ Ae_t, Ae_t%) will be summarized descriptively for Day 1 and Day 4. C_{min} for Day 2, Day 3, and Day 4 will be summarized.

The plasma and urine concentration data will be listed and summarized descriptively by PK sampling time for Day 1 and Day 4. Summary profiles (means and medians) of the concentration-time data will be plotted for Day 1 and Day 4. Individual participant 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 participant plots by time, the actual PK sampling time will be used.

CCI [redacted]

Safety data (AEs, vital signs, ECGs and laboratory data) will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

1.2. Schema


Obtain Informed Consent
Screening (Day -28 to Day -2)
Perform screening procedures
Confirmation of eligibility criteria
Confirmation of eligibility criteria
Admission to CRU (Day -1)
Single Dose Period (Day 1)
ATM-AVI (1500/500mg) administrated through IV infusion (3h) on Day 1
Collect full-profile PK sampling after administration in 24h
Repeated Dose Period (Day 2 to Day 5)
Receive loading dose and extended loading dose of ATM-AVI on Day 2
Receive maintenance dose on Day 2 to Day 4 (totally 8 doses)
Collect full-profile PK sampling after last dose administration in 24h on Day 4
Check out (Day 5), after complete all PK and safety collection
Follow-up (Day 28+7)

1.3. SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENT AND PROCEDURES section 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 participant.

Study Plan	**Screening**	**Treatment phase**						**Follow-up[l]**	**Early termination/ Discontinuation**
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**28+7 after last dose**	
Informed consent[a]	X								
CRU confinement		X	→	→	→	→	X		
Inclusion/exclusion criteria	X	X							
Medical history	X	X							
Medication history	X	X							
History of tobacco, illegal drug and alcohol use	X	X							
Physical examination	X[b]	X[c]					X[d]		X[m]
Demography, height and weight[e]	X	X							
Pregnancy test[f]	X	X					X		X
Contraception check	X	X						X	X
Serum FSH[g]	X								
Urine drug testing	X	X							
Safety laboratory (chemistry, hematology, coagulation, and urinalysis)	X	X			X	X	X		X
12-lead ECG[h]	X	X	X	X		X	X		X
Vital signs[i]	X	X	X	X	X	X	X		X
HIV, HBsAg, HBcAb, HCVAb testing	X								
Single dose ATM-AVI administration (3 hour infusion)			X						

Study Plan	Screening	Treatment phase						Follow-up[l]	Early termination/ Discontinuation
Day	-28 to -2	-1	1	2	3	4	5	28+7 after last dose	
ATM-AVI loading dose (30 min infusion)				X					
ATM-AVI extended loading dose (3 hour infusion)				X					
ATM-AVI maintenance dose (3 hour infusion) q6h				X	X	X			
PK blood sampling (see PK sampling schema below)			X	X	X	X	X		X
PK urine sampling (see PK sampling schema below)			X			X			X
Prior/Concomitant treatment(s)			X	→	→	→	X		X
Local tolerability Assessment[j]			X	X	X	X	X		X
Standardized meals[k]		X	→	→	→	→	X		X
CRU discharge							X		X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	X	X

Abbreviations: = ongoing/continuous event; ATM = aztreonam; AVI = avibactam; CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; PK = pharmacokinetic; q6h = every 6 hours.

a. Informed consent must be obtained prior to undergoing any study specific procedure and may occur prior to the screening period which will be up to 28 days prior to administration of the investigational product.
b. Conduct full physical examination, further examinations will be performed at the discretion of the investigator; if deferred, conduct limited physical examination at screening and the full physical examination should be performed on Day -1.
c. Conduct full physical examination, if deferred from the screening visit, further examinations will be performed at the discretion of the investigator; otherwise, limited physical examination will be conducted.
d. Limited physical examination.
e. Collect demography, height and weight information at screening, and collect height and weight at Day -1.
f. Serum or urine beta-human chorionic gonadotropin (β-hCG) level for all female participants of childbearing potential.
g. 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.
h. Single 12-lead ECG will be done at screening and repeated if abnormal, see exclusion criterion 12 in Section 5.2 Single 12-lead ECG will also be done on Day -1. Perform triplicate baseline 12-lead ECG on Day 1 prior to dosing, single ECG will be performed at the end of infusion (within ±15 minutes) on Day 1. On Day 2, obtain single

Study Plan	Screening	Treatment phase						Follow-up[l]	Early termination/ Discontinuation
Day	-28 to -2	-1	1	2	3	4	5	28+7 after last dose	

12-lead ECG measurements at 0.5 hour after administration of loading dose infusion (within±15 minutes). On Day 4, single ECG will be taken prior to last dose infusion and at the end of last dose (within±15 minutes) infusion. On Day 5, single ECG will be taken at the end of treatment phase prior to blood sample collection.

i. Vital signs include blood pressure (BP), pulse rate (PR) and body temperature. Single BP should be taken with the participant in the supine position after the participant has been resting quietly for approximately 5 minutes. On Day 1, vital signs will be taken prior to infusion, and only BP and PR at the end of infusion (within±10 minutes). On Day 2, vital signs (except body temperature) will be taken prior to loading dose infusion, and at the end of loading dose infusion (within±10 minutes). On Day 3, vital signs will be taken prior to infusion (Second maintenance dose infusion on Day 3). On Day 4, vital signs (except body temperature) will be taken prior to last dose infusion, and at the end of last dose infusion (within±10 minutes). On Day 5, vital signs will be taken at the end of treatment phase prior to blood sample collection.

j. Assessment performed on Day 1 before the start of the infusion and at the end of the infusion; on Days 2 through 4 before the start and at the end of each infusion; and on Day 5 before blood sample collection.

k. See section 5.3 or more details.

l. Follow-up visit occurs on Day 28 (the visit time window is 28+7 days). Follow- up visit can be via telephone.

m. Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit. If there is no new or open AE or clinically significant abnormal physical finding from the last visit, a limited physical examination is needed.

Pharmacokinetic Sampling Schema

Visit Identifier																			
Study Day	**Day 1**											**Day 2**					**Day 3**	**Day 4**	**Day 5**
Hours	**0**	**2**	**3**	**3.25**	**3.5**	**4**	**5**	**6**	**8**	**12**	**16**	**0**	**0.5**	**3.5**	**6.5**	**12.5**			
ATM-AVI single dose (3 hour infusion)	X																		
ATM-AVI loading dose (30 min infusion)[a]												X							
ATM-AVI extended loading dose (3 hour infusion)													X[a]						
ATM-AVI maintenance dose (3 hour infusion) q6h[b]															X[b]	→[b]	→[b]	X[b]	
Blood sampling for ATM-AVI PK	X[c]	X	X[d]	X	X	X	X	X	X	X	X	X[c]	X[e]	X[f]				X[g]	X[c]
CCI																			
Urine sampling for ATM-AVI PK[i]	X[i]	→	→	→	→	→	→	→	→	X[i]								X[i]	

Abbreviation: → = ongoing/continuous event; ATM = aztreonam; AVI = avibactam; IV = intravenous; PK = pharmacokinetic q6h = every 6 hours.

a. Loading dose and extended loading dose will be prepared in one infusion bag with an infusion rate change after the first 30 minutes.
b. Total of 8 maintenance doses administration from Day 2 to Day 4, two maintenance doses on Day 2, four maintenance doses on Day 3, two maintenance doses on Day 4.
c. Pre-dose sample collection. Only on Day 1, the pre-dose blood sample is to be collected within 1 hour before infusion with volume of about 10 mL (about 6 mL will be used for evaluation of the matrix effect on the bioanalytical method and validation as appropriate, and 4 mL for pharmacokinetics analysis). On Day 2, the pre-dosesample collection is the 24 hour sample for Day 1. On Day 5, the sample collection is the 24 hour sample for Day 4.
d. Collect PK blood sample within 15 min before IV infusion stop.
e. Collect PK blood sample within 5 min before the end of the loading dose IV infusion.
f. Collect PK blood sample within 15 min before the end of extended loadng IV infusion.
g. On Day 4, collect CCI blood sample for PK analysis CCI ; after administration of final infusion, collect blood samples at 2, 3 (within 15 min before end of IV infusion), 3.25, 3.5, 4, 5, 6, 8, 12 and 16 hours.
h. CCI
i. Urine will be collected on Day 1 and Day 4, pre-dose and after dosing during collection periods of 0-2, 2-4, 4-6, 6-8 and 8-12 hours. Instruct participant to void prior to administration of investigational product. On day 1, approximately 20 mL of pre-dose blank urine will be colletected for bioanalytical method evaluation and validation as appropriate. On Day 4, approximately 10 mL of pre-dose urine will be collected before the final dose administration. Instruct participant to void into the collection container at the end of each collection period.

2. INTRODUCTION

Aztreonam (ATM), with more than 30 years of use worldwide, 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 (including penicillins and cephalosporins), as well as several chemical side groups that interfere with degradation by metallo-β-lactamases (MBL). 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 (AVI) is a novel, non β-lactam, β-lactamase inhibitor of a broad spectrum of enzymes, including Ambler Class A extended spectrum β-lactamases (ESBL), Class A Klebsiella pneumoniae carbapenemase (KPC), and Class C (AmpC) enzymes, and some Class D enzymes, notably oxacillinase-48 (OXA-48), a problematic carbapenemase in the European Union (EU) and Middle East. AVI's β-lactamase inhibition occurs through formation of a covalent bond between AVI and enzyme. Alone, AVI has no meaningful antibacterial activity; rather, its beneficial effect in combination with ATM occurs by rendering inactive those enzymes that inactivate ATM.

Together, ATM and AVI 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 a multiple-drug resistant (MDR) phenotype.

2.1. Study Rationale

The purpose of the study is to investigate the Pharmacokinetic characteristic, safety and tolerability of aztreonam-avibactam administered as single and repeated IV infusion of doses in healthy Chinese participants.

Results from this study will be used to support clinical development of ATM-AVI in China and to support China registration.

2.1.1. Indication

The combination product referred to as ATM-AVI is being developed for the treatment of serious infections caused by susceptible Gram-negative bacteria for which there are limited or no treatment options. These include infections caused by MBL-producing pathogens that can also co-produce ESBLs, KPC and/or AmpC β-lactamases. Relevant to the clinical development of the study therapy is the fact that ATM-AVI has shown excellent activity in pre-clinical studies against a broad range of Gram-negative pathogens, including several of the most problematic MDR pathogens (see current aztreonam-avibactam Investigator's Brochure for further details).

2.2. Background

2.2.1. Metallo-β-Lactamases And Metallo-β-Lactam Resistant Gram-Negative Bacteria

The incidence of 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 Gram-negative pathogens. 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]

One of the most common resistance mechanisms in Gram-negative pathogens is the production of ESBLs.[1] Infections due to ESBL-producing organisms present a major therapeutic dilemma especially as isolates are also increasingly expressing resistance to other first line agents such as fluoroquinolones or aminoglycosides, leaving few available options for therapy. ESBL are found in a significant percentage of Enterobacteriaceae (including *E. coli, Klebsiella pneumoniae, Enterobacter, Citrobacter, Proteus, Morganella morganii, Serratia marcescens*, and *Shigella dysenteriae*). They can also be found in *Pseudomonas aeruginosa* although they do not contribute significantly to resistance in this organism.

Carbapenems are the preferred treatment option for serious infections due to such MDR Gram-negative pathogens but carbapenemases have steadily accumulated in the *Enterobacteriaceae* with the epidemiology of carbapenem resistant *Enterobacteriaceae* (CRE) characterized by large heterogeneity in genotypes (with >20 reported resistance gene families, such as New Delhi Metallo-β-lactamase (NDM), KPC, Verona Integron encoded metallo-β-lactamase (VIM, a type of Class B β-lactamase), OXA-48.[4] The expression of MBLs such as VIM and NDM-1, in addition to other resistance mechanisms, is of increasing concern as the treatment options are extremely limited.

A particular threat is posed by a family of MBLs known as NDM. NDM-1-producing pathogens have already been reported in a number of countries outside of the regions where the first producing strains were identified in 2009 (India, Pakistan, Sweden, UK), including Australia, Singapore, Taiwan, and the United States. The recent emergence of NDM-1 has caused particular concern in the international infection community, as the genetic element encoding NDM-1 is able to rapidly spread amongst bacteria in both community and hospital settings.

The spread of resistance due to the ESBL cefotaximase-M (CTX-M, a type of Class A β-lactamase) may provide a useful model for the spread of NDM-1 as the *bla*$_{\text{NDM-1}}$ gene is found on the same promiscuous ST131 clone as CTX-M. In particular, organisms that produce NDM-1 have spread geographically and are now seen in community-acquired infections, similar to the spread of CTX-M, which has reached endemic levels in much of Asia, Europe, and South America. These pathogens have become endemic in the Indian subcontinent, where they have been detected in the environment.[5]

A representative example of a serious Gram-negative infection includes complicated intra-abdominal infection (cIAI). Most commonly, *Enterobacteriaceae* are isolated in cIAI. For therapy, the current Guidelines of the Infectious Diseases Society of America[6] recommend surgical intervention along with broad spectrum single agent (β-lactam/β-lactamase inhibitor, carbapenem) or combination antibiotic regimens (metronidazole plus cephalosporin or aztreonam or fluoroquinolone). Specific regimens are recommended for higher risk patients with severe or postoperative nosocomial intraabdominal infections where resistant pathogens such as *Enterococcus spp.* or *Pseudomonas aeruginosa* may occur.

The combination product ATM-AVI is being developed for intravenous (IV) treatment of serious infections caused by Gram-negative pathogens producing MBLs in addition to other β-lactamases. Commonly, such organisms termed MDR show non-susceptibility to at least 3 classes of antibiotics.

2.2.2. Summary of Preclinical Information

The preclinical toxicological evaluation of AVI comprised single- and repeat-dose toxicity studies of up to 3 months duration in rats and dogs, studies to assess genetic and reproductive toxicology (male and female fertility in rats, embryo-foetal development in the rat and rabbit), local tolerance studies, an in vitro phototoxicity study, and immunotoxicology and hemolytic-potential studies. These studies show that AVI is well tolerated in preclinical species and is not associated with target organ toxicity with the exception of local tolerance issues when administered via a peripheral vein. These local tolerance issues are not seen when AVI is administered intravenously via a central vein in surgically prepared animals.

For further information please refer to the current aztreonam-avibactam Investigators Brochure.

2.2.3. Human Experience

Aztreonam alone is an established injectable antibiotic indicated for the treatment of various infections caused by susceptible Gram-negative bacteria. Additional information regarding ATM is available in the approved prescribing information.[7]

The serum half-life of aztreonam averaged 1.7 hours (1.5 to 2.0 hours) in participants with normal renal function, independent of the dose. In healthy participants, based on a 70 kg person, the serum clearance (CL) was 91 mL/min and renal clearance (CL_r) was 56 mL/min; the mean apparent 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 every 8 hours (q8h) for 7 days to healthy participants produced no apparent accumulation of aztreonam or modification of its disposition characteristics; serum protein binding averaged 56% and was independent of dose.

To date, human experience with AVI comes from Phase I to Phase III studies in which AVI was administered either as a single agent or in combination with other antibiotics

(ceftazidime or ceftaroline) in other clinical development programmes. From these programmes, the clinical pharmacology of AVI has been well characterised.

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 plasma 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 (q8h for up to 10 days).

At the time of developing this Clinical Study Protocol, 92 healthy volunteers have been dosed with the investigational medicinal product (ie, ATM-AVI, placebo or ATM-AVI separately), in a Randomised, Double-blind, 3-Part Phase I study in Healthy Young and Elderly Participants (D4910C00001). Key aztreonam-avibactam PK findings in this Study are as follows:

- Comparison of exposure parameters (C_{max} and area under the curve [AUC]) between the combination or individual therapy (ie, ratio of aztreonam-avibactam/aztreonam and aztreonam-avibactam/avibactam) in a statistical model (not powered) produced estimates and 90% confidence intervals [CI]s which indicated that single-dose PK of aztreonam or avibactam was not affected when it was co-administered compared to separate administrations.

- Systemic exposure of both avibactam and aztreonam increased in a dose-proportional manner in the studied dose range, following multiple dosing exposure of both aztreonam and avibactam; it was similar on Day 1 compared to Day 11, showing there was minimal accumulation and providing supportive evidence of a lack of drug-drug interaction.

- Data indicate avibactam displays approximately linear PK over the studied dose range (375 to 600 mg) following multiple doses administered as a 1- to 3-hour infusion every 6 hours (q6h) in healthy young participants.

- Consistent plasma PK and urinary excretion data were obtained for aztreonam (1500 to 2000 mg) and avibactam (375 to 600 mg) administered alone or in combination (1 to 3 hours IV infusion) after single doses and multiple doses. No drug accumulation was observed and linear PK was observed for both aztreonam and avibactam. Renal clearance accounted for the most part of plasma clearance, indicating urinary excretion of unchanged drug as the primary elimination pathway for both aztreonam and avibactam.

- 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 participants (aztreonam area under the curve

at steady-state [AUC_{ss}] increased by 22.6%; observed maximum plasma concentration at steady state ($C_{ss,max}$) increased by 15.8% and observed minimum plasma concentration at steady state ($C_{ss,min}$) was increased by 54.4% in elderly participants). Corresponding changes were observed for avibactam where AUC_{ss} increased by 32.7%, $C_{ss,max}$ increased by 31.1% and $C_{ss,min}$ increased by 74.2% in elderly compared to young participants. Post-hoc modeling suggested this may be related to difference in renal function in these patients.

- In cohorts of 8-10 patients, the proportion of healthy volunteers who developed transaminase excursions decreased after reduction of both of aztreonam and avibactam doses, and extension of the infusion time. Post-hoc PK modeling of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by exposure did not suggest a relationship between avibactam concentration and ALT increases.

A Phase 2a study D4910C00009/C3601001 was completed to investigate the PK, safety, and tolerability of ATM-AVI in patients with a serious bacterial infection (ie, cIAI) and to support dose selection for the Phase 3 studies. Assessment of treatment outcome was a secondary objective. 34 adult patients with cIAI and requiring surgical intervention were treated with ATM-AVI in this single-arm study. Key aztreonam-avibactam PK findings in this study are as follows:

- Following the end of a 3 hour infusion of aztreonam-avibactam maintenance dose regimen on Day 4 (steady-state), aztreonam and avibactam plasma concentrations declined with a mean $t_{½}$ (within the 6 hour dosing interval) of 2.3 to 2.8 and 1.8 to 2.2 hours, respectively. Geometric mean V_{ss} and CL were approximately 20 L and 6.4 L/h, respectively for aztreonam and 23.7-26.0 L and 10.1-10.5 L/h, respectively for avibactam.

- Exposures of aztreonam and avibactam achieved in the cIAI patients were consistent with the predicted exposures (C_{max} and $AUC_{24,ss}$) for both avibactam dose groups based on the updated population PK models used to define the doses for Study D4910C00009/C3601001.

- Since the population PK models performed well, it gives assurance that the exposures for the dosing regimens for patients with moderate and severe renal impairment, are adequately well predicted.

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.

Based on the mechanisms clearance summarized above, there are no ethnic associated differences in clearance expected.

In the completed Phase 1 study for ATM-AVI in healthy participants (Study D4910C00001), ATM-AVI was considered well tolerated, with a safety profile similar to that expected with aztreonam monotherapy. The most common adverse effects (AEs) reported in the ATM-AVI treatment arms were headache, liver function test (LFT) abnormal, diarrhea, and infusion/cannula site pain/reaction, which are all expected events for aztreonam. Elevations in liver transaminases were seen in a number of healthy participants who received aztreonam in combination with avibactam. None of the liver transaminase elevations was associated with signs or symptoms of hepatic dysfunction, and all cases rapidly resolved after cessation of therapy.

In the completed Phase 2a study (Study D4910C00009/C3601001), the overall observed patterns of AEs is in line with that described for aztreonam alone in the UK summary of product characteristics (SmPC) and United States Package Insert(USPI) for Azactam™. Based on the available safety and efficacy data for ATM-AVI, the expected benefit-risk profile of the medicinal product remains favorable, and supports the further development of the compound in patients with serious infections.

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

2.3. Benefit/Risk Assessment

ATM-AVI is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK, safety and tolerability, and pharmacokinetic data for further clinical development.

Aztreonam has been in use worldwide for more than 30 years, and its safety profile is well characterized. Preclinical toxicity and safety profiles for avibactam, along with early clinical findings, suggest no serious liabilities with avibactam alone or when used in combination with other antibiotics.

Increases in transaminase levels are expected for ATM-AVI on the basis of the aztreonam labeling. In Section 4.8 ("Undesirable effects") of the UK aztreonam SmPC[9], AEs of transaminases increased are listed as expected events occurring at an unknown frequency and are considered to be "usually reversing during therapy and without overt signs or symptoms of hepatobiliary dysfunction". The LiverTox aztreonam monograph (US National Library of Medicine 2017) quotes the frequency from literature of asymptomatic serum aminotransferase elevations as common during high dose, IV aztreonam therapy (10% to 38%). Although data are limited at this stage of development in the ATM-AVI clinical program, the transaminase elevations observed in the completed Studies D4910C00001 and D4910C00009/C3601001 show a similar pattern to that expected with aztreonam monotherapy, ie, generally asymptomatic, mild, and reversible. Post hoc exposure-response analyses for AST and ALT elevations in Study D4910C00001 do not suggest that avibactam contributes to the expected effect of aztreonam on AST and ALT.

Hepatitis and jaundice are also listed as expected events in the aztreonam SmPC occurring rarely (≥1/10,000 to <1/1000). Drug-induced liver injury is considered an important potential risk for ATM-AVI.

While increases in transaminase levels are not currently considered expected adverse drug reactions (ADRs) with avibactam alone, increases in transaminase levels are noted as expected ADRs for aztreonam and thus for ATM-AVI. Currently, this finding does not alter the benefit-risk profile for ATM-AVI. However, liver-related AEs and increases in serum transaminases will continue to be kept under close surveillance in the studies within the ATM-AVI clinical program and managed appropriately. This will include risk mitigation measures in the individual clinical study protocols, such as liver function test monitoring and the use of individual patient liver-specific withdrawal criteria.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ATM-AVI may be found in the investigator's brochure, which is the SRSD for this study.

3. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To investigate the PK profile of ATM and AVI after single and repeated IV infused doses of ATM-AVI.	• For plasma concentration data, the PK parameters C_{max}, AUC_6, AUC_{last}, AUC_{24}, AUC_{inf} for Day 1; C_{max}, AUC_{τ}, AUC_{last}, AUC_{24}, $AUC_{24,ss}$, AUC_{inf} for Day 4; • For urine concentration data, the PK parameter CLr.
	Secondary Endpoint(s):
	• For plasma concentration data, the PK parameters $t_{1/2}$, V_{ss}, V_z, CL, T_{max}, $R_{ac, Cmax}$, R_{ac}.
	Tertiary Endpoint(s):
	• For plasma concentration data, the PK parameters C_{min} for Day 2, Day 3, and Day 4; • For urine concentration data, the PK parameters Ae_t, Ae_t%.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To investigate the safety and tolerability of ATM-AVI as single and repeated intravenous (IV) infusions in healthy Chinese participants.	• Safety and tolerability as assessed by adverse events (AEs), physical examination, vital signs, ECGs, and laboratory assessments.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, single center, open label study to assess the PK, safety and tolerability of ATM and AVI after single and repeated IV infusion of doses ATM-AVI in healthy Chinese participants.

Twelve (12) healthy male and female Chinese participants, aged 18 to 55 years, inclusive, will be recruited in this study in order to have at least 9 participants complete the study procedures and have sufficient post-dose PK samples to calculate PK parameters.

The study will consist of a screening phase, a treatment phase and a follow-up phase. All screening evaluations will occur within up to 28 days prior to administration of the investigational product. All participants will provide informed consent and undergo screening evaluations to determine their eligibility. Eligible participants will check into the Clinical Research Unit (CRU) on Day -1. Participants will receive a 3 hour IV infusion of 1500 mg ATM plus 500 mg AVI as a single dose on Day 1. 24 hrs later (Day 2), participants will receive a loading/extended loading dose followed by multiple maintenance doses of ATM-AVI IV infusion. The loading dose in this study 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 3 hour period. Three (3) hours after the extended loading dose is completed, a maintenance dose of 1500 mg ATM and 500 mg AVI will be infused over 3 hours and administered q6h.

Serial blood samples and urine samples at specified intervals will be collected pre-dose and for 24 hours following the single dose administration on Day 1 and final maintenance dose administered on the morning of Day 4 for PK assessments. PK samples will also be collected 0.5 and 3.5 hours after start of loading dose on Day 2 as well as trough samples collected just prior to administration of specific maintenance doses (please refer to Schedule of Activities.

Participants will be monitored for safety during the screening and treatment phases and at least 28 and up to 35 calender days after the last dose of investigational product.

The total participation time for each participant in this study will be up to 68 days.

4.2. Scientific Rationale for Study Design

Currently, a Phase 1 (D4910C00001) and a Phase 2a (D4910C00009/C3601001) study are completed, and a pivotal Phase 3 (C3601002) study is ongoing, and a Phase 1 study in the participants with renal impairment (C3601006) and a supplemental Phase 3 (C3601009) study is planned.

In order to facilitate development of ATM-AVI in China, this study will investigate the PK, safety and tolerability after single and repeated IV infused doses of ATM with AVI to healthy male and female Chinese participants. This study will be the first time to investigate PK profile of ATM when dosed in combination with AVI, evaluate the PK exposure of ATM

when combined with AVI, and determine safety and tolerability of this combination in Chinese participants. No control or reference group is needed, and no blinding is needed.Among enrolled participants, the number of female or male participants should be no less than 1/3 of the total participants. In order to investigate comprehensively ATM-AVI PK characteristics of Chinese participants, and confirm whether there are differences between participants of different genders.

Human reproductive safety data are limited for ATM and AVI, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Female participants with childbearing potential are permitted to join the study. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

Blood and urine are to be collected for PK parameter calculations, including renal clearance of ATM and AVI.

4.3. Justification for Dose

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 (ATM:AVI=3:1)_. The ATM-AVI doses for this Phase I study have been selected based on pre-clinical and clinical data on ATM-AVI, using PK data for aztreonam, avibactam and ATM-AVI and including covariate information collected in healthy participants and as presented in the Investigator's Brochure. Furthermore, PK and safety data together with PK/PD modelling results obtained during development of the new ceftazidime-avibactam (CAZ-AVI) combination product Zavicefta have been taken into account.[8]

At the time of dose selection for the start of this study, PK data for both ATM and AVI were available from a Phase I study with 66 healthy volunteers and a Phase 2a study receiving ATM-AVI (D4910C00001 and D4910C00009/C3601001 as displayed in the Investigator's Brochure) and were used in development of a population PK model.

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. On Day 1, participants will receive a 3 hour IV infusion of a single dose of 1500 mg ATM plus 500 mg AVI. On Day 2, participants will receive a loading/extended loading dose followed by multiple doses of ATM-AVI IV infusion. The loading dose 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 3 hour period. Three (3) hours after the extended loading dose is completed, a maintenance dose of 1500 mg ATM and 500 mg AVI will be infused over 3 hours and administered q6h till morning of Day 4.

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 pharmacokinetic/pharmacodynamic

(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 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 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 creatinine clearance [CL_{CR}] >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.

The PK of ATM and AVI observed in the cIAI patients in Phase 2a study (D4910C00009/C3601001) confirm the maintainance dosing regimen of 1500 mg ATM/500 mg AVI infused over 3 hours q6h for further evaluation in the Phase 3 program.

4.4. Stopping Rules

Participants may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment;
- Positive pregnancy test at any time during the study;

- Occurrence of an AE or any other condition posing a risk to a participant or jeopardizing a safe continuation of the study treatment for the respective participant (as judged by the investigator, and/or the national coordinators, and/or the Medical Monitor and the Study Sponsor).
- Hepatic disorder:
  - alanine aminotransferase (ALT) >3x upper limit of normal (ULN);
  - alkaline phosphatase (ALP) >2x ULN;
  - Total bilirubin >2x ULN.
- Severe non-compliance to study protocol;
- Incorrect enrollment;
- Subject lost to follow-up.

4.4.1. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled follow-up (can be via a phone call) shown in the SCHEDULE OF ACTIVITIES, and the investigator has reviewed the final safety data and have determined that no additional evaluation is required.
The end of the study is defined as the date of the last follow-up (can be via a phone call) of the last participant shown in SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants 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 participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Investigators should keep a record, ie, subject screening log, of volunteers who entered prestudy screening.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Healthy Chinese female participants and/or male participants who, at the time of signing ICD, are between the ages of 18 and 55 years, inclusive. Among enroll participants, the number of female or male participants should be no less than 1/3 of the total participants.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), or clinical laboratory tests.

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

    Weight:

4. Body mass index (BMI) of 17.5 to 30.5 kg/m^2 (both not inclusive); and a total body weight >50 kg (110lb).

    Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

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

2. Known history of severe allergy to betalactam and/or L-arginine. History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the principal investigator (PI) or history of hypersensitivity to drugs with a similar chemical structure or class to ATM or AVI. History of food allergy.

    - Allergy is a disorder characterized by an adverse local or general response from exposure to an allergen. The serious allergy includes anaphylaxis, angioedema and bronchospasm, hypersensitivity or any serious reactions. Hypersensitivity is an inappropriate immune response to generally harmless antigens, representing a continuum from minor to severe manifestations. Assessment of allergy/hypersensitivity are based on investigator's discretion[10].

3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks prior to the first administration of IP.

4. Current evidence of drug abuse or history of drug abuse within one year of enrollment, and/or positive results of urine drug and alcohol test at screening and at admission.

5. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a regular rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

6. Use within 14 days (or 5 half-lives, whichever is longer) prior to the first study dose or intended use of any over-the-counter (including St. John's Wort or any herbal products) or prescription medication.

7. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 30 days (on the condition that 5 half-lives of the compound is <30 days) of screening in this study. The period of exclusion begins at the time of the last follow-up visit of the prior study.

8. Has participated in a clinical study of a biologic within 6 months of screening.

9. Treatment in the previous 3 months with any drug with well defined toxicity potential to a major organ.

10. Presence or sequelae of liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.

11. Participant has known Clostridium difficile associated diarrhea.

12. Estimated Creatinine clearance ≤80 mL/min calculated by Cockcroft-Gault equation. CL_{CR} will be calculated when the participants are selected according to exclusion criteria in the SoA.

$$\text{Males: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight})}{(72 \times \text{mg/dl serum creatinine})}$$

$$\text{Females: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight}) \times 0.85}{(72 \times \text{mg/dl serum creatinine})}$$

13. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If the baseline uncorrected QT interval is >450 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

14. Any clinically significant abnormalities in physical examination, ECG, clinical chemistry, hematology, coagulation, or urinalysis results, as judged by the Investigator. If the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) /total bilirubin (TBili)/alkaline phosphatase (ALP) is greater than 1.0 × ULN, activated partial thromboplastin time (aPTT), prothrombin time (PT) and/or international normalized ratio (INR) >1.0 × ULN at screening, the volunteer must be excluded and deemed a screen failure. Healthy volunteers with clinically determined Gilbert's syndrome must be excluded.

15. Abnormal vital signs, after 5 minutes supine rest, defined as any of the following:

    - Systolic blood pressure (SBP) >140 mmHg;
    - Diastolic blood pressure (DBP) >90 mmHg;
    - Pulse rate <40 or >99 beats per minute.

16. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol

(Section 10.4.4) for the duration of the study and for at least 28 days after the last dose of investigational product.

17. Known history of past or current epilepsy or seizure disorders, excluding febrile seizures of childhood.

18. Use any of prescription or nonprescription drugs or 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 participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

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

    The dietary supplements include such ingredients as vitamins, minerals, herbs, amino acids, and enzymes according to FDA website[11].

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

20. Smoker of more than 5 cigarettes/day or equivalent use of nicotine products during the previous 3 months.

21. Consumption of grapefruit or grapefruit-containing products within 7 days of the first study dose.

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

23. History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed.

24. Unwilling or unable to comply with the criteria in the Life Considerations (Section 5.3) of this protocol.

25. Participants 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 participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

26. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants 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 prior to administration of the single dose on Day 1 or final dose on Day 4 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.

- Participants 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 meals for all participants should be standardized meals provided by CRU.

5.3.2. Alcohol, Caffeine, Tobacco and Others

- Participants 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. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Energy drinks containing taurine or glucuronolactone eg, Red Bull from 72 hours before admission and during the residential periods.

- Refrain from consumption of xanthine-containing foods or beverages (including all caffeine-containing products) within 24 hours preceding investigational product infusion until collection of the final PK sample of each study period, and at least 3 hours prior to ECG evaluations.

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

5.3.3. Activity

Participants 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.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual

participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4)and will confirm that the participant 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 participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants 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 participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For this study, the investigational product(s) are avibactam and aztreonam.

Investigational product will be prepared using standard aseptic IV infusion preparation using saline. An IV infusion will be used.

6.1. Study Intervention(s) Adiministered

6.1.1. Dosage Form and Packaging

Aztreonam and avibactam will be provided by Pfizer 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]) at CRU.

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

Table 1. Identity of Investigational Product

Investigational Product [a]	Dosage form and strength
Aztreonam	Aztreonam for injection, powder for solution for infusion 2 g.
Avibactam	Avibactam lyophilisate for concentrate for solution for infusion 600 mg.

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.

6.1.2. Administration

Participants will receive the single dose of the investigational product on Day 1. No fasting is required in respect to dosing as ATM-AVI is administered intravenously. Fasting will only be required prior to safety laboratory and ECG assessments (see Section 5.3). The single dose administration on Day 1 needs to occur in morning to allow 24 hours for sample collection prior to start of Day 2 dosing.

On Day 2, 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 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	Infusion Duration Time (5 minutes)	Dosing regimen
1	3 hr	Single dose infusion (1500/500 mg ATM-AVI)
2	30 min	IV loading dose infusion (500/167 mg ATM-AVI)[a]
	3 hr	3 hr IV extended loading (1500/500 mg ATM-AVI)[a]
	3 hr	IV maintenance infusion q6h (1500/500 mg ATM-AVI) (×2)
3	3 hr	IV maintenance infusion q6h (1500/500 mg ATM-AVI) (×4)
4	3 hr	IV maintenance infusion q6h (1500/500 mg ATM-AVI) (×2)

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

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

The start and stop time of the infusion will be recorded. Time 0 is the time when the investigational product infusion begins. The infusion rate and volume infused will be recorded. The full contents of the infusion bag must be administered.

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

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual or other specified location.

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

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the Investigational Product Accountability Log (IPAL) or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

Refer to 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. A second staff member will verify the dispensing.

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject 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, participantin accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator will assign subject numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

This identifying number will be retained throughout the study. All participants enrolled will receive 4 days of IV ATM-AVI according to the dose/schedule provided in the Section 6.1.2.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

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

Participants must not receive any antipyretic medications on Day -1 prior to the body temperature assessments.

Participants must not receive any premedications for the purpose of suppressing infusion related reactions.

Fever or chills should not routinely be managed with any antipyretic medications unless body temperature is greater than or equal to 38°C (ie, ≥ Grade 1 Common Terminology Criteria for Adverse Events ([CTCAE], v5.0) and/or clinically indicated in the opinion of the investigator.

Participants will abstain from all concomitant treatments, except for the treatment of AEs. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants 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.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following :safety consideration, or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for a complete early discontinuation visit. See the SCHEDULE OF ACTIVITIES for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, post-treatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SCHEDULE OF ACTIVITIES for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this

information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.2.2. Participant Replacement

Participants who do not receive the full dose of ATM-AVI, for whom significant protocol violations are identified or who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the Sponsor.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SCHEDULE OF ACTIVITIES. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SCHEDULE OF ACTIVITIES, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

Participants screened for another study may participate in this study provided they meet the participant selection criteria and informed consent for this study is obtained by the investigator, or delegate. Screening data from another study will be considered sufficient if those data satisfy the requirements of this protocol. Procedures required by this protocol will only be done if they were not performed as part of the requirements for the other study.

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 participant. 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 the study period described in the SoA, 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/body temperature (if applicable): 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 body temperature) should be collected prior to the insertion of the catheter. Below blood sample collection requirements are applicable to all related

procedures during the study. **Blood samples must be drawn from the arm contralateral to the arm in which the infusion will be administered. In no case may blood samples be obtained via the catheter through which the investigational product was administered.**

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.

The total blood sampling volume for male participants in this study is approximately 176 mL, and is approximately 186.5mL for female participants of childbearing potential (another 10.5mL may be collected for Serum β-hCG test) or 179.5mL for female participants who are amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause (another 3.5mL for FSH test). And if the blood sample is collected with in-dwelling catheter, 1ml of blood will be discarded before sample collection. The actual collection times of blood sampling may change from SoA. Additional blood samples may be taken for safety assessments at times specified by Pfizer or at the discretion of investigators, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.
To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations (Section 5.3) and Concomitant Therapy (Section 6.5) of the protocol.

8.1. Efficacy Assessment

Not applicable.

8.2. Safety Assessment

Planned time points for all safety assessments are provided in the SCHEDULE OF ACTIVITIES. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SCHEDULE OF ACTIVITIES for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SCHEDULE OF ACTIVITIES. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be

repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.2. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SCHEDULE OF ACTIVITIES. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.3. Physical Examinations

A complete physical examination will include, at a minimum, general check (including head, ears, eyes, nose, mouth), skin and musoca, chest examination (including heart and lung examinations), lymph nodes, and gastrointestinal, musculoskeletal (limbs and spine), and neurological systems.

A limited physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician.

8.2.4. Weight and Height

Height and weight will also be measured and recorded as per the SCHEDULE OF ACTIVITIES. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants 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.

8.2.5. Vital Signs

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

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg after approximately 5 minutes of supinerest. As much as possible, the same arm (preferably the dominant arm) will be used throughout the study. BP should not be taken from the arm with an intravenous infusion. Participants 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.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

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

8.2.6. Electrocardiogram

12-Lead ECGs should be collected at times specified in the SoA of this protocol.

All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained within approximately 2 to 5 minutes; the average of the triplicate ECG measurements collected at nominal time point on Day 1 will serve as each participant's time-controlled baseline QTc value.

To ensure safety of the participants, 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 the average of QTc values from the triplicate measurements 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 participant 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.

ECG values of potential clinical concern are listed in Appendix 6.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant'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.

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

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Non-Serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or infusion.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and untilthe pregnancy completion (or until pregnancy terminaiton).

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant 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.

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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. 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 including 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 study intervention.

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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so 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.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant 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.

8.3.6. Cardiovascular and Death Events

Not applicable

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.3.8. Adverse Events of Special Interest

Not applicable

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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 within 24 hours.

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 nonserious, are recorded on the 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. Treatment of Overdose

For this study, any dose of ATM or AVI in excess of that specified in Table 2, Treatment Schema will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety only when associated with an SAE.

5. Obtain a blood sample for PK analysis within 24h from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of ATM-AVI

Whole blood samples (4 mL, with exception of additional 6 mL of the pre-dose blood sample only on Day 1 for evaluation of the matrix effect on the bioanalyticalmethod and validation) to provide a minimum of 1.5 mL plasma for PK analysis will be collected into appropriately labeled tubes containing Sodium Fluoride/Potassium Oxalate at times specified in the SoA of the protocol. Sample handling details 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 (eg, CRF). Pre-dose PK samples on Day 1 should be taken no more than 1 hour prior to infusion. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to 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 the data collection tool (eg, CRF).

- Samples will be used to evaluate the PK of ATM and AVI. The only exception was the10 mL pre-dose blood sample collected in Day 1, which will be divided into 2 tubes (1 tube contains 4 mL to evaluate PK of ATM and AVI, and 1 tube contains 6mL to evaluate the matrix effect on the bioanalytical method evaluation and validation).

- Samples collected for analyses of ATM and AVI plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will not be included in the CSR.

- Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

- Samples collected for measurement of plasma concentrations of ATM and AVI will be analyzed using a validated analytical method in compliance with applicable 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.

8.5.2. Urine for Analysis of ATM-AVI

Urine will be collected at times specified in the SoA of the protocol. Each participant will empty his or her bladder just prior to dosing on Day 1 and Day 4. On day 1, approximately 20 mL of pre-dose blank urine sample will be collected for bioanalytical method evaluation and validation as appropriate. On Day 4, approximately 10 mL of pre-dose (last maintance dose) urine sample will be collected for PK analysis.Each participant will be instructed to void into the collection container at the end of each collection period. Samples obtained within 10% of the nominal time interval (eg, ±12 minutes when collection urine PK sample within 120 minutes) 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 (eg, CRF).

Samples will be analyzed using a validated analytical method in compliance with Pfizer and vendor SOPs. Sample handling details are provided in the Laboratory Manual.

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 ATM and AVI, 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.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Sample Size Determination

There is no statistical hypothesis for this study, therefore, the study sample size is not based on statistical calculations. The sample size has been chosen based on the need to fulfill the National Medical Products Administration (NMPA) requirement for a PK study to support the registration in China. A sufficient number of participants will be screened to achieve 12 participants enrolled to study intervention and at least 9 participants complete the study procedures and have sufficient post-dose PK samples to calculate PK parameters.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Pharmacokinetics	The PK concentration population is defined as all enrolled and treated participants who have at least 1 ATM and AVI concentration. The PK parameter population is defined as all enrolled and treated participants who have at least 1 of the ATM and AVI PK parameters of interest.
Safety	All participants enrolled to study intervention and who take at least 1 dose of study intervention (ATM-AVI). Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

9.4.1. General Considerations

Aztreonam (ATM) and AVI PK parameters partial AUC, area under the plasma concentration-time profile from time 0 to 6 hours [AUC_6] and area under the plasma concentration-time profile from time 0 to 24 hours [AUC_{24}] for Day 1, area under the plasma concentration-time profile from time 0 to to the time of the end of the dosing interval (τ) (AUC_τ), total daily area under the plasma concentration-time profile from time 0 to 24 hours at steady-state ($AUC_{24,ss}$) for Day 4, area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}), area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration (C_{last}) (AUC_{last}), maximum observed plasma concentration (C_{max}), time for C_{max} (T_{max}), 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}), accumulation ratio for C_{max} ($R_{ac,Cmax}$): C_{max} (Day 4)/C_{max} (Day 1), accumulation ratio for AUC following multiple dosing (R_{ac}), total amount of unchanged drug excreted in the urine over dosing interval [Ae_t], total amount of unchanged drug excreted in the urine over dosing interval, expressed as percent of dose [Ae_t %] will be summarized descriptively for Day 1 and Day 4. Minimum observed plasma concentration (C_{min}) for Day 2, Day 3, and Day 4 will be summazied.

Concentrations will be listed and summarized descriptively by PK sampling time for Day 1 and Day 4. Summary profiles (means and medians) of the concentration-time data will be plotted for Day 1 and Day 4. Individual participant 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 participant plots by time, the actual PK sampling time will be used.

CCI [redacted]

Safety data (AEs, vital signs, ECGs and laboratory data) will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

9.4.2. Pharmacokinetics Endpoints

9.4.2.1. Plasma PK

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

Parameter	Definition	Method of Determination
AUC_6	Area under the plasma concentration-time profile from time 0 to 6 hours	Linear/Log trapezoidal rule

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration-time profile from time 0 to 24 hours	Linear/Log trapezoidal rule
$AUC_{24,ss}$	Total daily area under the plasma concentration-time profile from time 0 to 24 hours at steady-state	AUCτ*4
AUC_{last}	Area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal rule
AUC_{τ}	Area under the plasma concentration-time profile from time 0 to to the time of the end of the dosing interval (τ), where τ=6 hours	Linear/Log trapezoidal rule
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	AUC_{last} + (C_{last}*/k_{el}), where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum observed plasma concentration	Observed directly from data
C_{min}	Minimum observed plasma concentration during dosing interval	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
CL[a]	Clearance	Dose/AUC_{inf}
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression through at least 3 data points in the terminal phase 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
V_{ss}[a]	Apparent volume of distribution at steady-state	Volume of distribution at steady state is calculated as: $V_{ss} = CL \times MRT$
V_z[a]	Apparent volume of distribution during terminal phase	Dose /(AUC_{inf}*k_{el})
$R_{ac, Cmax}$	Accumulation ratio for C_{max}	C_{max} (Day 4)/C_{max} (Day 1)
R_{ac}	Accumulation ratio for AUC_{τ} following multiple dosing	AUC_{τ} (Day 4) /AUC_6 (Day 1)

a. If data permit.

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

9.4.2.2. Urine PK

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

Parameter	Definition	Method of Determination
Ae_t	Total amount of unchanged drug excreted into urine from time 0 to time t.	Sum of amount excreted for each collection period. Calculated as the product of the urine volume and the urine concentration. The amount will be calculated and reported for each collection interval and cumulatively.
Ae_t%	Total amount of unchanged drug excreted in the urine from time 0 to time t, expressed as percent of dose.	$100 \times (Ae_t/Dose)$.
CL_r	Renal clearance.	Ae_t/AUC_t for single dose; Ae_τ/AUC_τ at steady-state on Day 4.

9.4.3. Safety Endpoints

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

Medical history and physical examination and neurological examination information, as applicable, 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.

9.5. Interim Analysis

No formal interim analysis is planned 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.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 study intervention, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant 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 medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' 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 will 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 participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), 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 results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts results on EudraCT for all Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

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 the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the study monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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 Investigator Site Master File.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant 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 participant'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 participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SCHEDULE OF ACTIVITIES section 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 issues.

Table 3. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis[a]	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) or carbondioxide combining power (CO_2CP) 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[b]	Urine drug screening[c] β-hCG[d] FSH[e] **Serology**[f] panel to include: • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C core antibody • Human immunodeficiency virus
	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		

Table 3. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis[a]	Other

a. Obtain a fresh 10 mL urine sample for urinalysis.
b. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site specific).
d. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
e. Only females who are amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause.
f. Serology at screening only, additional 7 mL blood sample required.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • 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.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. 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.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4 Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3);

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

- Documented hysterectomy;

- Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

    - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

    - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

4. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

5. Intrauterine device.

6. Intrauterine hormone-releasing system.

7. Bilateral tubal occlusion.

8. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

9. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

10. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

11. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede 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 laboratory 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 participant's individual baseline values and underlying conditions. Participants 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:

- Participants 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 participants 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 participant 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 for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. 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/paracetamol (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) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.7. Appendix 7. Abbreviations

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

Abbreviation	Term
Abs	absolute
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
Ae_t	total amount of unchanged drug excreted in the urine from time 0 to time t
Ae_t%	total amount of unchanged drug excreted in the urine from time 0 to time t, expressed as percent of dose
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AmpC	A Class C β-lactamase (Amp = ampicillin)
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATM	aztreonam
ATM-AVI	aztreonam-avibactam
AUC	area under the curve
AUC_6	area under the plasma concentration-time profile from time 0 to 6 hours
AUC_{24}	area under the plasma concentration-time profile from time 0 to 24 hours
$AUC_{24,ss}$	total daily area under the plasma concentration-time profile from time 0 to 24 hours at steady-state
AUC_τ	area under the plasma concentration-time profile from time 0 to to the time of the end of the dosing interval (τ)
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration (C_{last})
AUC_{ss}	area under the curve at steady-state
AV	atrioventricular
AVI	avibactam
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

Abbreviation	Term
C-G	Cockcroft-Gault
CAZ	ceftazidime
CAZ-AVI	ceftazidime-avibactam
CFR	Code of Federal Regulations
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CL_{CR}	creatinine clearance
CLr	renal clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CO_2	carbon dioxide (bicarbonate)
CO_2CP	carbondioxide combining power
CRE	carbapenem resistant *Enterobacte*
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
$C_{ss,max}$	observed maximum plasma concentration at steady state
$C_{ss,min}$	observed minimum plasma concentration at steady state
C_T	threshold concentration
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTX-M	cefotaximase-M
DBP	diastolic blood pressure
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
ESBL	extended spectrum β-lactamase
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
INR	international normalized ratio
IP	investigational product
IP Manual	Investigational Product Manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
KPC	Klebsiella pneumonia carbapenemase
LBBB	left bundle branch block
LFT	liver function test
LSLV	last subject last visit
MBL	metallo-β lactamase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multiple-drug resistant
MIC	minimum inhibitory concentration
N/A	not applicable
NDM	New Delhi Metallo-β-lactamase
NMPA	National Medical Products Administration
OAT	organic anion transporter
OXA	oxacillinase
PCD	primary completion date
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

Abbreviation	Term
QTc	corrected QT interval
QTcF	QTcF corrected using the Fridericia's formula
qual	qualitative
RAUC	accumulation ratio for AUC following multiple dosing
RBC	red blood cell
RC_{max}	accumulation ratio for C_{max} (RC_{max}): C_{max} (Day 4)/C_{max} (Day 1)
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCr	serum creatinine
SmPC	Summary of Product Characteristics
SOA	schedule of activities
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}
UK	United Kingdom
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
WOCBP	woman of childbearing potential

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