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A Phase IIa prospective, open-label, multicenter study to determine the pharmacokinetics (PK) and safety and tolerability of aztreonam-avibactam (ATM-AVI) for the treatment of complicated Intra-Abdominal Infections (cIAIs) in hospitalized adults

Sponsor: *Pfizer Inc., 235 East 42nd Street, New York, NY 10017, USA (as of Amendment 3)*

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	**Date of Amendment**	**Local Amendment No:**	**Date of Local Amendment**
1	31 March 2016		
2	05 August 2016		
3	29 March 2017		

Administrative Change No.	**Date of Administrative Change**	**Local Administrative Change No.**	**Date of Local Administrative Change**

The clinical study protocol is publicly registered and the results are disclosed and/or published in compliance with the sponsor and COMBACTE-CARE publication policies and in

compliance with prevailing laws and regulations. COMBACTE-CARE is a consortium of 19 academic and 3 pharmaceutical partners focussing on carbapenem resistance in Europe.

PROTOCOL SYNOPSIS

A Phase IIa prospective, open-label, multicenter study to determine the pharmacokinetics (PK) and safety and tolerability of aztreonam-avibactam (ATM-AVI) for the treatment of complicated Intra-Abdominal Infections (cIAIs) in hospitalized adults adults

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Study sites and number of patients planned

This will be a multicenter study enrolling 40 hospitalized patients (18 to 90 years of age, inclusive) with a diagnosis of complicated intra-abdominal infection (cIAI). There will be an early safety and PK review after 10 patients having completed all safety and PK assessments. The trial is planned to be performed in study centers in France, Germany and Spain.

Study period		Phase of development
Estimated date of first subject enrolled	First quarter 2016	Phase IIa
Estimated date of last subject completed	Fourth quarter 2017	Phase IIa

Study design

This is a prospective, open-label, single-arm, dose-confirming multicenter study to determine the pharmacokinetics (PK), safety and tolerability of aztreonam-avibactam (ATM-AVI) in the treatment of hospitalized patients with a complicated intra-abdominal infection (cIAI). Forty adult patients with a diagnosis of cIAI and the need for a surgical intervention will be enrolled. The surgical intervention may take place within 24 hours before or after administration of the first dose of study drug. After obtaining written informed consent and confirming eligibility, patients will be assigned the following treatment:

From the study start, only patients with normal renal function or mild renal impairment (i.e. creatinine clearance >50 mL/min) will be eligible (Cohort 1). The proposed administration of ATM-AVI for these patients is a loading dose (500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period), immediately followed by a maintenance infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period (to be administered every 6 hours). The targeted total dose on Day 1 will be 6500 mg ATM and 1777 mg AVI. From Day 2 onwards, this will be 6000 mg ATM / 1640 mg AVI. For anaerobic coverage, patients will also receive 500 mg metronidazole infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion.

The PK, safety and tolerability of the dosing regimen described above will be assessed in Cohort 1. Recruitment into this initial cohort of patients will continue until 10 patients with creatinine clearance (CrCl) >50 mL/min have completed all scheduled safety and PK assessments. Upon completion, an early patient review regarding safety and PK data will be made. Patient safety laboratory data will be monitored on ongoing basis and a summary output will be available for the 10 patients. There will be a pause in enrolment to complete the ongoing safety review and provide confirmation that the study can proceed beyond Cohort 1, based on the available safety data. Patients with moderate renal impairment (creatinine clearance of 31 to 50 mL/min) must not be included prior to the completion of the 10 patient early safety and PK review and subsequent confirmation of an appropriate dosing regimen.

Following review of safety and PK data from Cohort 1, the Scientific Advisory Committee (SAC) will make recommendations to either;

- Discontinue the study
- Initiate Cohort 2 - continue dosing with no dose change (compared to Cohort 1) or escalate to a higher AVI dose.
    - The SAC will also have an opportunity to recommend recruitment of patients with moderate renal impairment, and select an appropriate dose regimen, taking into account the dose to be used in Cohort 2.

In the event that a higher AVI dose will be administered in Cohort 2, all patients with normal renal function or mild renal impairment (CrCl > 50 mL/min) will receive a loading dose (500 mg ATM plus 167 mg AVI by intravenous [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 every 6 hours (maintenance infusion). Patients will also receive 500 mg metronidazole infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion.

In the event a higher AVI dose will be administered in Cohort 2, a second safety and PK review will occur once at least10 patients in Cohort 2 have completed all safety and PK assessments. There will be another pause in enrolment at this time to complete the second safety and PK review and provide confirmation that the study can proceed, based on the available safety data. The SAC will make recommendations for the continuation of the study, i.e., to continue treating patients in Cohort 3 at the higher AVI dose, or to de-escalate the AVI dose in Cohort 3 according to the dose regimen used for Cohort 1.

For all cohorts, intravenous study therapy (ATM-AVI plus metronidazole) will be continued for a period of time (5 to 14 full days, where a full day is defined as a 24-hour period) deemed appropriate by the investigator based on the patient's clinical response. After at least 5 full days of IV study therapy and at the discretion of the investigator, all study therapies may be discontinued if the patient has shown significant clinical improvement.

All patients will undergo sparse pharmacokinetic sampling on Day 1 of treatment. On Day 4 (± 1 day if required), the first twenty five (25) patients will undergo intensive pharmacokinetic sampling, whereas the following fifteen (15) patients will undergo sparse sampling.

Study periods are defined in the following table.

Study periods

Eligibility/Screening	
Visit 1 (Eligibility/Screening)	Day 0
Treatment period [a]	
Visit 2 (baseline assessments and Day 1 of study therapy)	Day 1
Visits 3 to 15 (Days 2 to 14)	Ongoing study therapy
Visit 16 (End of Treatment with study therapy)	Within 24 hours after the completion of the last infusion of the intravenous study therapy
Follow-up period	
Visit 17 (Test of Cure)	Day 25 visit (allowed visit window: Day 22 - 28)
Visit 18 (Late Follow-up)	Day 35 visit (allowed visit window: Day 32 - 38)

[a] : Treatment period is defined as a minimum of 5 full days to a maximum of 14 full days, where a full day is defined as a 24-hour period. Treatment period starts with administration of the first dose of intravenous study therapy which marks the beginning of Study Day 1. Visit 2 includes the baseline assessments and Day 1.

Objectives

Primary Objectives:	Outcome Measure:
To determine the pharmacokinetics (PK) of ATM-AVI in this patient population	• Concentrations of ATM and AVI in plasma; concentration-time profile of ATM and AVI • The derived PK parameters C_{max}, t_{max}, $AUC_{(0-6)}$, $AUC_{(0-last)}$, t_{last}, $t_{1/2}$, V_{ss}, V_z and CL for the patients undergoing intensive sampling on Day 4
To assess the safety of ATM-AVI in this patient population	Safety and tolerability as assessed by adverse events, physical examination, vital signs, ECGs, and laboratory assessments
Secondary Objectives:	
To assess the treatment outcome per patient at the test of cure (TOC) visit	Proportion of patients with clinical cure at the TOC visit
To assess the relationship between exposure and clinical cure for ATM-AVI	Correlation of derived PK parameters for ATM-AVI and clinical cure at TOC
Exploratory Objective:	
To develop and evaluate pharmacokinetic / pharmacodynamic (PK/PD) models (Nonlinear Mixed Effect Model analysis [NONMEM], simulation) and to characterize population PK	Estimates of model parameters and their precision, goodness-of-fit, individual and mean predictions

Target subject population

Forty adult patients (18 to 90 years of age, inclusive) with a diagnosis of complicated intra-abdominal infection and the need for a surgical intervention will be enrolled.

Duration of treatment

Intravenous study therapy (ATM-AVI) plus metronidazole will be continued for a period of time (5 to 14 full days, where a full day is defined as a 24-hour period) deemed appropriate by the investigator based on the patient's clinical response. After at least 5 full days of IV study therapy and at the discretion of the investigator, all study therapies may be discontinued if the patient has shown significant clinical improvement. Thus, the total expected duration of the study for a patient is 32 to 39 days, depending on the exact timing of Visit 1 and Visit 18 (see above).

Investigational medicinal product (IMP), dosage and mode of administration

IMP	Dosage form and strength
Avibactam	Avibactam lyophilisate for concentrate for solution for infusion 600 mg
Aztreonam	Aztreonam powder for solution for infusion 2 g or 1 g
Metronidazole	Metronidazole 500 mg / 100 ml solution for infusion

The Investigational Medicinal Products (IMPs) ATM and AVI will be supplied in vials. The IMP ATM-AVI will be prepared using standard aseptic intravenous infusion preparation using saline. The IMP Metronidazole will be supplied in infusion bags. All IMPs will be administered by intravenous infusion.

Patients in Cohort 1 with creatinine clearance >50 mL/min will receive a loading dose (500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period), immediately followed by maintenance infusions of 1500 mg ATM plus 410 mg AVI over a 3 hour period every 6 hours. The targeted total dose on Day 1 will be 6500 mg ATM and 1777 mg AVI. For the following (full) days, this will be 6000 mg ATM / 1640 mg AVI.

In the event that a higher AVI dose will be administered in Cohort 2, patients with normal renal function or mild renal impairment (CrCl > 50 mL/min) will receive a loading dose (500 mg ATM plus 167 mg AVI by intravenous [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 every 6 hours (maintenance infusion).

Patients in Cohort 2 with moderate renal impairment (CrCl 31 - 50 mL/min) will receive either;

- A loading dose consistent with Cohort 1 (500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period), immediately followed by an extended loading infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period. The subsequent maintenance infusions (starting 3 hours after stop of the second loading infusion) will be 750 mg ATM plus 205 mg AVI over a 3 hour period (to be administered every 6 hours). The targeted total dose on Day 1 will be 4250 mg ATM:500 mg (loading dose) + 1500 mg (extended loading infusion) + 3x 750 mg = 2250 mg (maintenance infusion) and 1162 mg AVI: 137 mg (loading dose) + 410 mg (extended loading infusion) + 3x 205 mg (maintenance infusion). From Day 2 onwards, the targeted total daily dose will be 3000 mg ATM (4x 750 mg maintenance infusion) / 820 mg AVI (4x 205 mg maintenance infusion).

Or

- A loading dose consistent with a higher AVI dose in Cohort 2 (500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period), immediately followed by an extended loading infusion of 1500 mg ATM plus 500 mg AVI over a 3 hour period. The subsequent maintenance infusions (starting 3 hours after stop of the second loading infusion) will be 750 mg ATM plus 250 mg AVI over a 3 hour period (to be administered every 6 hours). The targeted total dose on Day 1 will be 4250 mg ATM: 500 mg (loading dose) + 1500 mg (extended loading infusion) + 3x 750 mg = 2250 mg (maintenance infusion) and 1417 mg AVI: 167 mg (loading dose) + 500 mg (extended loading infusion) + 3x 250 mg (maintenance infusion). From Day 2 onwards, the targeted total daily dose will be 3000 mg ATM (4x 750 mg maintenance infusion) / 1000 mg AVI (4x 250 mg maintenance infusion).

Overview: Proposed ATM-AVI dosing regimens			
	Loading dose	**Extended loading infusion**	**Maintenance infusion**
Patients in Cohort 1 with normal renal function or mild renal impairment (CrCl > 50 mL/min)	500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period	Not applicable	1500 mg ATM plus 410 mg AVI over a 3 hour period (to be administered every 6 hours)
Patients in Cohort 2 & 3 with normal renal function or mild renal impairment (CrCl > 50 mL/min)	500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period	Not applicable	1500 mg ATM plus 410 mg AVI over a 3 hour period (to be administered every 6 hours)
	Or		
	500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period)	Not applicable	1500 mg ATM plus 500 mg AVI over a 3 hour period (to be administered every 6 hours)
Patients in Cohort 2 & 3 with moderate renal impairment (CrCl 31 - 50 mL/min)	500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period	Extended loading infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period	750 mg ATM plus 205 mg AVI over a 3 hour period (to be administered every 6 hours)
	Or		
	500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period	Extended loading infusion of 1500 mg ATM plus 500 mg AVI over a 3 hour period	750 mg ATM plus 250 mg AVI over a 3 hour period (to be administered every 6 hours)

In the case that renal function recovers or deteriorates (i.e., local or central lab results show CrCl increases from 31 – 50 mL/min at baseline to >50 mL/min, or decreases from >50 mL/min at baseline to 31 – 50 mL/min) during the treatment period, the dose of ATM-AVI should be adjusted by the investigator to meet the applicable dose regimen, based on the latest CrCl value.

In addition, anaerobic coverage for cIAI will be provided for all patients by administration of 500 mg metronidazole, infused over 1 hour. Metronidazole will be administered every 8 hours, starting after the first ATM-AVI maintenance infusion and maintained until end of study therapy.

Statistical analyses

Up to 40 patients will be enrolled into the study in total. Although the study is not powered to perform statistical tests, assessment of safety, and complete PK assessments from at least 30 patients with cIAI, is considered sufficient to adequately confirm the PK and safety profile of ATM-AVI in a population with a representative burden of disease. It is expected that 10 patients in Cohort 1 (and 10 patients in Cohort 2 if the higher AVI dose is used) having completed all safety assessments are sufficient for an initial review of key safety criteria of ATM-AVI, in order to progress with the continued treatment of patients. A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient included.

Definitions of analysis sets

The modified intent to treat (MITT) population will include all enrolled patients who receive any amount of study drug.

The microbiologically modified intent-to treat (mMITT) population is a subset of the MITT population and includes all enrolled patients who have a diagnosis of cIAI and have an intra-abdominal pathogen at baseline (regardless of susceptibility to the study drug).

The pharmacokinetic (PK) population includes all patients who have at least 1 plasma concentration data assessment available for ATM-AVI, no fundamental violations of the inclusion and exclusion criteria and no important protocol violations affecting assessment of PK as defined in the finalised Statistical Analysis Plan. The reason for exclusion will be listed for all subjects in question.

There are two efficacy analysis sets: the MITT and mMITT population. The safety analysis set is the MITT population. The PK analysis set is the PK population.

Outcome measures for analyses

The primary outcome measures will be:

- ATM and AVI concentrations in plasma (samples to be collected for 6 hours after the start of an ATM-AVI 3 hour infusion). They will be analyzed in the PK analysis set.
- Derived PK parameters C_{max}, t_{max}, $AUC_{(0-6)}$, $AUC_{(0-last)}$, t_{last}, $t_{1/2}$, V_{ss}, V_z and CL for the patients undergoing intensive sampling on day 4. They will be analyzed in the PK analysis set.
- Safety and tolerability as assessed by adverse events, physical examination, vital signs, ECGs, and laboratory assessments. They will be analyzed in the safety analysis set.

The secondary outcome measures will be:

- Proportion of patients with clinical cure at the TOC visit. This will be analyzed in the MITT and mMITT populations.
- Correlation of derived PK parameters for ATM-AVI and clinical cure at TOC. This will be analyzed in the mMITT population.

Methods for statistical analyses

The following characteristics will be summarised in the safety population: demographics (age, sex, and race), medical and surgical history, description of cIAI, baseline assessments of clinical signs and symptoms, microbiological assessment of primary infection site or blood, study therapy administration and baseline pathogens. Minimum inhibitory concentration frequencies for each infecting species isolated from either the abdominal site or blood at baseline will be reported. Pathogens isolated from cultures obtained post-baseline will be listed.

No confirmatory interim analysis is planned. However, safety and PK of the ATM-AVI dosing regimen will be assessed in an early review of the first 10 patients having completed all PK and safety assessments in Cohort 1, including a careful evaluation of patient liver transaminases. The assessment will be both a per patient assessment throughout the study period and per a cohort review. It will input to a decision on whether

(a) the study can continue and, if so

(b) the remainder of the study will continue (Cohort 2) with the same dose regimen for patients with normal renal function or mild renal impairment (CrCl >50 mL/min),

or:

(c) Cohort 2 will commence at the higher AVI dose regimen (see above) for patients with normal renal function or mild renal impairment (CrCl > 50 mL/min) and

- patients with moderate renal impairment (creatinine clearance 31-50 mL/min) should be included and administered a reduced dose to reflect the agreed dose regimen in Cohort 2.

In the event that the AVI dose is escalated in Cohort 2, a second safety and PK review of 10 patients in Cohort 2 having completed all safety and PK assessments (including Day 35) will input into the decision on whether

a) the remainder of the study will continue (Cohort 3) at the same (higher AVI dose) regimen, or:

b) the remainder of the study will continue (Cohort 3) with the lower AVI dose regimen for patients with CrCl > 50 mL/min and for patients with CrCl 31-50 mL/min, respectively (as described in section 7.2)

Analysis of the primary variables

Descriptive statistical analyses will be performed. Number of observations, arithmetic mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum will be given for quantitative variables. If reasonable, geometric mean and coefficient of variation will also be given. Absolute and relative frequencies are given for qualitative variables. If variables are measured over time, each time point will be summarized. Summaries of the number and frequency of AEs will be presented. 95% confidence intervals will be given where reasonable.

Adverse events occurring from the first dose of study therapy up to the Late Follow-up visit will be summarized by preferred term, system organ class, relationship to study therapy and severity. Summaries and listings of death, Adverse Events (AEs), Serious Adverse Events, other significant AEs, and AEs that led to discontinuation or withdrawal will be presented.

Analysis of the secondary variables

The number and percentage of patients with clinical cure (shown with 80% and 95% confidence intervals) will be tabulated for the MITT and mMITT analysis set. Key patient subgroups (e.g. the group of patients with extended-spectrum β-lactamase phenotype pathogens) will be summarised in the same way, and illustrated graphically as a forest plot.

The proportion of clinical cure at the Test of Cure visit will be determined excluding any patients with concomitant antibiotics not administered for failure (mMITT). Refer to section 7.7 for rules relating to concomitant antibiotics (mMITT).

Evaluation of the pharmacokinetics of ATM and AVI

The actual sampling times will be used in all final plasma PK parameter calculations. Pharmacokinetic parameters will be derived for the first 25 patients (undergoing intensive PK sampling on Day 4) using non-compartmental methods.

The final data may be pooled with data from other studies to conduct population PK analysis. Using these parameter estimates (mean PK parameters including inter-individual variance estimates), Monte-Carlo simulations will be undertaken and potential PK/PD relationships will be explored. A detailed population PK/PD analysis plan will be prepared prior to any such analysis/es, the results of which will be reported separately.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATM	Aztreonam
$AUC_{(0-6)}$	Area under the plasma concentration vs. time curve from time point zero up to 6 hours
$AUC_{(0-last)}$	Area under the plasma concentration vs. time curve from time point zero up to the last measured concentration above LOQ
AVI	Avibactam
β-hCG	β-human chorionic gonadotropin
bpm	beats per minute
cIAI	Complicated Intra-Abdominal Infection (see definition in section 3)
CK	Creatine kinase
CL	Clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum plasma concentration
COMBACTE-CARE	A consortium which consists of 19 academic and 3 pharmaceutical partners, focussing on carbapenem resistance in Europe
CrCl	Creatinine Clearance
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C_T	Threshold concentration
CTCC	Clinical Trial Centre Cologne, Medical Faculty University of Cologne
CTCAE	Common Terminology Criteria for Adverse Event

Abbreviation or special term	Explanation
CTX-M	A type of Class A β-lactamase (CTX = cefotaximase)
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of treatment (with intravenous therapy)
ESBL	Extended spectrum β-lactamases
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the investigator coordinating the investigators and/or activities internationally.
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LFU	Late Follow-up
LOQ	Limit of quantification
LSLV	Last Subject Last Visit
LH	Luteinizing hormone
MBL	Metallo-β-lactamases

Abbreviation or special term	Explanation
MDR	Multiple-Drug Resistant
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MITT	Modified intent-to-treat
mMITT	Microbiologically modified intent-to-treat
MRI	Moderate renal impairment
NDM	New Delhi Metallo-β-lactamase
NONMEM	Nonlinear Mixed Effect Model analysis
OXA	A type of Class D β-lactamase (OXA = oxacillin)
PET	Positron Emission Tomography
PHL	Potential Hy's Law case
PK/PD	Pharmacokinetic/Pharmacodynamic
PI	Principal Investigator
q6h	Every 6 hours
q8h	Every 8 hours
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
STAR	Staged Abdominal Repair
$t_{1/2}$	Plasma elimination half-life
t_{last}	Time of last measured concentration above LOQ
t_{max}	Time of observed maximum concentration
TOC	Test of Cure
ULN	Upper Limit of Normal
VIM	A type of Class B β-lactamase (VIM Verona Integron encoded)
V_{ss}	Apparent volume of distribution at steady state after IV administration
V_z	Volume of distribution during terminal phase after IV administration

1. INTRODUCTION

1.1 Background and rationale for conducting this study

The incidence of multiple-drug resistant (MDR) bacteria is increasing worldwide. This has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by MDR bacteria (Lucasti et al. 2013; Magiorakos et al. 2012). 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 (IMI 2015).

One of the most common resistance mechanisms in Gram-negative pathogens is the production of extended-spectrum β-lactamases (ESBL) (Lucasti et al. 2013). 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 NDM, KPC, VIM, OXA48 (Nordmann et al. 2013). The expression of metallo-β-lactamases (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 (New Delhi metallo-β-lactamases). 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 CTX-M 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 (Walsh et al. 2011).

A representative example of a serious Gram-negative infection includes complicated intra-abdominal infection (cIAI; see definition in section 3). Most commonly, *Enterobacteriaceae* are isolated in cIAI. For therapy, the current Guidelines of the Infectious Diseases Society of America (Solomkin et al. 2010) 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 intra-abdominal infections where resistant pathogens such as *Enterococcus spp.* or *Pseudomonas aeruginosa* may occur.

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

ATM, with more than 25 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 MBLs. In this way, activity against MBL (Class B) producing pathogens is possible, although potential inactivation by Class A, C, or D β-lactamases remains problematic.

AVI (formerly AVE1330 or NXL104) is a novel, non β-lactam, β-lactamase inhibitor of a broad spectrum of enzymes, including Ambler Class A ESBLs, Class A KPC, and Class C (AmpC) enzymes, and some Class D enzymes, notably 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 MDR phenotype.

The combination product referred to as ATM-AVI in this Clinical Study Protocol (CSP) 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 as listed above (see Investigator's Brochure for further details).

Most intra-abdominal infections are polymicrobial and caused by organisms residing in the gastrointestinal tract, including aerobes and facultative and obligate anaerobes. In this study, metronidazole will be added to ATM-AVI to provide coverage for anaerobic organisms such as the *Bacteroides fragilis* group. The spectrum of activity of ATM-AVI when combined with metronidazole is well suited to treatment of pathogens commonly responsible for cIAIs.

To date, 92 healthy volunteers have been dosed with the investigational medicinal product (i.e., ATM-AVI, placebo or ATM/AVI separately), in a single Phase I study. Additional details can be found in section 1.2 and in the ATM-AVI Investigator's Brochure (IB).

The objective of this Phase IIa, patient PK study is to investigate the PK, tolerability and safety of ATM-AVI in patients with a serious bacterial infection (cIAI) and to provide dose confirmation. The PK/PD data generated will contribute to a robust package of data, supported by prior experience with ATM and AVI administered separately, and validated by qualitative data for the combination from a proposed randomized Phase III clinical trial in patients with infections suspected to be caused by these specific but rare pathogens.

This ATM-AVI Phase IIa trial is part of the work package 2 (WP2a) in the Innovative Medicines Initiative (IMI) supported COMBACTE-CARE project. IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA (see http://www.imi.europa.eu). COMBACTE-CARE is a consortium of 19 academic and 3 pharmaceutical partners focussing on carbapenem resistance in Europe. The trial is registered in the EudraCT database with the number 2015-002726-39.

1.2 Rationale for study design, doses and control groups

Study design and control group

This ATM-AVI study is a Phase IIa prospective, open-label, multicenter study to determine the PK, safety and tolerability of aztreonam-avibactam (ATM-AVI) in the treatment of hospitalized patients suffering from complicated intra-abdominal infections (cIAI).

The non-comparative, single arm study design is sufficient to enable an intensive patient PK analysis and a within patient cohort safety evaluation. As a single arm study there is no requirement for blinding or randomization. Given the risk to patients and severity of disease, a placebo controlled trial would not be ethically appropriate. The duration of study drug therapy (5 to 14 full days, where a full day is defined as a 24-hour period) takes into account the current FDA recommendations for the development of drugs for treatment of cIAI (FDA 2015).

A multicenter design was chosen for this trial. This approach accounts for the selected patient population. In order to be able to include the required number of 40 patients within a reasonable timeframe, parallel recruitment in several study sites is indispensable. Thus, the study is expected to start in the first quarter 2016 and to end by the fourth quarter 2017.

The chosen design as described below takes into account the current regulatory guidelines, i.e. the European Medicines Agency (EMA) "Guideline on the evaluation of medicinal products

indicated for treatment of bacterial infections" (EMA 2011) and the U.S. Food and Drug Administration (FDA) Guidance for Industry "Complicated Intra-Abdominal Infections: Developing Drugs for Treatment" (FDA 2015).

Dose selection (ATM-AVI)

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. The ATM-AVI doses for this Phase IIa trial 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 volunteers 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 (European Commission: Product information Zavicefta 2016).

At the time of dose selection for the start of this study partial PK data for both ATM and AVI were available from a Phase I study with 28 healthy volunteers receiving ATM-AVI (D4910C00001; dosing cohorts A, B1, B2, and B3 as displayed in the Investigator's Brochure) and were used in development of a population PK model. For AVI dose finding, additional data obtained during development of the new ceftazidime/avibactam combination (i.e. four Phase I studies and one Phase II study in patients with cIAI) were utilised in the population PK model. The population PK model was used in Monte Carlo simulations to select a dosing regimen which achieved a joint probability of target attainment (PTA) for ATM and AVI of approx. >90%; based on PK/PD targets of free (unbound) concentrations of ATM ≥60% T >MIC (time concentration exceeds minimum inhibitory concentration) and free concentrations of AVI ≥50% T > C_T (time concentration exceeds threshold concentration; calculated for a C_T of 2.5 mg/L). The chosen dose is to ensure (based on current knowledge) that the study drugs can achieve the required level of activity in patients with cIAI while taking also safety aspects into account.

Dose selection (ATM-AVI) for patients with normal renal function or mild renal impairment (CrCl >50 mL/min)

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 and prolonging time over MIC with extended infusion time and shorter intervals. The rationale for selected dose regimen is based upon an empirical approach taken to modify the transaminase elevation observed in the Phase I healthy volunteer study (see section 1.3 and IB), but also with objective of obtaining optimal exposure to maintain probability of target attainment (PTA).

The empirical approach taken during the Phase I healthy volunteer study was to yield lower maximum plasma concentrations (C_{max}), with the same exposure (AUC) over the dosing interval to modify observed transaminase elevations. Based on representative population PK modeling, target attainment simulations were conducted during the Phase I study to support dose adjustments. The modeling data shows that extension of the infusion time up to a 3 hour intravenous [IV] infusion every 6 hours (i.e., extended infusion) results in adequate target attainment for the joint ATM-AVI PK/PD target. The modeling data also show that inclusion

of a loading dose results in more patients achieving the predicted target attainment during the initial dosing interval and duration of treatment.

Thus, for both components of the study therapy, the final dosing regimen evaluated – and demonstrated to be well tolerated in both normal aged and elderly human volunteer cohorts in the Phase I study – was a dosing regimen of a loading dose (500 mg ATM plus 137 mg AVI by IV infusion) over a 30 minute period immediately followed by a first maintenance dose of 1500 mg ATM plus 410 mg AVI by IV infusion for 2.5 hours, which was followed by maintenance infusions of 1500 mg ATM plus 410 mg AVI over a 3 hour period every 6 hours. This dosing regimen was simplified with a minor adjustment to be more clinically acceptable.

Thus, the dose regimen that will be evaluated in Cohort 1 is a loading dose of 500 mg ATM plus 137 mg AVI by IV infusion over a 30 minute period, immediately followed by a maintenance infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period every 6 hours. The targeted total dose on Day 1 will be 6500 mg ATM / 1777 mg AVI. From Day 2 onwards, this will be 6000 mg ATM / 1640 mg AVI. This minor adjustment to the first 3 hour maintenance infusion, from 2.5 hours to 3 hours, does not make any significant difference to the exposure of either component and does not impact PTA predictions.

The population PK model has recently been updated, and for ATM now includes all the data from the Phase I study (65 healthy volunteers from Cohorts A, B1-5 and C1-2 of study D4910C00001) and AVI data from the CAZ-AVI Phase I, II and III program (1836 subjects of which 1491 were patients with complicated urinary tract infections or cIAI). The additional data has allowed variability of avibactam in the patient population to be more robustly predicted and the probability of target attainment for ATM and AVI has been calculated to be slightly lower than previously estimated based on the same PK/PD targets mentioned above. The data suggests that whilst the current ATM dose is expected to be adequate, the AVI dose could be further optimised.

Therefore, with the aim to optimise the dose going forward, while assessing the benefit/risk at this dose, it is proposed that a second cohort of patients (Cohort 2) will receive a higher dose of AVI. The proposed dose regimen is a loading dose of 500mg ATM plus 167mg of AVI over a 30 minute infusion, followed by maintenance doses of 1500 mg ATM plus 500 mg AVI over a 3 hour period every 6 hours. The targeted daily dose on Day 1 will be 6500 mg ATM/ 2167 mg AVI and from Day 2 onwards, this will be 6000 mg ATM / 2000 mg AVI.

A decision to proceed to the higher AVI dose in Cohort 2 will be taken following a favourable outcome of the early safety and PK assessment of the first 10 patients in Cohort 1 having completed all PK and safety assessments.

In the event that the higher AVI dose is administered in Cohort 2, a further review of the safety and PK data of the first 10 patients in Cohort 2 will be conducted (see section 5.2.5.2) and a decision taken as to the continuation of treatment in the remaining patients (Cohort 3) either at the higher AVI dose from Cohort 2 or return to the dose from Cohort 1.

Dose selection for patients with moderate renal impairment (CrCl 31 to 50 mL/min)

As both ATM and AVI are eliminated primarily as unchanged substances by the kidney, a population PK/PD model was developed to support an appropriate dose for patients with moderate renal impairment. Included in the population PK model is data from a renal impairment study of avibactam which was conducted as part of the CAZ-AVI development programme and also two published studies of aztreonam [El Guinaidy et al. 1989; Mihindu et al. 1983]. The updated population PK model described above was used in simulations to derive a dose whose predicted exposure is comparable to the exposure in patients with normal renal function, whilst still maintaining >90% PTA against the PK/PD targets. The simulations predict that this is achieved by halving the dose in patients with moderate renal impairment (compared to patients with normal renal function).

Thus, if the maintenance dose for patients with normal renal function is 1500mg ATM plus 500mg AVI infused over 3 hours every 6 hours, the maintenance dose for patients with moderate renal impairment would be ATM 750 mg/AVI 250 mg infused over 3 hours, every 6 hours. Alternatively, if the dose for patients with normal renal impairment is 1500mg ATM plus 410mg AVI, the maintenance dose for patients with moderate renal impairment would be ATM 750 mg/AVI 205 mg.

In both scenarios, the loading dose and an extended loading infusion for patients with moderate renal impairment will be the same as the loading dose and maintenance doses in patients with normal renal function. It is anticipated that the exposure (AUC) following the extended loading dose in patients with moderate renal impairment will be greater than the predicted exposure at steady state in patients with normal renal function by 1.34 for ATM and 1.67-fold for AVI; however, this exposure is transient and will facilitate rapid and effective treatment in these critically ill patients.

In summary doses for patients with moderate renal impairment are as follows:

- If the maintenance dose selected for patients with normal renal function is 1500mg ATM plus 500mg AVI: 500mg ATM plus 167mg AVI as a 30 minute infusion, immediately followed by an extended loading infusion of 1500mg ATM plus 500mg AVI given over a 3 hour period. The maintenance infusions (starting 3 hours after stop of the extended loading infusion) will be 750 mg ATM plus 250 mg AVI over a 3 hour period (to be administered every 6 hours).

- If the maintenance dose selected for patients with normal renal function is 1500mg ATM plus 410mg AVI: 500mg ATM plus 137mg AVI as a 30 minute infusion, immediately followed by an extended loading infusion of 1500mg ATM plus 410mg AVI given as a 3 hour infusion. The maintenance infusions (starting 3 hours after stop of the extended loading infusion) will be 750 mg ATM plus 205 mg AVI over a 3 hour period (to be administered every 6 hours).

Dose selection for metronidazole

Metronidazole will be co-administered with ATM-AVI for the entire duration of study drug therapy (5 to 14 full days) to provide coverage for anaerobic pathogens. The dose to be

administered (500 mg metronidazole every 8 hours) was chosen based on the current Guidelines of the Infectious Diseases Society of America for management of cIAI (Solomkin et al. 2010) and is also in line with nationally approved SmPCs in Europe [Baxter Healthcare Ltd] which do not indicate a need for dose adjustments in patients with moderate renal impairment.

Pharmacokinetic sampling regimen

As this is the first ATM-AVI study in patients, a mixture of intensive and sparse sampling will be employed to define the PK in the patient population, whilst minimising the PK sampling burden. The intensive PK sampling in the first 25 patients (15 samples per patient) is similar to a schedule used in the completed Phase I study D4910C00001. All remaining patients will have reduced/sparse PK sampling (7 samples per patient) based on the population PK model developed in Phase I. Sampling will take place on days 1 and 4 of treatment to assess drug exposure following single and multiple doses of ATM-AVI.

PK and safety analyses

To further assess the safety and PK profile of ATM-AVI in the target population (cIAI patients), this trial will carefully obtain and evaluate comprehensive PK and safety data, including interim review of patient safety (in particular hepatic safety) and PK (see sections 1.3, 1.4, 5.2.5 and 5.3.3). There will be an assessment of the PK-PD relationship regarding clinical cure response on study completion.

Cohort 1: An early safety and PK review of 10 patients with CrCl>50mL/min (and having completed all PK and safety assessments; see section 5.2.5) will input into the decision on whether

a) the study will continue and, if so:

b) the remainder of the study will continue (Cohort 2) with the same dose regimen as Cohort 1 for patients with normal renal function or mild renal impairment (CrCl >50 mL/min), or:

c) Cohort 2 will commence at the higher AVI dose regimen for patients with normal renal function or mild renal impairment (see above) and

(d) patients with moderate renal impairment (CrCl 31 to 50 mL/min should be included and administered a reduced dose consistent with the agreed dose in Cohort 2 (see above).

In the event that the AVI dose is escalated in Cohort 2, a second safety and PK review of 10 patients having completed all PK and safety assessments will input into the decision on whether

a) The remainder of the study (Cohort 3) will continue at the same (higher AVI dose) regimen, or:

b) The remainder of the study (Cohort 3) will continue with the lower AVI dose regimen for patients with CrCl > 50 mL/min and for patients with CrCl 31-50 mL/min, respectively (as described above)

c) The dose regimen selected is confirmed for the development of ATM-AVI.

The overall objective of this trial including 40 patients is to confirm a suitable dose for the development of ATM-AVI and to provide for additional PK, PK/PD and safety/ tolerability data in patients with a representative burden of infection.

1.3 Benefit/risk and ethical assessment

Patients enrolled into this clinical study will have cIAIs that are of sufficient severity to require hospitalization and treatment with IV antibiotics and surgical intervention (including open laparotomy, percutaneous drainage of an abscess and laparoscopic surgery). The potential benefit to patients participating in this study is that they will receive effective antibiotic therapy for their infection. Avibactam has been shown to prevent hydrolysis of aztreonam in vitro by avibactam susceptible β-lactamases and has been shown to be effective in combination with ceftazidime in clinical studies in patients with cIAI. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for a representative serious bacterial infection, in the face of the changing pattern and increasing frequency of antibiotic resistance (see section 1.1).

It is however possible that ATM-AVI will not prove to be a sufficiently effective treatment for cIAI. This risk is mitigated in that the study patients are closely monitored and will be managed with appropriate therapies as determined by the investigator who is providing treatment, based on the clinical response of the patient.

The risk considerations for this study should encompass the known and potential risks for the development product ATM-AVI and its component drugs aztreonam and avibactam, as well as the risks associated with further study-related procedures and with the treatments that will be co-administered according to this protocol, i.e. the marketed metronidazole. As the risks for marketed products are widely available in their respective prescribing information, such risks will not be discussed in this section. Information on contraindications, special warnings and precautions and interactions with other medicinal products and other forms of interaction for metronidazole are available in the metronidazole SmPC and investigators are recommended to refer to this for further prescribing information.

General study-related risks encompass venepuncture and/or placement of indwelling catheters for blood sampling, which may cause pain and occasionally results in thrombosis or thrombophlebitis and/or peripheral nerve damage (numbness). The total volume of blood to be drawn from each patient is expected to range – depending on clinical response – from 106 to 200 mL; 21 to 45 mL thereof will be used for PK analysis (see Table 5). The results of safety lab sampling (clinical chemistry, hematology) will be made available to the investigators. Similarly, the results of microbiological blood cultures obtained for study purposes will be

made available to the investigators without delay and may yield clinically important additional information.

Discomfort may be caused by any further study procedure such as study-related examinations, microbiological sampling, and recording of ECGs etc. These procedures however are not considered as risks for the patients that would affect the benefit-risk assessment.

ATM-AVI is not approved for marketing in any country. The risks for ATM-AVI have not been fully elucidated; however it is assumed that known or potential risks for ATM-AVI should include those identified in the clinical study experience with ATM-AVI, ATM alone, and AVI alone.

ATM solution for injection (Azactam™) was first approved by the US Food and Drug Administration (FDA) in 1986 and subsequently approved in Europe and is indicated for intra-abdominal infections. The most frequent adverse drug reactions for ATM comprise gastrointestinal disorders (diarrhoea, nausea, vomiting: common according to CIOMS Working Group III standard categories; see IB). Further relevant ADRs are *Clostridium difficile* colitis, anaphylactic reactions and ventricular extrasystoles (uncommon). For further information regarding the risks attributable to ATM see IB and SmPC (ER Squibb & Sons Limited 2014).

Human experience with AVI includes studies of all phases in which AVI was administered either as a single agent or in combination with other antibiotics (ceftazidime or ceftaroline). As part of the ceftazidime-avibactam development program and in a Phase I study for the ATM-AVI development, the safety and PK of AVI have been investigated in more than 10 clinical pharmacology studies after IV administration of avibactam alone or in combination with ceftazidime or ATM. Ceftazidime-avibactam was approved by the FDA on 25 February 2015 (Trademark: Avycaz) and by the European Commission on 28 June 2016 (Trademark: Zavicefta).

In a single Phase I study in healthy Japanese volunteers, noteworthy elevations in liver transaminases in a single volunteer who received AVI alone was reported as another significant adverse event (see IB). As a result, drug-induced liver injury, while not considered an expected adverse reaction, is now considered an important potential risk. As such, appropriate pharmacovigilance and risk mitigation measures have been outlined for the clinical study programme, with details for this study given in sections 3.9, 5.2.5, 6.3.7, 6.7.3 and Appendix D. This finding, however, does not alter the benefit-risk profile for ATM-AVI.

Human experience with the ATM-AVI combination consists of a single Phase I First-Time-In-Man (FTiM) study (D4910C00001), in 92 healthy volunteers, of which 8 received single doses of ATM-AVI, 58 received multiple doses of ATM-AVI and the remainder received placebo. Data from this Phase I FTiM study suggest that the following ADRs are expected for the ATM-AVI combination: headache (very common), abnormal liver function test (common), diarrhoea (common) and infusion/cannula site pain or reaction (common). Clinical data with ATM-AVI remains limited at this time but provided no evidence that the benefit-

risk profile of the combination is different from that of the individual combination components.

Elevations in liver transaminases (in particular alanine aminotransferase (ALT) have been seen in a number of healthy volunteers in the Phase I FTiM study, all of which have rapidly resolved after cessation of therapy. Modifications taken over the course of the Phase I study to reduce the concentrations of both aztreonam and avibactam and extend the infusion times have significantly reduced the extent of transaminase elevation to facilitate the clinical utility of ATM-AVI. The clinical utility will be further examined in this Phase IIa, patient PK study, with an early evaluation of at least 10 patients in both Cohorts 1 and 2, initially to confirm the doses for patients with normal renal function and mild renal impairment, and with ongoing and final analyses to reconfirm tolerated doses to take forward into development of ATM-AVI.

Data from Phase I studies did not show evidence of a drug-drug interaction (DDI) between ATM and AVI. Based on current knowledge, also the potential for DDIs between ATM-AVI and other drugs is low. Both ATM and AVI:

- show linear (approximately dose proportional) pharmacokinetics, undergo limited metabolism and are eliminated primarily as unchanged substances by the kidney.
- showed no significant inhibition or induction of cytochrome P450 (CYP) enzymes in vitro and/or in vivo.
- have low binding to human plasma proteins (ATM: approx. 43% [Crandon and Nicolau 2013; Vinks et al. 2007]; AVI: 5.7% to 8.2% [FDA prescribing info: AVYCAZ™ 2015])

Furthermore, data from Phase I studies suggest that there is no clinically relevant influence of sex or age on the pharmacokinetics of AVI (Tarral et al. 2015). Additional risk information for ATM, AVI and ATM-AVI is located in the IB.

In summary, the known and potential risks of receiving ATM-AVI are expected to be similar to those seen with ATM. Thus far, no unique risks have been identified for the avibactam component or the combination of aztreonam and avibactam.

The potential risks and discomforts to the individual subject are well balanced by providing best practice medical monitoring and clinical care for each patient and by the group-ethical relevance of the study. Under the conditions of the study as described in the present protocol, the investigators and the sponsor consider the benefit/risk relation to be positive (i.e. medically and ethically justified).

1.4 Study Design

This is a prospective, open-label, dose-confirming multicenter Phase IIa study to determine the PK, safety and tolerability of aztreonam-avibactam (ATM-AVI) in the treatment of hospitalized patients with a complicated intra-abdominal infection (cIAI). Forty adult patients

with a diagnosis of cIAI and the need for a surgical intervention will be enrolled. The surgical intervention may take place within 24 hours before or after administration of the first dose of study drug. After obtaining written informed consent and confirming eligibility, patients will be assigned the following treatment:

Three potential cohorts are planned. From the study start, only patients with normal renal function or mild renal impairment (i.e. CrCl >50 mL/min; see Appendix E) will be eligible. The proposed administration of ATM-AVI for Cohort 1 patients is a loading dose (500 mg ATM plus 137 mg AVI by intravenous [IV] infusion over a 30 minute period), immediately followed by a dose of 1500 mg ATM plus 410 mg AVI by IV infusion over a 3 hour period every 6 hours (maintenance infusion). The targeted total dose on Day 1 will be 6500 mg ATM and 1777 mg AVI. From Day 2 onwards, this will be 6000 mg ATM / 1640 mg AVI. Patients will also receive 500 mg metronidazole infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion. Cohort 1 will contain a minimum of 10 and a maximum of 20 patients.

Cohort 2 may use an increased AVI dose. For patients with CrCl >50 mL/min, this would be an ATM-AVI loading dose (500 mg ATM plus 167 mg AVI by intravenous [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 every 6 hours (maintenance infusion). Thus, the targeted total dose on Day 1 will be 6500 mg ATM and 2167 mg AVI. From Day 2 onwards, this will be 6000 mg ATM / 2000 mg AVI. Patients will also receive 500 mg metronidazole infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion. In the event that Cohort 2 uses a higher AVI dose, Cohort 3 will be a safety expansion cohort at one of the two dose regimens detailed above (to bring total number of enrolled patients up to a maximum of 40). In the event that Cohort 2 uses the same AVI dose as Cohort 1, the study will continue up to a maximum of 40 patients with that same dosing regimen.

The PK, safety and tolerability of the dosing regimen described above will be assessed in a first cohort of at least 10 patients; i.e. recruitment into this initial cohort of patients will continue until 10 patients with CrCl >50mL/min have completed all scheduled safety and PK assessments. After completion of all safety and PK assessments in 10 patients, an early patient review regarding safety and PK data will be made (see sections 5.2.5 and 5.3.3). Patient safety laboratory data will be monitored on an ongoing basis and a summary output will be available for the 10 patients. Once 10 patients have completed all safety and PK assessments, there will be a pause in enrolment to complete the ongoing safety review and provide confirmation that the study can proceed beyond the first 10 patients, based on the available safety data.

At this time, the scientific advisory committee (SAC) will make recommendations to either discontinue the study, continue dosing Cohort 2 with no dose change, or to escalate to the higher AVI dose in Cohort 2.

In the event that a higher AVI dose will be administered in Cohort 2, a second safety and PK review will occur once at least10 patients in Cohort 2 have completed all safety and PK assessments. Patient safety laboratory data will be monitored on an ongoing basis and a

summary output will be available for the 10 patients. There will be a second pause in enrolment at this time to complete the second safety and PK review.

The SAC will make recommendations for the continuation of the study i.e., to continue treating patients in Cohort 3 (expansion) at the higher AVI dose, or to de-escalate the AVI dose.

Patients with moderate renal impairment (CrCl of 31 to 50 mL/min) must not be included prior to the completion of the early safety and PK review and subsequent confirmation of the dosing regimen for these patients (see also section 1.2). Based on available population PK/PD modelling, the proposed administration of ATM-AVI for patients with moderate renal impairment will be a dose consistent with the dose selected for Cohort 2:

- In the event that the AVI dose in Cohort 2 is increased, a loading dose (500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period), immediately followed by an extended loading infusion of 1500 mg ATM plus 500mg AVI over a 3 hour period. The maintenance infusions (starting 3 hours after stop of the extended loading infusion) will be 750mg ATM plus 250 mg AVI over a 3 hour period, to be administered every 6 hours. The targeted total dose on Day 1 will be 4250 mg ATM: 500 mg (loading dose) + 1500 mg (extended loading infusion) + 3x 750 mg = 2250 mg (maintenance infusion) and 1417 mg AVI: 167 mg (loading dose) + 500 mg (extended loading infusion) + 3x 250 mg (maintenance infusion). From Day 2 onwards, this will be 3000 mg ATM (4x 750 mg maintenance infusion) / 1000 mg AVI (4x 250 mg maintenance infusion).

Or

- In the event that Cohort 2 continues at the lower AVI dose, a loading dose (500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period), immediately followed by an extended loading infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period. The maintenance infusions (starting 3 hours after stop of the extended loading infusion) will be 750mg ATM plus 205 mg AVI over a 3 hour period, to be administered every 6 hours. The targeted total dose on Day 1 will be 4250 mg ATM: 500 mg (loading dose) + 1500 mg (extended loading infusion) + 3x 750 mg = 2250 mg (maintenance infusion) and 1162 mg AVI: 137 mg (loading dose) + 410 mg (extended loading infusion) + 3x 205 mg (maintenance infusion). From Day 2 onwards, this will be 3000 mg ATM (4x 750 mg maintenance infusion) / 820 mg AVI (4x 205 mg maintenance infusion).

For anaerobic coverage, patients will also receive 500 mg metronidazole infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion.

Where possible, the SAC will use available information from population modelling and simulation methods as part of the safety and PK assessment to evaluate the relationships between emerging safety and PK data and confirm the dose regimens to be used.

Patients with a creatinine clearance of 31 – 50 mL/min will be eligible if the results of the early PK and safety review (along with respective PK modelling including confirmation of the PK model used)

- support inclusion of such patients and
- confirm the proposed dosing regimen for these patients

In all Cohorts, intravenous study therapy (ATM-AVI) plus metronidazole will be continued for a period of time (5 to 14 full days, where a full day is defined as a 24-hour period) deemed appropriate by the investigator based on the patient's clinical response. After at least 5 full days of IV study therapy and at the discretion of the investigator, all study therapies may be discontinued if the patient has shown significant clinical improvement. Clinical improvement will be assessed by the investigator based upon fever and other signs and symptoms that demonstrate clear evidence of local and systemic improvement. The white blood cell count should be <12500/µL. The patient should be afebrile [<37.8°C] for at least 24 hours, without the influence of antipyretic drugs, if possible. If analgesic medication is required for pain, the use of analgesics without antipyretic properties is preferred.

It is anticipated that each patient will complete the study, including the Late Follow-up (LFU) visit. In the event the patient is discharged from the hospital before the End of Treatment (EOT), Test of Cure (TOC), or LFU visit, they will return to the study centre for their scheduled assessment (see section 4.1). If treatment with antibiotics is required beyond 14 days, the designated COMBACTE-CARE national coordinator or other designated study personnel should be contacted (see section 6.10).

All patients will undergo sparse pharmacokinetic sampling on Day 1 of treatment. On Day 4, the first twenty five (25) patients will undergo intensive pharmacokinetic sampling, whereas the following fifteen (15) patients will undergo sparse sampling.

A flow-chart of the overall study design is shown in Figure 1. The study outline (visit schedule) is displayed in Figure 2.The detailed study plan and timing of procedures is presented in Table 1. For details on doses and treatment regimes, see section 7.2.

Figure 1 Study Flow

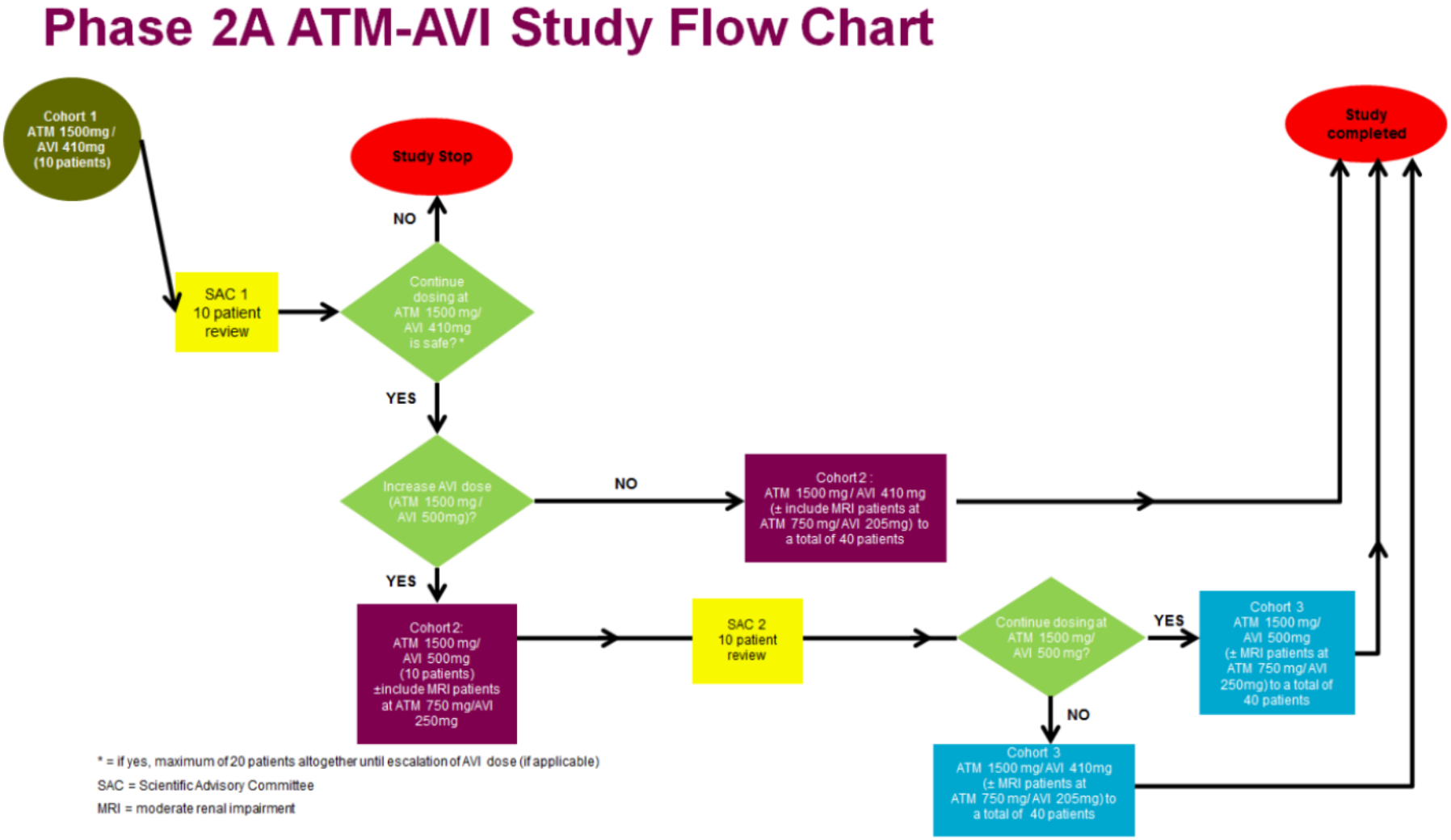
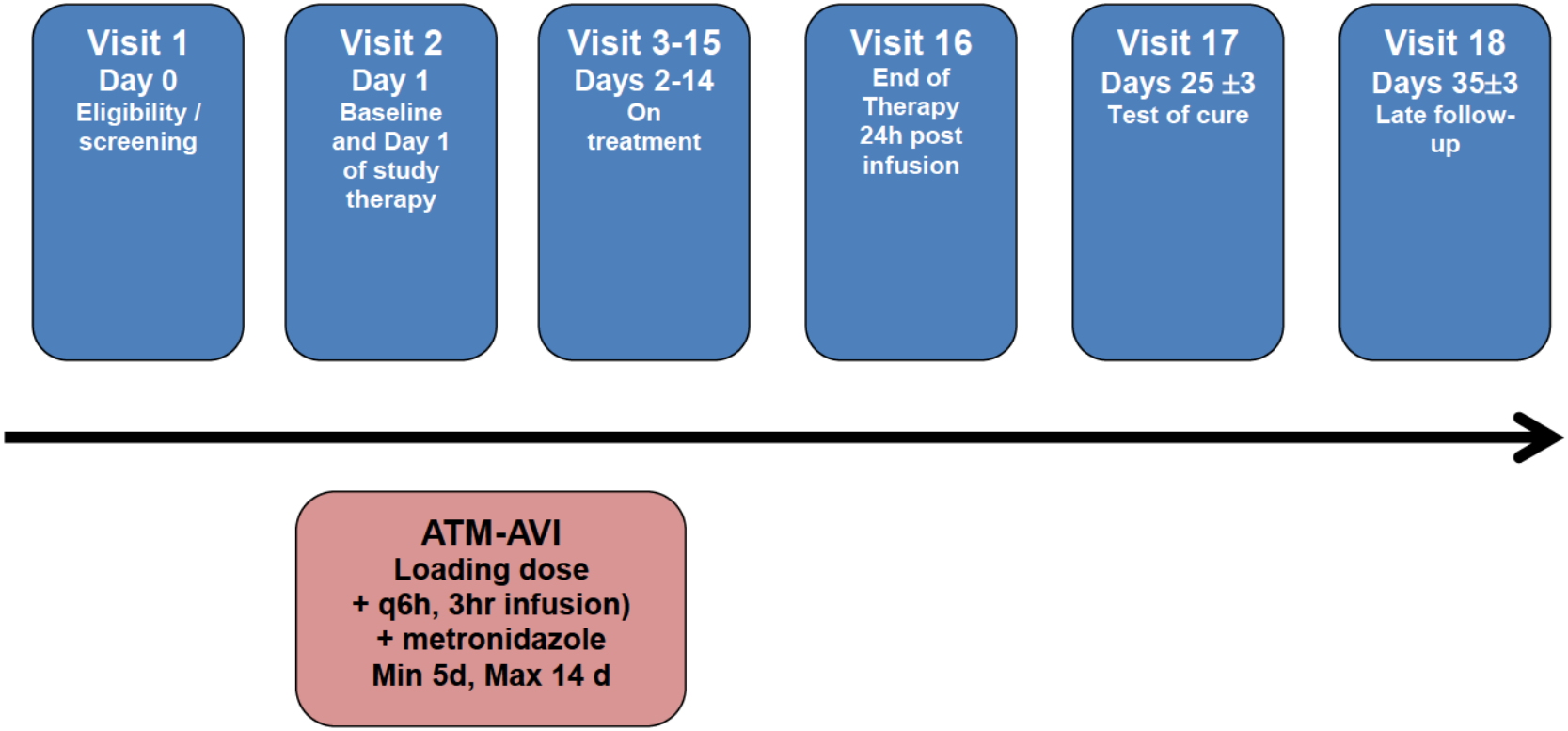


Figure 2 Study Outline



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To determine the pharmacokinetics (PK) of ATM-AVI in this patient population	• Concentrations of ATM and AVI in plasma; concentration-time profile of ATM and AVI • The derived PK parameters C_{max}, t_{max}, $AUC_{(0-6)}$, $AUC_{(0-last)}$, t_{last}, $t_{1/2}$, V_{ss}, V_z and CL for the patients undergoing intensive sampling on day 4
To assess the safety of ATM-AVI in this patient population	Safety and tolerability as assessed by adverse events, physical examination, vital signs, ECGs, and laboratory assessments

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To assess the treatment outcome per patient at the test of cure (TOC) visit	Proportion of patients with clinical cure at the TOC visit
To assess the relationship between exposure and clinical cure for ATM-AVI	Correlation of derived PK parameters for ATM-AVI and clinical cure at TOC

2.3 Safety objectives

Safety Objective:	Outcome Measure:
See section 2.1 (primary objective)	

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To develop and evaluate pharmacokinetic / pharmacodynamic (PK/PD) models (Nonlinear Mixed Effect Model analysis [NONMEM], simulation) and to characterize population PK	Estimates of model parameters and their precision, goodness-of-fit, individual and mean predictions

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

The target subject population is 40 patients with a diagnosis of complicated intra-abdominal infection (cIAI). A presumed diagnosis of cIAI is necessary for enrolment. The diagnosis of cIAI will be based on the patient's clinical syndrome and will be supported by intra-operative findings, including intra-operative cultures. Operative intervention must be required and includes open laparotomy, laparoscopic surgery, and percutaneous drainage of an abscess. All patients will undergo a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study therapy.

Clinically indicated antibiotic treatment must not be delayed because patient is being considered for clinical trial participation.

According to current scientific guidelines ("Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America" [Solomkin et al. 2010]) and regulatory guidelines (FDA guideline on cIAI drug development as of February 2015 [FDA 2015]), cIAI is defined as follows:

Intra-abdominal infections comprise a wide variety of clinical presentations and differing sources of infection. cIAIs extend beyond the hollow viscus of origin (e.g. a singularly infected organ) into the peritoneal space and are associated with either abscess formation or peritonitis. Different bacterial pathogens are responsible for cIAIs, including Gram-negative aerobic bacteria, Gram-positive bacteria, and anaerobic bacteria, and there are also mixed infections. Uncomplicated intra-abdominal infections and complicated intra-abdominal infections may be difficult to distinguish, but in general cIAIs extend beyond local viscera into peritoneal or retroperitoneal spaces and are associated with systemic signs and symptoms of illness. Complicated intra-abdominal infections require operative intervention or percutaneous drainage in conjunction with broad-spectrum antibacterial therapy.

The exact clinical diagnoses and brief descriptions that define the population of patients with cIAI eligible for this study are given in section 3.1. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. The inclusion and exclusion criteria will be assessed by a site investigator before enrolment of the patient to the study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria which will be assessed by a site investigator:

1. Provision of informed consent prior to any study specific procedures. If a patient is unable to provide informed consent at Screening, he/she may be entered into the study by his/her guardian or legal representative if in accordance with national and

local regulations and as approved by the institutional specific guidelines. Those patients who are entered by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with national and local regulations.

2. Male or female from 18 to 90 years of age inclusive

3. Female patients are authorized to participate in this clinical study if at least one of the following criteria are met:

a) Surgical sterilization, including hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy, but excluding bilateral tubal occlusion;

b) Age ≥50 and post-menopausal as defined by amenorrhea for 12 months or more following cessation of all exogenous hormonal treatments;

c) Age <50 and post-menopausal as defined by luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range PLUS amenorrhea for 12 months or more following cessation of all exogenous hormonal treatments (Note: if desired, LH and FSH may be checked at study entry to determine if women <50 and amenorrheic for 12 months are post-menopausal, but the patient must meet criterion "d" until LH and FSH confirm menopausal status);

d) Both of the following conditions are met:

- Patient has a negative serum pregnancy test (serum β-human chorionic gonadotropin [β-hCG]) within 1 day prior to enrolment (if the results of the serum β-hCG cannot be obtained prior to dosing of the investigational medicinal product [IMP], a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained after enrolment). If either test is positive, the patient must be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant menstrual history and sexual history, including methods of contraception, should be considered.

- Patient agrees not to attempt pregnancy while receiving study drugs and for a period of 7 days after last dose of IV study therapy and agrees to the use of the following acceptable methods of contraception: prior to and during the study (including 7 days after the last dose of IV study therapy) use of an intrauterine device (with copper banded coil), levonorgestrel intrauterine system (e.g., Mirena®), regular medroxyprogesterone injections (e.g. Depo-Provera®), or sexual intercourse with only vasectomized partners (and verbal confirmation of azoospermia), or complete sexual abstinence for the recommended period. The woman should be stable on her chosen method of birth control for a minimum of

3 months at the time of signing informed consent forward to initiation of the IMP. See additional restrictions in section 3.8.

4. Diagnosis of cIAI as defined in section 3 as

EITHER:

Intra-operative/postoperative enrolment with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. Specimens from the surgical intervention must be sent for culture. Patients who undergo a surgical procedure with complete fascial closure are appropriate for the trial. The skin incision may be left open for purposes of wound management as long as complete fascial closure is accomplished. The patient has at least 1 of the following diagnosed during the surgical intervention:

(a) Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall

(b) Diverticular disease with perforation or abscess

(c) Appendiceal perforation or peri-appendiceal abscess

(d) Acute gastric or duodenal perforations, only if operated on >24 hours after diagnosis

(e) Traumatic perforation of the intestines, only if operated on >12 hours after diagnosis

(f) Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites)

(g) Intra-abdominal abscess (including of liver or spleen provided that there is extension beyond the organ with evidence of intraperitoneal involvement)

OR

Preoperative enrollment where the following clinical criteria are met with confirmation of infection by surgical intervention within 24 hours of entry:

(h) Requirement for surgical intervention, defined per protocol as open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery

(i) Evidence of systemic inflammatory response, with at least one of the following:

- Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
- Elevated white blood cells (>12000 cells/µL)
- Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg, or a systolic blood pressure decrease of >40 mmHg
- Increased heart rate (>90 bpm) and respiratory rate (>20 breaths/min)
- Hypoxemia (defined as oxygen saturation < 95% by pulse oximetry)
- Altered mental status.

(j) Physical findings consistent with intra-abdominal infection, such as:

- Abdominal pain and/or tenderness, with or without rebound
- Localized or diffuse abdominal wall rigidity
- Abdominal mass.

(k) Supportive radiologic imaging findings of intra-abdominal infection such as perforated intraperitoneal abscess detected on computed tomography scan, magnetic resonance image, or ultrasound.

(l) Specimens from the surgical intervention will be sent for culture for isolation of both aerobic and anaerobic bacteria.

5. If applicable: Patients who failed prior antibacterial treatment for their current cIAI can be enrolled but must:

- Have a known or suspected pathogen causing cIAI resistant to the prior therapy while assuming the organism is sensitive to ATM-AVI.
- Require surgical intervention.

Such patients can be enrolled before the results of the culture are known (see also exclusion criterion 10).

6. Patient must have had or will have a surgical intervention within 24 hours (before or after) the administration of the first dose of study drug. As a prerequisite for inclusion, a specimen from an abdominal source must be obtained for culture during surgical intervention. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. Isolates taken from surgical wound exudates must not be used.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled which will be assessed by a site investigator:

1. Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site)

2. Patient has been previously enrolled in this study, previously treated with ATM-AVI or previously participated in an investigation study containing AVI

3. Patient has participated or intends to participate in any other clinical study that involves the administration of an investigational medication at the time of presentation, during the course of the study, or during the 30 days prior to study start

4. Patient has a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to aztreonam, carbapenem, monobactam or other β-lactam antibiotics, avibactam, nitroimidazoles or metronidazole, or any of the excipients of the respective (investigational) medicinal products to be administered during the study

5. Patient has a diagnosis of abdominal wall abscess; small bowel obstruction or ischemic bowel disease without perforation; traumatic bowel perforation with surgery within 12 hours of diagnosis; perforation of gastroduodenal ulcer with surgery within 24 hours of diagnosis (these are considered situations of peritoneal soiling before infection has become established); another intra-abdominal process in which the primary etiology is not likely to be infectious

6. Patient has a simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, infected necrotizing pancreatitis, pancreatic abscess or ischaemic/necrotic intestine without perforation

7. Patient has a cIAI managed by staged abdominal repair (STAR), open abdomen technique or any situation where infection source control is not likely to be achieved or in whom the abdomen is left open, or those unlikely to solely respond to antimicrobial therapy

8. At screening, if it is known the patient has an infection due to a pathogen that is unlikely to respond to ATM-AVI plus metronidazole treatment

9. Patient has a rapidly progressive (expected to die in <30 days) or terminal illness, including acute hepatic failure, respiratory failure or septic shock with a high risk of mortality due to other causes than cIAI

10. Patient has received systemic antibacterial agents within the 72-hour period prior to study entry, unless either of the following pertains:

    (a) Patient has a new infection (not considered a treatment failure) and the following is met:

- Patient received no more than 24 hours of total prior antibiotic therapy within the 72 hour period prior to study entry

(b) Patient is considered to have failed the previous treatment regimen (see Inclusion criterion no 5)

In this case, preoperative treatment of any duration with non-study systemic antimicrobial therapy for peritonitis or abscess is permitted provided that all of the following are met:

- The treatment regimen has been administered for at least 72 hours and is judged to have been inadequate.
- The patient has an operative intervention completed within 24 hours prior to study entry or an operative intervention is intended no more than 24 hours after study entry
- Findings of infection were documented at surgery.
- Specimens for bacterial cultures and susceptibility testing are taken at operative intervention.
- Non-study antibacterials are discontinued at the time of study enrolment

11. Patient has a concurrent infection that may interfere with the evaluation of clinical cure for the study therapy

12. Patient needs effective concomitant systemic antibacterials (oral, IV, or intramuscular) or antifungals in addition to ATM-AVI and metronidazole, except vancomycin, linezolid, or daptomycin if started for suspected or documented methicillin-resistant Staphylococcus aureus (MRSA) or Enterococcus spp. (see section 7.7)

13. Patient has creatinine clearance ≤30 ml/min as calculated by Cockcroft-Gault formula (Cockcroft and Gault 1976; see Appendix E) or requirement for peritoneal dialysis, hemodialysis or hemofiltration, or oliguria (<20 mL/h urine output over 24 hours).

14. Patient has had acute hepatitis in the prior 6 months, chronic hepatitis, cirrhosis (any Child-Pugh class), acute hepatic failure, or acute decompensation of chronic hepatic failure

15. Presence of hepatic disease as indicated by aspartate aminotransferase (AST) or alanine transaminase (ALT)>3 × upper limit of normal (ULN) at Screening. Patients with AST and/or ALT >3 × ULN and <5 × ULN are eligible if these elevations are acute, not accompanied by a total bilirubin ≥2xULN and documented by the investigator as being directly related to the infectious process being treated

16. Patient has a total bilirubin >3 × ULN, unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease

17. Alkaline phosphatase (ALP) >3 × ULN. Patients with values >3 × ULN and <5 x ULN are eligible if this value is acute and directly related to the infectious process being treated.

18. Patients with an immunocompromising illness, including known human immunodeficiency virus (HIV) with<200/ µL CD4+ positivity or acquired immunodeficiency syndrome (AIDS), organ (including bone marrow) transplant recipients, and uncontrolled hematological malignancy. Immunosuppressive therapy, including use of high-dose corticosteroid therapy (e.g. >40 mg prednisone or equivalent per day for greater than 2 weeks)

19. Known active *Clostridium difficile* associated diarrhoea

20. Any other condition that, in the opinion of the investigator, may confound the results of the study or pose additional risks in administering the study therapy to the patients

21. Patient with a do not resuscitate order (i.e., those patients in whom life sustaining measures [cardio-pulmonary resuscitation and / or mechanical ventilation] would not be undertaken when medically indicated)

22. Patient has an absolute neutrophil count <1000/µL

23. Patient has a hematocrit <25% or hemoglobin <8 gm/dL.

24. Patient has a platelet count <75,000/µL. Patients with a platelet count as low as 50,000 /µL are permitted if the reduction is historically stable

25. Patient is currently receiving treatment with probenecid.

26. Patient is pregnant or breastfeeding or if of child bearing potential, not using a medically accepted, effective method of birth control as listed in the Inclusion criteria. Any patient whose menstrual or sexual history suggests the possibility of early pregnancy must be excluded. A serum β-hCG pregnancy test must be performed for women of childbearing potential at the screening visit. If the results of a serum β-hCG pregnancy test cannot be obtained prior to dosing of the investigational medicinal product, a patient may be enrolled on the basis of negative urine pregnancy test though serum β-hCG must still be obtained. If either test is positive, the patient will be excluded.

27. Patient is unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for LFU visits and unlikelihood of completing the study

28. Patient is currently receiving anti-convulsant therapy to prevent recurrence of a past history of seizures. Past history of seizures or epilepsy (excluding febrile seizures of childhood).

29. Patient has a prior liver, pancreas or small-bowel transplant.

Procedures for withdrawal of incorrectly enrolled subjects: see section 3.4.

3.3 Patient enrolment

All investigators should keep a record, the patient screening log, of patients who entered pre-study screening.

The investigators will:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed. If a patient is unable to provide informed consent at Screening, he/she may be entered into the study by his/her guardian or legal representative if in accordance with national and local regulations. Those patients who are entered by the consent of a legally acceptable representative should provide their own informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with national and local regulations.

2. Assign the potential patient a unique enrolment number, beginning with 'E#'. (EXXXX-YYY)" where XXXX reflects the center number and YYY will be allocated sequentially to enrolled patients at each center. Example: "E0001-001" represents patient number one at center number one.

3. Confirm patient eligibility (according to inclusion and exclusion criteria)

As this is an open-label study with PK and safety as primary objectives, there will be no randomization (see section 1.2). The enrolment number is assigned to each subject as a unique identifier. Upon completing the enrolment information in the eCRF, a notification will be sent out to the sponsor and Clinical Trial Center Cologne (CTCC).

If a subject withdraws from participation in the study, then his/her enrolment number cannot be reused. Withdrawn or discontinued patients will not be replaced.

3.4 Procedures for handling incorrectly enrolled subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where a subject does not meet all the eligibility criteria but is enrolled in error, or incorrectly started on study treatment, the investigator should contact the country specific national study coordinator or the sponsor's Medical Monitor as outlined in section 6.10. A discussion should occur between the sponsor's Medical Monitor and the investigator regarding whether to continue or discontinue the patient from study treatment. The study physician must ultimately ensure all decisions are appropriately documented. Contact details of the respective national coordinators and the sponsor's medical contacts are also provided in appropriate site documents.

3.5 Methods for assigning treatment groups

All patients being enrolled and fulfilling all eligibility criteria will receive an intravenous treatment with ATM-AVI and metronidazole. There will be no randomization (see section 1.2).

In a first cohort of 10 patients, with CrCl>50 mL/min, having completed all safety and PK assessments, an early patient review regarding safety and PK data will be undertaken. There will be a pause in enrolment to complete the ongoing safety review and provide confirmation that the study can proceed beyond the first 10 patient cohort, based on the available safety data. For the first cohort, only subjects with normal renal function or mild renal impairment (CrCl >50 mL/min; to be determined as described in Appendix E) will be eligible.

After completion of the early safety and PK review, recruitment of patients with moderate renal impairment (CrCl 31 to 50 mL/min) may be allowed with a separate dosing regimen. In Cohort 2, and in a potential Cohort 3, an increased AVI dose may be administered. For details on the dosing regimens and on the criteria for assigning patients to treatments in Cohorts 2 and 3, see sections 1.4 Study design and 7.2 Dose and treatment regimens.

In some patients, the creatinine clearance estimated from serum creatinine can change quickly, especially early in the course of treatment for the infection. Renal function should be closely monitored throughout the treatment period i.e., daily, and the dose of ATM-AVI adjusted according to the CrCl value calculated by the Cockcroft- Gault formula (Appendix E), using serum creatinine measurement by the local laboratory. Local laboratory test results will be entered into the eCRF.

In the case that renal function recovers or deteriorates in Cohort 2 or 3 patients during the treatment period (i.e., local or central lab results show CrCl increases from 31 – 50 mL/min at baseline to >50 mL/min, or decreases from >50 mL/min at baseline to 31 – 50 mL/min), the dose of ATM-AVI should be adjusted by the investigator to meet the applicable dose regimen, based on the latest CrCl value.

All patients will undergo sparse pharmacokinetic sampling on Day 1 of treatment. On Day 4, the first twenty five (25) patients will undergo intensive pharmacokinetic sampling, whereas the following fifteen (15) patients will undergo sparse sampling.

3.6 Methods for ensuring blinding: Not applicable

3.7 Methods for unblinding: Not applicable

3.8 Restrictions for patients during the study

- Patients must abstain from donating blood/plasma from the time of informed consent and for at least 3 weeks after the last dose of the investigational medicinal product (i.e. until late follow-up visit).
- Hormonal contraceptives potentially subject to drug-drug interaction, such as oral contraceptives, patches and intra-vaginal devices, are not acceptable methods of

contraception during this study based on the potential of antibiotics to alter gut flora, hormone absorption and hormone effectiveness. The effect of ATM-AVI on the efficacy of such contraceptives has not yet been established. If a female study participant was previously using hormonal contraceptives such as pills, patches and intra-vaginal devices, she should follow her health care provider's specific recommendations for effective use of these methods after completing the study drugs. Such recommendations may address the need for a second method of contraception until the hormonal method becomes fully effective.
During the study, barrier methods (such as male condom or diaphragm with spermicide) can be used only if another method of acceptable contraception is also used. Acceptable methods are listed in section 3.1.

3.9 Discontinuation of Investigational Medicinal Product (IMP)

Patients may be prematurely discontinued from IMP (i.e., prior to cure) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Occurrence of an adverse event or any other condition posing a risk to a patient or jeopardizing a safe continuation of the study treatment for the respective patient (as judged by the investigator and/or the national coordinators, and/or the CTCC on behalf of COMBACTE-CARE and the sponsor).
- Severe noncompliance to study protocol, as judged by the investigator and/or CTCC or the sponsor.
- Positive pregnancy test at any time during the study.
- Treatment failure.
- In the opinion of the investigator, it is not in the best interest of the patient to continue the IV study therapy or at the request of national coordinators, and/or the CTCC on behalf of COMBACTE-CARE and the sponsor, that the patient stops participation.
- Prior to availability of the results of the early patient safety and PK review:
  If CrCl falls to ≤ 50 mL/min, the IV study therapy should be stopped and the patient followed up to the end of the study. Recruitment into this initial cohort of patients will continue until 10 patients with CrCl > 50 mL/min have completed all PK and safety assessments as scheduled.

  After availability of the results of the early patient safety and PK review:
  Provided the results confirm the eligibility of patients with CrCl of 31 – 50 mL/min,

the following discontinuation criterion applies: If CrCl falls to ≤ 30 mL/min, the IV study therapy should be stopped and the patient followed up to the end of the study.

- In the absence of any alternative explanation for an increase in the following abnormalities, individual patients should be withdrawn if the following criteria are met:
  - ALT or AST >8 × ULN
  - ALT or AST >5 × ULN for more than 2 weeks
  - ALT or AST >3 × ULN and either total bilirubin >2 × ULN or evidence of coagulopathy. Evidence of coagulopathy should be discussed with the study physician where possible.
  - ALT or AST >3 × ULN and with appearance of symptoms suggestive of new or progressive liver disease. Symptoms suggestive of new or progressive liver disease should be discussed with the study physician where possible.
  - Patients with initial baseline transaminases >3xULN and <5xULN, documented as being directly related to infection being treated, progressing to:
    - ALT or AST ≥ 5×ULN and evidence of coagulopathy
    - ALT or AST ≥ 5×ULN with symptoms suggestive of new or progressive liver disease

For monitoring of liver-related laboratory parameters, see section 6.7.3. For early safety review, see section 5.2.5. For (potential) Hy's Law cases, see section 6.3.7 and Appendix D.

3.9.1 Procedures for discontinuation of a patient from IMP

A patient who decides to discontinue IMP will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of discontinuation from the IMP. For patients who discontinue IMP, their scheduled follow-up visits, data collection and study procedures / assessments should be performed according to study plan until study closure.

The patient should be scheduled for the EOT visit within 24 hours after IV study therapy discontinuation. Liver CRF modules should be completed for patients discontinued after meeting hepatic/liver criteria. Adverse events and SAEs will be followed up as described in sections 6.3 and 6.4. For handling of unused IMP see section 7.6.

3.10 Withdrawal from study

Patients are at any time free to withdraw from the study (i.e. IMP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and

assessed by an investigator at the time of withdrawal and at the LFU visit. Adverse events and SAEs will be followed up as described in sections 6.3 and 6.4. For handling of unused IMP see section 7.6.

Any withdrawal should be notified immediately to the CTCC and the sponsor. To this end, study center personnel should fill out the end of study form in the study database. If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused.

Withdrawal of consent for the use of donated biological samples is discussed in Section 5.6.4.

3.11 Discontinuation of the study

Criteria for discontinuation of the study before (or following) the early safety review are described in sections 5.2.5.4 and 5.2.5.5. Furthermore, the entire study may be stopped by the Sponsor at any time if concerns for safety arise within this study or in any other study with ATM-AVI. In particular, the study may be stopped, if (in the judgment of the Sponsor) trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant (see also section 3.9)
- are assessed as causally related to study therapy
- are not considered to be compatible with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

The study may be terminated at individual centers at any time by the Sponsor if the study procedures are not being performed according to GCP, if concerns for safety arise or if recruitment is slow.

For end-of-study definition and timetable see section 9.4.

4. STUDY PLAN AND TIMING OF PROCEDURES

Study periods are defined in Figure 2. Details of the study plan and timing of procedures are provided in Table 1.

Every effort should be made to collect all the data, blood samples, and cultures and to complete all assessments required for each visit as detailed in the Study Plan detailing the procedures and discussed by visit in the following sections.

Table 1 Study Plan detailing the procedures

Procedures and Assessments	Eligibility/ Screening	Treatment Period[a]		EOT	TOC	LFU
	Visit 1 Day 0	Visit 2 Day 1 (Baseline)	Visit 3 - 15 Days 2 to 14	Visit 16 Within 24 hours after last infusion	Visit 17 Day 25 ± 3	Visit 18 Day 35 ± 3
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Smoking and alcohol history	X					
Medical and surgical history	X					
Review prior and concomitant medications (including prior antibiotic therapy)	X	X	Daily	X	X	X
Complete physical examination	X			X	X	X
Assess infection-related signs and symptoms and perform focused physical / wound examination	X	X[b]	Daily	X	X	X
Vital sign measurements	X	X	Daily	X	X	X
12-Lead digital ECG		X	Day 3	X		
Adverse Events	X	X	Daily	X	X	X
Obtain clinically relevant culture and send to central laboratory	As clinically indicated					
Blood cultures	X	As clinically indicated. If blood cultures are positive: repeat at least every 3 days until negative				
Culture from intra-abdominal site of infection	At surgical intervention					
Safety Labs (Chemistry, Hematology, Urine, CrCl[c])	X	X[b]	Days 4, 7, 10, and 13[e]	X	X	X
Assess AST, ALT, ALP, GGT, total bilirubin, CrCl on treatment			Daily[g]			
Serum β-hCG for women of childbearing potential	X					X
Pharmacokinetic sample: intensive regimen (see Table 4)		Day 1 4 samples	Day 4[f] 11 samples			
Pharmacokinetic sample: sparse regimen (details: see Table 4)		Day 1 4 samples	Day 4[f] 3 samples			
Description of operative procedures	As available	As available	As available	As available	As available	As available
Administer study therapy		X	X			
Clinical response assessment				X	X	X
Record radiologic examination	X[d]					
Mortality assessment				X	X	X

[a]: Treatment period is defined as a minimum of 5 full days to a maximum of 14 full days, where a full day is defined as a 24-hour period. Treatment period starts with administration of the first dose of IV study therapy which marks the beginning of Study Day 1. Visit 2 includes the baseline assessments and Day 1.

[b]: Repeat assessments are only required if Visit 1 and Visit 2 are separated by surgery OR are >12 hours apart (see 4.1.2).

[c] : Following each determination of serum creatinine until LFU (inclusive), also the estimate creatinine clearance will be calculated.

[d]: Radiological examinations are not required for the study but the results should be recorded if done as part of the cIAI diagnosis. Radiological examinations include but are not limited to white blood cell scans, PET scans, plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

[e] : On days 4, 7, 10 and 13, samples can be collected ± 1 day.

[f] : To provide greater flexibility, these samples can be collected on Day ±1 day.

[g]: To be assessed daily in local lab. Review of calculated CrCl and, where necessary, adjustment of ATM-AVI dose (see 7.2)

4.1 Study visits and procedures

Prior to any study specific procedures, patients (or their legally acceptable representative if applicable) must provide written informed consent. Enrolment/screening procedures will be performed according to the Study Plan detailing the procedures. At screening, patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet all of these criteria must not be enrolled in the study.

All subjects will be asked to provide consent to supply blood, urine and microbiological samples as required for the eligibility assessment and further study procedures. This consent is included in the patient informed consent form (ICF).

4.1.1 Visit 1: eligibility/screening procedures (Day 0)

Procedures for Visit 1 will vary depending on the timing of surgery relative to the visit. At Eligibility/Screening (Day 0), each potential patient (or his/her legally acceptable representative) will provide written informed consent prior to starting any study-specific procedures. Visit 1 (eligibility/screening) may occur up to 24 hours pre- or postoperatively.

Each patient will undergo screening assessment procedures within 24 hours prior to the first dose of IV study therapy. Local laboratory test results will be used to qualify patients for inclusion. To this end, the following assessments need to be performed in the local lab and entered in the eCRF: serum creatinine (including calculation of CrCl), serum pregnancy test (or urine pregnancy test for preliminary enrolment if serum test result is not available at screening; see section 3.1d)), AST, ALT, ALP, total bilirubin, and hematology as listed in section 3.1 and 3.2. GGT and INR will be determined in the local lab at screening as baseline safety assessment.

Provided all lab values to be determined in the local lab (see above) have been determined for routine clinical management of the patient within 24 hours prior to the first dose of IV study therapy, additional sampling for analyses in the local lab at screening is not required, and the values already obtained should be entered in the eCRF.

In addition, safety lab samples must be sent to the central reference laboratory for testing (see section 5.2.1).

Screening assessments will consist of:

1. Obtaining informed consent.
2. Reviewing of the inclusion and exclusion criteria with the patient or a legally acceptable representative.
3. Collecting demographics.
4. Collecting smoking and alcohol history
5. Collecting medical and surgical history.

6. Reviewing prior and current medications (including prior antibiotic therapy).

7. Performing complete physical examination as defined in Section 5.2.2

8. Assessing infection-related (e.g. abdominal) signs and symptoms.

9. Measuring vital signs including supine blood pressure, heart rate, body temperature and height/weight prior to dosing as defined in Section 5.2.4.

10. Collecting AEs.

11. Obtaining blood cultures.

12. Obtain clinically relevant cultures and send any pathogen isolated to the central lab. Clinically relevant isolates may originate from both intra-abdominal and other sites.

13. Obtaining blood and urine samples for safety analysis (central reference laboratory)

14. Obtaining blood samples for eligibility and baseline safety assessments at the local lab: serum creatinine (including calculation of CrCl), serum pregnancy test (or urine pregnancy test for preliminary enrolment if serum test result is not available at screening; see section 3.1d)), AST, ALT, ALP, GGT, INR, total bilirubin, and hematology.

15. Estimating creatinine clearance using the serum creatinine results from the local laboratory. In case a local lab result is not available, the creatinine result of the safety lab must be used (to be sent to central lab). See Appendix E for calculation.

16. Obtaining blood sample for serum β-hCG for women of childbearing potential (central reference laboratory)

17. Recording radiological examinations (only if done as part of the diagnosis of the disease under study). Radiological examinations include - but are not limited to - white blood cell scans, PET scans, plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast

Patients who have Visit 1 postoperatively should have the following additional assessments:

18. Focused physical and wound examinations postoperatively.

19. Must have obtained a specimen for culture from the site of abdominal infection as described in section 5.1.2 during a surgical procedure.

20. Collecting description of operative procedures (as available).

4.1.2 Visit 2: eligibility/baseline procedures and Day 1 of treatment

Procedures for visit 2 will vary depending on the timing of the visits 1 and 2 relative to surgery. Visit 2 may occur pre- or postoperatively.

Local laboratory test results obtained at Visit 1 will be used to qualify patients for inclusion (see section 4.1.1). At Visit 2, blood and urine samples for safety analysis (and further assessments as listed in points 12 to 15 of this section) are only required if Visit 1 and Visit 2 are separated by surgery or are more than 12 hours apart. If safety lab samples are required, they should be collected prior to dosing (exception: if visit 2 occurs pre-operatively, study drug may be administered before collecting abdominal cultures; see below 7). The samples must be sent to the central reference laboratory for testing.

The following assessments should be performed for all patients at Visit 2:

1. Reviewing of the inclusion and exclusion criteria with the patient or a legally acceptable representative.

2. Reviewing prior and concomitant medications.

3. Measuring vital signs including supine blood pressure, heart rate and body temperature as defined in Section 5.2.4.

4. Performing a standard 12-lead electrocardiogram (ECG) prior to dosing. The patient should be resting in a supine position for at least 10 minutes prior to the evaluation (see section 5.2.3).

5. Collecting new AEs and reviewing ongoing AEs.

6. If a previous blood culture result was positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. Blood cultures may also be obtained as clinically indicated.

7. Obtaining culture from site of abdominal infection (if not already collected at Visit 1 [Note: if Visit 2 occurs pre-operatively, study drug may be administered before collecting abdominal cultures; however, they must be collected during the surgery]).

8. Obtain isolates from any body sites where infection is suspected. Any isolated pathogen must be sent to the central lab. Clinically relevant isolates may originate from both intra-abdominal and other sites.

9. Collecting description of operative procedures (as available and if not obtained at Visit 1).

10. Administering IV study therapy. Note: all other baseline assessments should be completed before the patient receives the first dose of IV therapy. The only

exception to this is that patients may receive study therapy before obtaining abdominal cultures if Visit 2 occurs pre-operatively.

11. Obtaining blood samples for PK analysis (see section 5.3.1 for details)

In addition, the following assessments must be performed only if Visit 1 and Visit 2 are separated by surgery or occur >12 hours apart:

12. Assessing infection-related signs and symptoms plus abdominal and wound examinations postoperatively. If Visit 2 occurs preoperatively, this assessment needs to be done after surgery.

13. Obtaining blood and urine samples for safety analysis (central reference laboratory).

14. Estimating creatinine clearance using the serum creatinine results from the local laboratory. In case a local lab result is not available, use the creatinine clearance result of the Safety lab (samples sent to central lab). Check applicable dose according to CrCl result (see section 7.2). See Appendix E for calculation.

4.1.3 Visits 3 to 15 (Days 2 to 14): ongoing treatment period

The total duration of combined treatment with IV study therapy will be a minimum of 5 and a maximum of 14 full days (one day = 24 hours). Those patients who require continuation of IV study therapy after 5 days (i.e. after the loading dose and 20 maintenance IV doses) will continue to receive their IV study therapy by study center personnel in the hospital. Following discharge from the hospital, the patients are to return to the study center for their scheduled visits. The following assessment procedures will be performed during treatment with IV study therapy:

1. Reviewing concomitant medications (daily).

2. Assessing infection-related signs and symptoms plus abdominal and wound examinations postoperatively (daily).

3. Measuring vital signs (daily) including supine blood pressure, heart rate and body temperature as defined in section 5.2.4.

4. On Day 3 only - two ECG measurements: one measurement at the end of an ATM/AVI infusion period and one measurement prior to starting the next ATM-AVI infusion (see section 5.2.3).

5. Collecting new AEs and reviewing ongoing AEs (daily). Should a patient experience significant diarrhea during or after IV study therapy, the investigator should obtain a stool sample for *Clostridium difficile* toxin testing.

6. Obtaining culture from site of abdominal infection and any other body site where infection is suspected (as clinically indicated).

7. If a previous blood culture result was positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. Blood cultures may also be obtained as clinically indicated.

8. Obtaining blood and urine samples for safety analysis and calculation of CrCl (only day 4, 7, 10 and 13; i.e. every 3 days until EOT; send samples to central reference laboratory). Samples collected on day 4, 7, 10 and 13 can be collected ±1 day.

9. During treatment, daily assessment of AST, ALT, ALP, GGT, total bilirubin and creatinine clearance in local lab. On treatment days where clinical chemistry samples are taken for routine clinical management of the patient, these samples should be used to assess AST, ALT, ALP, GGT, total bilirubin and CrCl, in order to avoid additional sampling for study purposes. Enter values in the eCRF. Review of calculated CrCl and, where necessary, adjustment of ATM-AVI dose (Cohort 2 and 3 only; see section 7.2). Review of AST, ALT, ALP, GGT and total bilirubin value and, where necessary, initiation of additional measures as listed in sections 6.7.3 and 3.9.

10. On Day 4 only - obtaining blood samples for PK analysis (see section 5.3.1 for details). To provide greater flexibility, PK samples can be collected on Day 4 ± 1 day.

11. Collecting description of operative procedures (any post-baseline procedures as available and if not obtained at prior visits).

12. Administering IV study therapy (daily for a minimum of 5 full days to a maximum of 14 full days, where a full day is defined as a 24-hour period).

4.1.4 Visit 16: end of IV therapy (EOT) procedures

The following procedures will be performed within 24 hours after the completion of the last infusion of IV study therapy:

1. Reviewing concomitant medications.

2. Performing complete physical examination as defined in Section 5.2.2

3. Assessing infection-related signs and symptoms plus abdominal and wound examinations postoperatively.

4. Measuring vital signs including supine blood pressure, heart rate and body temperature as defined in Section 5.2.4.

5. Performing a standard 12-lead electrocardiogram (ECG). The patient should be resting in a supine position for at least 10 minutes prior to the evaluation (see section 5.2.3).

6. Collecting new AEs and reviewing ongoing AEs (daily). Should a patient experience significant diarrhea after IV study therapy, the investigator should obtain a stool sample for *Clostridium difficile* toxin testing.

7. Obtaining culture from site of abdominal infection and any other body site where infection is suspected (as clinically indicated).

8. If a previous blood culture result was positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. Blood cultures may also be obtained as clinically indicated

9. Obtaining blood and urine samples for safety analysis (central reference laboratory).

10. Assessing creatinine clearance using the creatinine clearance results from the safety analysis (samples sent to central lab).

11. Collecting description of operative procedures (any post-baseline procedures as available and if not obtained at prior visits).

12. Determining clinical response assessment (see section 5.1.1 for details)

13. Mortality assessment by the investigator in case of death (including causality attribution and reason of death)

4.1.5 Visit 17 test of cure (TOC) procedures (Day 25 +/- 3 days)

If it is not possible to perform the TOC on study Day 25 (e.g., the patient is on holiday), then the allowed visit window is Day 22 to 28.

TOC visit assessment procedures include:

1. Reviewing concomitant medications.

2. Performing complete physical examination as defined in Section 5.2.2

3. Assessing infection-related signs and symptoms plus abdominal and wound examinations postoperatively.

4. Measuring vital signs including supine blood pressure, heart rate and body temperature as defined in Section 5.2.4.

5. Collecting new AEs and reviewing ongoing AEs (daily). Should a patient experience significant diarrhea after IV study therapy, the investigator should obtain a stool sample for *Clostridium difficile* toxin testing.

6. Obtaining culture from site of abdominal infection and any other body site where infection is suspected (as clinically indicated).

7. If a previous blood culture result was positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. Blood cultures may also be obtained as clinically indicated.

8. Obtaining blood and urine samples for safety analysis (central reference laboratory).

9. Assessing creatinine clearance using the creatinine clearance results from the safety analysis (sent to central lab).

10. Collecting description of operative procedures (any post-baseline procedures as available and if not obtained at prior visits).

11. Determining clinical response assessment (see section 5.1.1 for details)

12. Mortality assessment by the investigator in case of death (including causality attribution and reason of death)

4.1.6 Visit 18: late follow-up (LFU) procedures (Day 35 +/- 3 days)

If it is not possible to perform the LFU on study Day 35 (e.g., the patient is on holiday), then the allowed visit window is Day 32 to 38.

LFU visit assessment procedures include:

1. Reviewing concomitant medications.

2. Performing complete physical examination as defined in Section 5.2.2

3. Assessing infection-related signs and symptoms plus abdominal and wound examinations postoperatively.

4. Measuring vital signs including supine blood pressure, heart rate and body temperature as defined in Section 5.2.4.

5. Collecting new AEs and reviewing ongoing AEs (daily). Should a patient experience significant diarrhea after IV study therapy, the investigator should obtain a stool sample for *Clostridium difficile* toxin testing.

6. Obtaining culture from site of abdominal infection and any other body site where infection is suspected (as clinically indicated)

7. If a previous blood culture result was positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. Blood cultures may also be obtained as clinically indicated.

8. Obtaining blood and urine samples for safety analysis (central reference laboratory).

9. Assessing creatinine clearance using the creatinine clearance results from the safety analysis (sent to central lab).

10. Obtaining blood sample for serum β-hCG for women of childbearing potential (central reference laboratory).

11. Collecting description of operative procedures (any post-baseline procedures as available and if not obtained at prior visits).

12. Determining clinical response assessment (see section 5.1.1 for details).

13. Mortality assessment by the investigator in case of death (including causality attribution and reason of death)

5. STUDY ASSESSMENTS

The web based Electronic Data Capture (EDC) and Clinical Data Management System TrialMaster (OmniComm Systems, Inc.) will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

The central laboratory will provide ongoing safety laboratory data, including liver function test data, to the CTCC and the sponsor and the scientific advisory committee, to inform per patient decisions and for the early patient safety and PK review.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site at the end of the trial.

5.1 Clinical and microbiological assessments

5.1.1 Efficacy assessment: Clinical response

The investigator will determine the treatment outcome (clinical response) at the EOT, TOC and LFU visit as either cure, failure or indeterminate in the MITT populations according to the definitions given in Table 2. In case of failure, the reason for failure will be indicated according to the clinical response definitions shown in Table 2.

Table 2: Definitions of clinical response at the EOT, TOC, LFU visits

Clinical Response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection (cIAI) such that no further antimicrobial therapy, drainage, or surgical intervention is necessary and does not meet any of the failure criteria listed below.
Failure	Patients who meet any 1 of the following criteria will be considered a treatment failure: • Death related to intra-abdominal infection • Patient who received treatment with additional antibiotics for ongoing symptoms of cIAI (including patients prematurely discontinued from study therapy due to an adverse event who require additional antibiotics for cIAI) • Patient previously met criteria for failure (i.e. prior to respective visit) • Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively (exception: the re-intervention was already planned at initial surgery to check proper infection/focus control, occurs within 96 hours after enrolment, does not show deterioration and includes fascial closure) • Post-surgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: Patient lost to follow-up or assessment not undertaken such that a determination of clinical response cannot be made

Abbreviations: cIAI, complicated intra-abdominal infection; EOT, End of Treatment (with study therapy); LFU, Late follow-up; TOC, Test of Cure.

5.1.2 Microbiological assessments

All microbiological assessments will be initiated at the local laboratory for specimen collection, shipment of isolates, and analysis of isolates according to the sections below and as outlined in more detail in the microbiological (study site) manual. Details regarding the microbiological analyses in the Central Laboratory are described in the Laboratory Manual. The data obtained at the Central Laboratory will be used for further study-related assessments (see below).

Specimen collection:

An adequate intra-abdominal culture specimen (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) should be obtained from all patients at surgery and sent to the local laboratory for culture, identification, and in vitro susceptibility testing. The specimens should be processed according to recognized methods that culture for both aerobic and anaerobic organisms (Murray et al 2007) following the standard operating procedures of the clinical microbiology laboratory at each study center. Furthermore, throughout the study, specimens from relevant infection sites should be obtained and cultured at the local lab as

clinically indicated. Clinically relevant isolates may originate from both intra-abdominal and other sites (e.g., additional specimens should be collected in case of second surgery or bacteraemia).

Blood culture specimens will be taken at eligibility/screening (visit 1). Thereafter, blood culture specimens will be taken as clinically indicated (e.g. repeated sampling if prior blood cultures were positive). Two sets of blood cultures should be collected (i.e., 4 bottles) from 2 different sites for aerobic and anaerobic incubation. One set of blood cultures must be obtained through a venepuncture. Each bottle should be inoculated with 10 mL of blood for a total of 40 mL per collection. Details concerning the collection of blood cultures are provided in the laboratory manual.

Pure cultures of all pathogenic isolates must be sent to the central reference laboratory for confirmation of identification and susceptibility testing. Duplicate copies of the isolates should be kept by the local laboratory at –20°C or colder (preferably at –70°C) until the end of the study or when contacted by the central reference laboratory that they may be destroyed. All microbiological sampling and pathogens isolated in the local lab during the study (i.e. in the blood at baseline or thereafter, intra-abdominal cultures at surgery, and clinically relevant cultures throughout the study from any site) will be recorded and entered in the eCRF, along with disc susceptibility testing results.

If treatment is discontinued early because the patient is failing therapy and the patient requires a second surgery, an appropriate specimen for culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered. The eCRF should indicate whether or not a sample was obtained.

Analysis of isolates

The local laboratory must identify all aerobic bacterial pathogens to the genus and species level using confirmatory (not presumptive) identification methods from blood, intra-abdominal or other specimens. Antimicrobial susceptibility should be determined for each aerobic pathogen isolated according to local practices. In addition, a disk diffusion test for ATM-AVI must be performed on each aerobic isolate using CLSI methods [CLSI document M2]. Reporting of susceptibility results on ATM-AVI to the principal investigator will be detailed in the study site manual. The local laboratory can perform any additional testing on further agents as they normally do to provide susceptibility results of isolated aerobic microorganisms.

All anaerobic bacterial pathogens must be identified to at least the genus level. If the local laboratory cultures and performs susceptibility testing on anaerobic organisms, it should follow CLSI methodologies by either broth microdilution (*Bacteroides fragilis* group) or agar dilution with minimum inhibitory concentration (MIC) testing only on metronidazole. However, all anaerobic isolates must be sent to the central reference laboratory for confirmation of identification and susceptibility testing.

Handling of microbiological data and shipment of isolates

The investigator should record information on all specimens according to the microbiological investigator's manual supplied by the central reference laboratory. All specimens collected at baseline or post baseline should be entered in the eCRF with regards to a) day, time and site of sampling b) local identification for each pathogen and c) disc susceptibility / MIC to the study therapy for each pathogen.

An isolate ID number will be allocated to all isolates obtained at the local lab, using the reference number allocated to the transportation kit provided by the central lab. Samples of all microbiological isolates must be shipped to the central reference laboratory for confirmation of microbiological assessments. The central reference laboratory will supply the local laboratory with all media containing transport vials and instructions for shipment of isolates to the central reference laboratory. The central lab will also supply susceptibility testing discs for ATM-AVI and monitor / verify resistant isolates reported by the local lab.

The central reference laboratory will confirm pathogen identifications and susceptibility test results on all clinical isolates reported and shipped by the local laboratory. Thus, the central laboratory is responsible for the definitive identification for each microbiological organism and determination of MICs for ATM-AVI and comparator antibiotics. If a) discrepancies occur between the results obtained at the central lab and those obtained at the local lab or b) microorganisms that are isolated at the local lab do not survive shipping to the central lab, a sponsor representative or delegate may request to ship a second sample of the isolate in question. In the instance of differences in pathogen identification or susceptibilities, the central reference laboratory results will take precedence over the local laboratory results.

The data obtained at the central reference lab will be used to determine descriptively a) the pathogen(s) causing the patient's infection and b) the efficacy of the study therapy at the pathogen level. Local laboratory results may be used if a microorganism does not survive shipping or is not recoverable from the local laboratory. The central reference lab will transfer all microbiological data directly to CTCC where they will be merged into the study database (without being entered in the eCRF). The isolate ID number will be used to match the data obtained at the central lab with the data obtained at the local lab. Details will be described in a data transfer agreement.

5.2 Safety assessments

Safety and tolerability assessment will be undertaken on individual patient and cohort basis, for the early patient safety and PK review, through a determination of serious adverse events (SAE) and adverse events (AE) based on signs and symptoms, examinations and laboratory tests. If deterioration in a laboratory value or vital sign is associated with clinical signs or symptoms, the sign or symptom will be reported as an adverse event (AE) and the associated laboratory result or vital sign will be considered as additional information. For details on AE definition and reporting see section 6.

5.2.1 Laboratory safety assessments

Blood and urine safety samples for determination of clinical chemistry, haematology and urinalysis will be taken at the following sampling time points as described in section 4: at screening, at baseline (note: baseline assessment only required if Visit 1 and Visit 2 are separated by surgery OR are >12 hours apart); days 4, 7, 10, and 13 (+/- 1 day); end of therapy (EOT; within 24 hours after end of last infusion), test of cure (TOC; day 25 +/- 3 days), and late follow-up (LFU; day 35 +/- 3 days).

Safety samples will be sent to the central laboratory for analysis. The date and time of collection will be recorded on the patient's eCRF. The results of safety lab sampling will be made available to the investigators. The laboratory safety variables to be measured at the central laboratory are displayed in Table 3.

For eligibility assessment (additional determination of serum creatinine / calculation of CrCl, serum pregnancy test (or urine pregnancy test for preliminary enrolment if serum test result is not available at screening), AST, ALT, ALP, total bilirubin, hematology as defined in section 3.1 and 3.2), local laboratory test results will be used and entered in the eCRF.

Hepatic and renal function should be closely monitored throughout the treatment period. AST, ALT, ALP, GGT, total bilirubin and creatinine clearance will be assessed daily in the local lab and the values entered in the eCRF. The CrCl value (calculated by the Cockcroft- Gault formula using serum creatinine; see Appendix E) will be reviewed and, where necessary, the ATM-AVI dose will be adjusted (see section 7.2). Following review of AST, ALT, ALP, GGT and total bilirubin values, additional measures as listed in sections 6.7.3 and 3.9 will be initiated where required.

Further safety samples may be collected if clinically indicated at the discretion of the investigator and analysed in the local laboratory of the study site.

Table 3: Laboratory Safety Variables

Clinical chemistry	Hematology	Urinalysis
Alanine aminotransferase	Hematocrit	Appearance (color, clarity)
Albumin	Hemoglobin	Bilirubin
Alkaline phosphatase	INR (local lab only)	Glucose
Aspartate aminotransferase	Platelet count	Ketones
β-hCG [a]	Red blood cell count	Leukocyte esterase
Bicarbonate	White blood cell count (total and differential)	Nitrite
Blood urea nitrogen		pH
Calcium, total		Protein
Chloride		Specific gravity
Creatinine [b]		Urobilirubin
Gamma glutamyl transferase (local lab only)		Microscopic examination:
Glucose (nonfasting)		Red blood cells
Inorganic phosphorus		White blood cells
Potassium		Casts
Sodium		Crystals
Bilirubin (total, direct and indirect)		Bacteria, yeast cells, or parasites
Total protein		
Other		
Blood cultures[c]		

[a] β-hCG: β-human chorionic gonadotropin; will be determined for woman of childbearing potential at screening (visit 1) and LFU only.
[b] following each determination of serum creatinine until LFU (inclusive), also the estimate creatinine clearance will be calculated.
[c] samples for blood cultures should be taken at eligibility/screening and as clinically indicated thereafter (e.g. if previous blood cultures were positive). See section 4.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities and criteria for intensified monitoring and/or discontinuation of study drug (see sections 3.9 and 6.7.3). The laboratory results should be signed and dated and retained at study centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see section 6.3.6.

For each determination of serum creatinine until EOT (inclusive), also the estimate creatinine clearance will be calculated as defined according to Appendix E. The investigator will assess the patient's eligibility regarding renal function continuously during the study (for criteria and timing see section 6.7.2 and the Study Plan detailing the procedures. For monitoring of liver-related laboratory parameters, see section 6.7.3. For discontinuation of individual patients based on laboratory safety assessments, see section 3.9.

5.2.2 Physical examination

A complete physical examination will be performed as scheduled and displayed in the Study Plan detailing the procedures. The physical examinations will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen including wound examination, musculoskeletal, and neurological systems.

If pathologic findings emerge or worsen compared to the physical examination at screening, these findings should be documented as AEs on the respective page of the eCRF. If the findings meet the criteria for an SAE, procedures for reporting such events should be followed (refer to section 6.4).

Height and weight will be measured at the screening visit, and the body mass index will be calculated as the ratio of weight in kg/(height in cm/100)^2. If these assessments cannot be performed due to the patient's clinical condition, they may be done later (as soon as possible). After the screening visit, weight should be measured as clinically indicated.

A detailed focused (abdominal) assessment will be performed at screening, at baseline (note: baseline assessment only required if Visit 1 and Visit 2 are separated by surgery OR are >12 hours apart), daily during treatment with IV study therapy, at the EOT, TOC, and LFU visits.

5.2.3 ECG

Standard 12-lead ECGs (triplicates for each recording time point) will be recorded and assessed at Visit 2 (baseline), Day 3 and EOT (see Table 1). Two recordings will be taken on Day 3; one within 30 minutes of the end of the ATM-AVI infusion and one just prior to starting the next infusion. One recording only is required at Visit 2 (baseline) and EOT. The ECGs should be standard 12-lead ECGs with a lead II rhythm strip with the patient in the supine position after the patient has rested in this position for 10 minutes. If clinically indicated, additional ECG recordings can be made at the discretion of the investigator as unscheduled assessments. A single independent third party using uniform techniques will carry out formal analysis and reporting of ECG data for purposes of the study. For adverse event reporting of ECG abnormalities see section 6.3.6.

5.2.4 Vital signs

Vital sign measurements (including blood pressure, heart rate, body temperature and respiratory rate) should be assessed at Screening, Baseline, daily while the patient is receiving IV study therapy, at EOT, at TOC, and at the LFU visit (see Table 1).

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The results should be signed and dated and retained at study centre as source data. For information on how AEs based on vital signs should be recorded and reported, see section 6.3.6.

5.2.4.1 Blood pressure and heart rate

Supine blood pressure and heart rate will be measured using a semiautomatic blood pressure recording device with an appropriate cuff size. The patients will be required to rest in a supine position for at least 10 minutes prior to heart rate and blood pressure measurements.

5.2.4.2 Body temperature

Body temperature will be measured using an automated thermometer. The patient's body temperature will be evaluated at least twice a day (suggested at least 8 hours apart) and the

actual time of body temperature collection will be recorded. Fever will be defined as a body temperature >38°C. For each individual patient, the method of temperature measurement ideally should be consistent for the duration of the study.

5.2.4.3 Respiratory rate

Respiratory rate will be collected in breaths per minute.

5.2.5 Safety and PK Assessments by the Scientific Advisory Committee

5.2.5.1 Early safety assessment – Cohort 1 review

The safety and tolerability of the ATM-AVI dosing regimen (500 mg ATM plus 137 mg AVI loading dose by IV infusion over a 30 minute period, immediately followed by a maintenance dose of 1500 mg ATM plus 410 mg AVI by IV infusion over a 3 hour period every 6 hours) will be assessed based on the impact on patient liver transaminases. The assessment will be both a per patient assessment throughout the study period and per a cohort review of the first 10 patients having completed all PK and safety assessments.

The initial safety review (together with the parallel evaluation of the pharmacokinetics of ATM-AVI – see section 5.3.3) will be assessed by the SAC and the sponsor and input to a decision on whether

(a) the study is discontinued, or

(b) the remainder of the study will continue with the same dose regimen for patients with normal renal function or mild renal impairment (CrCl >50 mL/min), or

(c) patients in Cohort 2 with normal renal function or mild renal impairment (CrCl >50 mL/min) will receive the higher AVI dose (loading dose of ATM 500 mg / AVI 167 mg, followed by maintenance doses of ATM 1500 mg / AVI 500 mg)

and

(d) patients with moderate renal impairment (CrCl 31 to 50 mL/min) should be included and administered the proposed dosing regimen for these patients as described in section 7.2.

5.2.5.2 Second safety assessment – Cohort 2 review

In the event that the AVI dose is increased in Cohort 2, a second safety and PK review will occur once at least10 patients in Cohort 2 have completed all safety and PK assessments. The assessment will be both a per patient assessment throughout the study period and per a cohort review of the first 10 patients in Cohort 2 having completed all PK and safety assessments.

The second safety review (together with the parallel evaluation of the pharmacokinetics of ATM-AVI – see section 5.3.3) will be assessed by the SAC and the sponsor and input to a decision on whether

a) the remainder of the study (Cohort 3) will continue at the same (higher AVI dose) regimen, or

b) the remainder of the study will continue (Cohort 3) with the lower AVI dose regimen for patients with CrCl > 50 mL/min and for patients with CrCl 31-50 mL/min, respectively (as described in section 7.2), and

c) the dose regimen selected is confirmed for the development of ATM-AVI.

5.2.5.3 Criteria for immediate progression

The criteria for immediate progression after the safety reviews are as follows:

- All transaminase rises are asymptomatic and rapidly reversible upon end of (or discontinuation of) therapy.
    - Individual patient transaminase elevations:
    - Patients with normal baseline transaminases (elevations < 5xULN)
    - Patients with baseline transaminase >3xULN and <5xULN documented as being directly related to infection being treated (inclusion criteria) - elevations no higher than 8xULN
- No more than 2 individuals have transaminase elevation as described above

If the criteria for immediate progression are met, investigators will be informed of the decision to continue recruiting as soon as feasible (within a timeframe to be confirmed). The pharmacokinetic data will be evaluated when available but will not be required to confirm the decision for immediate progression.

5.2.5.4 Criteria for stop and review

The criteria for stop and review before enrolment of further patients are as follows:

- Any one transaminase elevation is not rapidly reversible (in the absence of an alternative explanation for transaminase elevation)
- Between 3 to 5 individuals have a transaminase elevation as described in section 5.2.5.3
- Any one patient meets the following individual transaminase discontinuation criteria in the absence of an alternative explanation:

    Patients with initial normal baseline transaminases progressing to:

    - ALT or AST ≥3×ULN and evidence of coagulopathy
    - ALT or AST ≥3×ULN with symptoms suggestive of new or progressive liver disease

    Patients with initial baseline transaminases >3xULN and <5xULN, documented as being directly related to infection being treated, progressing to:

- ALT or AST ≥ 5×ULN and evidence of coagulopathy
- ALT or AST ≥ 5×ULN with symptoms suggestive of new or progressive liver disease

In the event of a stop and review before progression, available pharmacokinetic data will be evaluated to determine the relationship between exposure and transaminase elevation. More extensive modelling may be required to determine if a change in dose is required and to identify an appropriate dose for the remaining patients.

5.2.5.5 Criteria for non-progression

The criteria for non-progression after the safety review of Cohort 1 are as follows:

- 1 patient meets Hy's Law criteria (see Appendix D)
- More than one transaminase rise is not rapidly reversible (in the absence of an alternative explanation for transaminase elevation)
- More than 5 individuals have a transaminase rise as described in section 5.2.5.3
- Three or more patients meet the following individual transaminase discontinuation criteria in the absence of an alternative explanation:

  Patients with normal baseline transaminases

  - ALT or AST ≥3×ULN and evidence of coagulopathy
  - ALT or AST ≥3×ULN with symptoms suggestive of new or progressive liver disease

  Patients with baseline transaminases >3xULN and <5xULN documented as being directly related to infection being treated

  - ALT or AST ≥5×ULN and evidence of coagulopathy
  - ALT or AST ≥5×ULN with symptoms suggestive of new or progressive liver disease

If any one of the above criteria for non-progression occurs before 10 patients have been recruited for the early safety review, then the study will be stopped. If any one of the above criteria for non-progression occurs before or at the time of the 10 patient safety review in Cohort 2, then dosing at the higher AVI dose will be stopped and the data reviewed prior to a decision to continue with recruitment at the lower AVI dose. Further criteria for discontinuation of the study are listed in section 3.11. Discontinuation criteria for individual patients are listed in section 3.9.

All patients observed with transaminase elevation will be monitored where required as per the criteria outlined in section 6.7.3.

5.3 Pharmacokinetics

5.3.1 Collection of samples

Blood samples (3 mL per sample) for plasma PK analysis of ATM-AVI will be collected at the times presented in Table 4 and Figure 3, Figure 4 and Figure 5. The sampling plan is based on the dosing schedule as described in section 7.2. Samples will be drawn from the opposite arm to that which is used for drug infusions. For detailed information on handling of samples and blood volume, see section 5.6 and Laboratory Manual.

All patients will undergo sparse pharmacokinetic sampling on Day 1 of treatment. On Day 4, the first twenty five (25) patients will undergo intensive pharmacokinetic sampling. The remaining 15 patients will have a sparse PK sampling regimen on Day 4. The date, starting and end time of infusion and exact time of collection of each sample will be recorded in the eCRF. To provide greater flexibility, Day 4 intensive and sparse PK samples can be collected on Day 4 ± 1 day, when steady state concentrations of ATM-AVI will have been attained.

Table 4: Pharmacokinetic ATM-AVI Sample Collection Time Points

Day	Sample time
Day 1	All patients: sparse sampling (4 samples/patient) **Sample 1:** 0h (within 1h before start of loading dose) **Sample 2**: within 5 min before the end of the loading dose infusion **Sample 3**: anytime within the 15 minutes prior to the end of the second IV infusion (3.25h – 3.5h after start of loading dose infusion) **Sample 4**: within 5-6 h after start of loading dose infusion
Day 4	First 25 patients: intensive sampling (11 samples/patient) Trough (within 10 min prior to IV infusion start), 0.5h 1, 2, 3 (within 15 min before IV infusion stop), 3.25, 3.5. 3.75, 4, 5, and 6 h after start of IV infusion (just before start of next infusion) Remaining 15 patients: sparse sampling (3 samples/patient) **Sample 1**: within 1 h of start of IV infusion **Sample 2:** within the 15min prior to the end of IV infusion (within 2.75 to 3 h after start of IV infusion) **Sample 3:** within 5-6 h after start of IV infusion (within one hour prior to start the next infusion)

Figure 3 Sampling regimen on Day 1

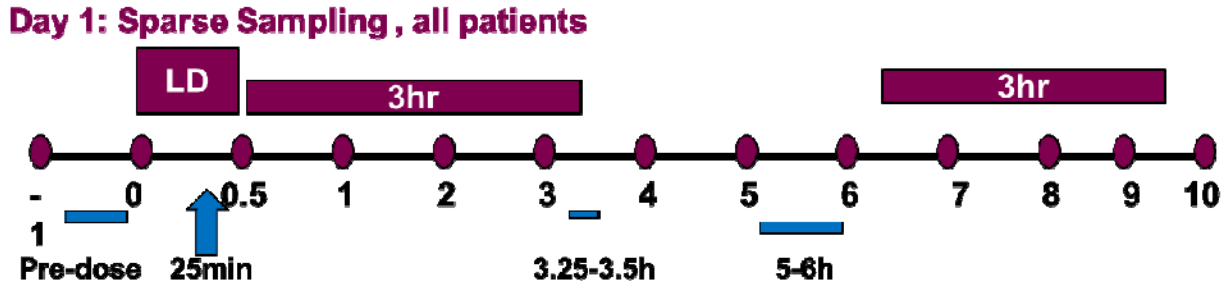


Figure 4 Sampling regimen on Day 4 – intensive sampling

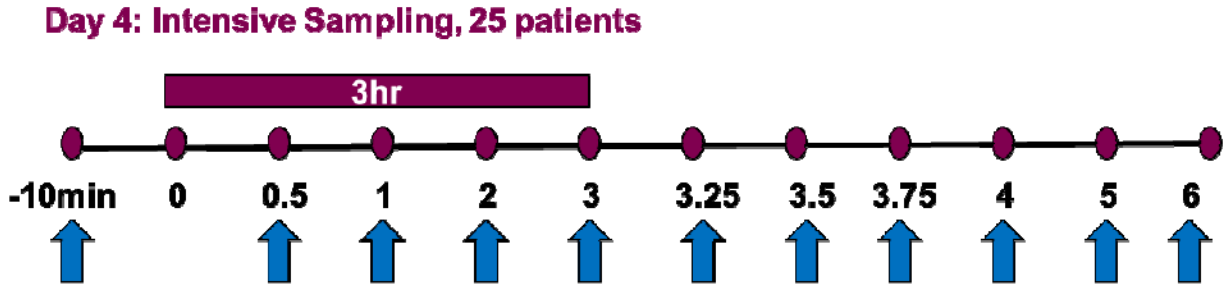
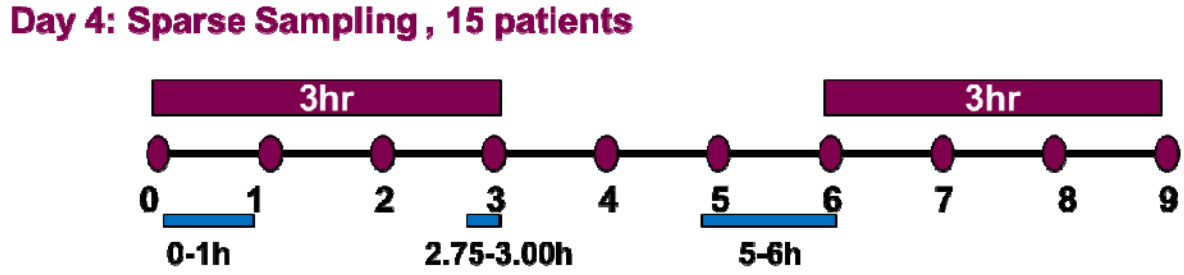


Figure 5 Sampling regimen on Day 4 – sparse sampling



5.3.2 Determination of drug concentration in plasma

Samples for determination of ATM and AVI concentrations in plasma will be analysed by Covance on behalf of the sponsor, using an appropriate validated bioanalytical method. Full details of the bioanalytical methods used will be described in a separate bioanalytical report. All samples within the known stability of the analytes of interest (i.e., ATM and AVI) at time of receipt by the bioanalytical laboratory will be analysed.

Incurred sample reproducibility analysis will be performed alongside the analysis of the PK samples and reported in a separate bioanalytical report. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Results from such analyses may also be reported separately from the CSR. For analysis of pharmacokinetic data, see section 8.5.4.

5.3.3 Early patient review and second safety and PK assessment– evaluation of the pharmacokinetics of ATM and AVI

Data from the first 10 patients having completed all PK and safety assessments (with normal/mild renal impairment status) in Cohort 1 (and in Cohort 2 in the event that AVI dose escalation has occurred) will be assessed to provide confirmation of the pharmacokinetic profile of ATM-AVI in patients in comparison to the profile previously observed in healthy human volunteers, when administered via a loading dose followed by a maintenance infusion regimen (q6h, 3h infusion). These patients will have sparse sampling on Day 1 and intensive sampling on Day 4, as described in Table 4. The reviews will contribute to the parallel safety and tolerability assessment in order to provide input for the decisions listed in section 5.2.5. Scheduled protocol (i.e. not actual) plasma PK sampling times will be used in the PK calculations for the early safety & PK review. Pharmacokinetic sampling will continue, if there is a positive decision to proceed (see section 5.2.5) to complete the full data set of 40 patients.

5.3.4 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses, see section 5.6.1.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

5.4 Pharmacodynamics

See section 5.1.1.

5.5 Pharmacogenetics: not applicable

Pharmacogenetic samples will not be taken during the study.

5.6 Biological sampling procedures

Samples for safety, microbiological and PK analyses will be collected as per the inclusion criteria, Study Plan (Table 1) and PK sampling schedule (Table 4). The volume of blood to be drawn from each patient is displayed in Table 5. Prior to any sampling, the patient's (or legally acceptable representative's) informed consent to the use and storage of donated

biological samples is to be obtained (as part of the Informed Consent Form). All samples will be processed and analysed using sensitive and validated bioanalytical methods.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on ATM-AVI become available. The results of safety lab sampling (clinical chemistry, hematology) will be made available to the investigators. Similarly, the results of microbiological blood cultures obtained for study purposes will be made available to the investigators without delay.

The total volume of blood that will be drawn from each patient in this study is presented in Table 5:

Table 5: Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	min. 6, max. 10[a]	min. 30, max. 50
	Hematology	2.5	min. 6, max. 10[a]	min. 15, max. 25
	Renal and hepatic function	2.5	max. 14[e]	max. 35[e]
Pregnancy test[b]		2.5	2	0 or 5
Pharmacokinetic sampling		3	7 or 15[c]	21 or 45
Blood culture		10	4[d]	40
Total				106 – 200

[a] Number of samples depends on clinical response (duration of therapy: 5 – 14 days) and timing of surgery relative to screening. Sampling time points: screening (local AND central lab), baseline (if Visit 1 and Visit 2 are separated by surgery or occur >12 hours apart), study days 4, 7, 10, and 13 (+/- 1 day); end of therapy (EOT; within 24 hours after end of last infusion), test of cure (TOC; day 25 +/- 3 days), and late follow-up (LFU; day 35 +/- 3 days).

[b] Determination of β-human chorionic gonadotropin (β-hCG) for woman of childbearing potential at screening (visit 1) and LFU only.

[c] Number of samples depends on which PK sampling regimen the patient will undergo (see Table 4).

[d] Blood cultures will be taken at eligibility / screening regardless of whether they are indicated for standard care. If the culture is positive at enrolment, additional samples will be collected as clinically indicated. Each blood culture will consist of 2 sets of 20 ml (10ml in aerobic bottle and 10ml in anaerobic bottle). The blood samples must be taken 30 min apart or at the same time from 2 different venepuncture sites (e.g. peripheral and central line).

[e] Hepatic and renal function (AST, ALT, ALP, GGT, total bilirubin and CrCl) will be assessed daily in the local lab during treatment. The number of additional samples depends on the duration of therapy (5 – 14 days) and on the number of samples taken anyway for the clinical management of the patient. On treatment days where clinical chemistry samples are taken for routine clinical management of the patient, these samples should be used to assess AST, ALT, ALP, GGT, total bilirubin, CrCl, and the values entered in the eCRF, in order to avoid additional sampling for study purposes.

5.6.1 Storage, re-use and destruction of biological samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses or research projects. Key samples for exploratory biomarker research or metabolite identification and/or analysis may be retained at an sponsor assigned Biobank, at the central laboratory, or possibly a COMBACTE-CARE partner laboratory on behalf of the sponsor for

a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results from investigation will not be reported in the CSR but separately in a scientific report or publication.

5.6.2 Labelling and shipment of biological samples

The investigator will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'. Any samples identified as Infectious Category A materials are not to be shipped and no further samples will be taken from the patient unless agreed upon by the sponsor and the appropriate labelling, shipping, and containment provisions are approved.

Samples must be collected, labelled, processed, analysed, stored and transported to the relevant storage site, as indicated in the Laboratory Manual. Tubes will be labelled with the study number, sample description and date and time of collection. The date and time of the sample collection will be recorded in the source documents and in the appropriate section of the eCRF.

An isolate ID number will be allocated to all pathogen isolates obtained at the local microbiological lab. Samples of all isolates will be sent to the central reference lab (see section 5.1.2). PK samples will be shipped periodically from the study centers to the responsible (sponsor-approved) laboratory at agreed intervals.

Samples should be shipped in batches if possible. Logistics should be coordinated between involved parties to ensure that samples will arrive during working hours. A requisition sheet should accompany the shipment that details the study number, centre number, enrolment number, date of sample collection, and a unique identifier for each of the samples in the shipment. Detailed instructions for sample processing and shipping are given in the study site manual and in the laboratory manual.

5.6.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigators at each study centre keep full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keep documentation of receipt of arrival. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

The sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers. Samples retained for further use are registered in the sponsor's Biobank system during the entire life cycle.

5.6.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples are already analysed, the sponsor is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, the patient may be withdrawn from further study participation at the discretion of the investigator.

The investigator:

- Ensures that the sponsor is notified immediately of a patient's withdrawal of informed consent to use donated samples
- Ensures that biological samples from that patient, if stored at the study center, are immediately identified, disposed of or destroyed, and the action documented
- Ensures the laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented, and the signed document returned to the study center
- Ensures that the patient and the sponsor are informed about the sample disposal.

The sponsor verifies that the laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of or destroyed and the action documented and returned to the study center.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The investigator is responsible for ensuring that all study centre personnel involved in the study are familiar with the content of this section. This is of the utmost importance.

Safety and tolerability assessment will be undertaken on individual patient and cohort basis through a determination of serious adverse events and adverse events based on signs and symptoms, examinations and laboratory tests.

6.1 Definition of adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no IV study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definition of serious adverse event

A serious adverse event is an AE occurring during any study phase after the patient has signed the ICF (i.e., treatment, follow-up) that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation excluding hospitalization due to worsening or failure of treatment for primary infection under study
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above, including suspected transmission of an infectious agent via the IV study therapy

Cases of liver dysfunction that meet Hy's Law criteria are defined and reported as SAEs, using the "important medical event" seriousness criterion if no other criteria are applicable (see Appendix D). For further guidance on the definition of a SAE, see Appendix B.

6.3 Recording of adverse events

Planned procedures or hospitalizations should not be recorded as SAEs, but complications arising from planned procedures or hospitalization / prolongation of hospitalizations meeting a seriousness criterion should be recorded and reported as SAEs.

6.3.1 Time period for collection of adverse events

Adverse Events and Serious Adverse Events must be collected for each patient from the time when informed consent is obtained at screening until the late follow-up visit (irrespective of whether the last follow-up visit attended by the patient is TOC or LFU; i.e. at the latest until Day 38).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment (LFU) will be followed up by the investigator for as long as medically indicated, i.e. until the event is resolved or stabilized. Pfizer /CTCC retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- Date and time when the AE started and stopped
- Maximum intensity:
  - mild (awareness of sign or symptom, but easily tolerated)
  - moderate (disturbing but still tolerable)
  - severe (intolerable)
- Whether the AE is serious or not
- Investigator causality rating against the IV study therapy (yes or no)
- Action taken with regard to the IV study therapy
- AE caused subject's withdrawal from study (yes or no)
- Outcome of the AE

In addition, the following variables will be collected for SAEs:

- Onset date (date AE met seriousness criteria)
- Detection date (date the investigator became aware of the SAE)
- AE is serious due to:

(a) Death; if fatal outcome, the following will be collected:

- Date of death
- Autopsy performed
- Primary/secondary cause of death

(b) Life threatening

(c) Inpatient hospitalization or prolongation of existing hospitalization (note: patients will be hospitalized at study entry. A planned hospitalization and the initial hospitalization that made the patient eligible for the study will not be considered an SAE but if the hospitalization is prolonged due to an AE, the hospitalization becomes an SAE)

- Date of hospitalization

– Date of discharge

(d) Result in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

(e) Congenital abnormality or birth defect

(f) Important medical event

- Suspected transmission of an infectious agent via investigational medicinal product
- Causality assessment in relation to study procedures
- Causality assessment in relation to other medication
- Description of SAE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity is not necessarily to be considered as serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in section 6.2.

6.3.4 Causality collection

The investigator will assess causal relationship between IV study therapy and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IV study therapy?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'. A guide to the interpretation of the causality question is found in Appendix B.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study center personnel: "Have you had any health problems since the previous visit or when you were last asked?" and "Have you had any new symptoms?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital sign measurements will be summarized in the CSR. Deterioration as compared with screening or baseline assessments in protocol-mandated laboratory values, vital signs, ECGs and safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IV study therapy.

If deterioration in a laboratory value, vital sign or ECG assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE or SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the screening assessment will be reported as an AE.

6.3.7 Hy's Law

The investigator is responsible for, without delay, determining whether the patient meets potential Hy's law criteria (according to European Commission: Product information Zavicefta 2016
European Commission: Community register of medicinal products for human use. Product information Zavicefta 2 g/0.5 g powder for concentrate for solution for infusion. Accessed on 13 July 2016. Available at http://ec.europa.eu/health/documents/community-register/2016/20160624135109/anx_135109_en.pdf

FDA 2009):

A Potential Hy's Law (PHL) case is defined as any situation where a patient has an increase in both AST **or** ALT ≥3xULN **and** total bilirubin ≥ 2xULN, irrespective of the patient's alkaline phosphatase value, at any point during the study following the start of study medication.

A Hy's Law (HL) case is defined as a patient with an increase in serum AST or ALT ≥3x ULN together with total bilirubin ≥2x ULN, where no other reason than the IMP can be found to explain the combination of increases, e.g., elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and Hy's Law the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. Details regarding the actions required in the cases of increases in ALT, AST, and total bilirubin can be found in Appendix D.

Other cases where a subject shows elevations in liver biochemistry may require further evaluation (see sections 5.2.5 and 6.7.3). If a patient reaches an ALT or AST ≥5 × ULN, the patient may continue with the IMP as planned unless discontinuation criteria as described in section 3.9 are met. The patient should be seen within 48 hours to instigate enhanced follow-up and monitoring as defined in section 6.7.3. Also patients with ALT or AST ≥3.0 x ULN and bilirubin ≥1.5 x ULN will require enhanced follow-up and monitoring as defined in section 6.7.3.

6.3.8 Exceptions from standard adverse event collection

Where there is deterioration in the condition for which the IV study therapy is being used, there may be uncertainty as to whether this is lack of efficacy, disease progression or constitutes an AE. In such cases, unless the Pfizer/CTCC or reporting physician considers that the study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration should be compared with the definitions below and considered to be either lack of effect (section 6.3.8.1) or disease progression (section 6.3.8.2) and not an AE.

6.3.8.1 Lack of effect

Insufficient therapeutic effect will be captured as an efficacy outcome. Instances of, or discontinuation due to insufficient therapeutic effect (i.e., lack of efficacy) should not be collected as AEs. A clinical failure should not be recorded as an AE.

6.3.8.2 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which ATM-AVI is being studied. It may be an increase in the severity of the disease under study (cIAI) and/or increases in the symptoms of the disease. Expected progression of the disease under study and /or expected progression of signs and symptoms of the disease under study, unless more severe in intensity or more frequent than expected for the patient's condition should not be reported as an AE. Any event or extended hospitalization that is unequivocally due to disease progression must not be reported as an SAE unless it is believed that the study drug actively contributed to the progression of the disease (i.e., not by way of insufficient therapeutic effect). Events, which are unequivocally due to disease progression, should not be reported as an AE.

6.4 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the IV study therapy or to the study procedures. All SAEs will be recorded in the eCRF.

Any SAE occurring in the course of the study must be reported by the investigators or qualified designee to the CTCC pharmacovigilance centre on the SAE Report Form **within 24 hours of investigator's awareness** of it. Contact details of the CTCC pharmacovigilance centre and applicable emergency contacts are given in section 6.10.

The designated Pfizer CTCC Pharmacovigilance representatives will work with the investigator (and national coordinator/medical monitor if required) to ensure that all the

necessary information is provided to Pfizer Safety **within 24 hours of investigator's awareness** Details regarding the handling of incoming SAE reports at CTCC are defined in the study specific Safety Handling Plan.

For all serious adverse events where important or relevant information is missing, active follow-up will be undertaken immediately by the investigator. Investigators or other study center personnel will inform Pfizer /CTCC Pharmacovigilance representatives of any follow-up information on a previously reported SAE **within24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the latest version of the IB for the IV study medication ATM-AVI.

Pfizer will provide regulatory authorities with safety updates/reports according to local requirements, including suspected and unexpected serious adverse reactions, where relevant. The national coordinator is responsible for reporting of such cases to the respective Ethics Committees and investigators.

6.4.1 Other significant adverse events

During the evaluation of the AE data, a CTCC or Pfizer medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuation of IV study therapy due to AEs. Based on the Pfizer physician or CTCC physician (as a Pfizer delegate) judgment, significant AEs of particular clinical importance may, after consultation with the Pfizer physician, be considered other significant AEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs, and other safety assessments will be performed for identification of other significant AEs.

Examples of these are marked haematological and other laboratory abnormalities and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

6.5 Overdose

Overdose is defined as a dose of study drug administered to a patient in excess of that specified in the IB for that product, unless specified otherwise in the clinical study protocol. Overdose does not automatically make an AE serious but if the consequences of the overdose are serious for example death or hospitalization, the event is serious and should be reported as such.

According the SmPC (ER Squibb & Sons Limited 2014), there have been no reported cases of ATM overdosage or intoxication but there is no post marketing pharmacovigilance data available. If necessary, ATM may be cleared from the serum by haemodialysis and/or peritoneal dialysis. ATM has been shown to be cleared from the serum by continuous arteriovenous hemofiltration.

In a Phase II study in the ceftazidime-AVI development programme, a patient was accidentally treated with 1000 mg of AVI in one IV dosing (ceftazidime was also overdosed). No clinical symptoms or changes in laboratory values were observed for this patient.

Inadvertent misdosing, such as administration of a higher dose than stated in the protocol, should be followed up expectantly. Patients misdosed or overdosed (when defined) should be treated with appropriate supportive care until recovery.

If an overdose or intoxication on the IV study therapy occurs in the course of the study, then the investigator or other site personnel will inform appropriate Pfizer/ CCTC representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated Pfizer/ CCTC representative will work with the investigator to ensure that all relevant information is provided to Pfizer Safety within the time limits given below.

Recording an overdose will be done according to the following:

- An overdose with associated AE(s) is to be recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the overdose eCRF module. Relevant information regarding any corresponding SAE(s) related to the overdose must be forwarded to Pfizer /CTCC pharmacovigilance representatives for data entry in the safety database. An overdose without associated symptoms is also to be recorded on the overdose eCRF module.
- For overdoses associated with a SAE, the standard SAE reporting timelines apply, see section 6.4.

6.6 Pregnancy

If a patient becomes pregnant during the course of the study, ATM-AVI should be discontinued immediately. All pregnancies and outcomes of pregnancy occurring from the date of the first dose of study drug until 3 months after the last dose of study drug should be reported to Pfizer and CTCC **within 24 hours** of awareness and documented as specified in section 6.6.1.

6.6.1 Maternal exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the IV study therapy may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other study center personnel will report this information to Pfizer CTCC pharmacovigilance centre in the Pregnancy Report Form **within 24 hours** from when he or she becomes aware of it. Outside

the CTCC pharmacovigilance business hours, the investigator should utilise the medical emergency contacts for reporting. Contact details of the CTCC pharmacovigilance centre, its business hours and applicable emergency contacts are given in section 6.10.

The designated Pfizer /CTCC representatives will work with the investigator (and national coordinator/medical monitor if required) to ensure that all relevant information is provided to Pfizer Safety **within 24 hours of investigator's awareness**. The same timelines apply when outcome information is available.

The "Pregnancy Report" module in the eCRF will be used to report the pregnancy and the "Pregnancy Outcome" safety module will be used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of any pregnancy occurring from the date of the first dose of study drug until 3 months after the last dose of study drug must be reported to Pfizer Safety/CCTC **within 24 hours of investigator's awareness** and documented as specified in Section 6.6.1.

6.7 Medical management and monitoring during the study

6.7.1 Coagulation and concomitant use of anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving ATM. In addition, numerous cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics, including β-lactams. Severe infection or inflammation, and the age and general condition of the patient appear to be risk factors. Appropriate monitoring (according to applicable medical guidelines and institutional standard of care) should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

6.7.2 Renal function

CrCl will be monitored throughout the study. Determination of creatinine will be part of each safety lab until LFU inclusive, i.e. every 3 days (+/- 1 day) until end of IV study therapy (as defined in Table 1), followed by calculation of CrCl at the central lab. For eligibility assessment, CrCl needs to be calculated at the study site, based on the creatinine value determined at local lab (see section 4 and Appendix E). In addition, a daily control of creatinine and CrCl will be done in the local lab during treatment (see section 4.1.3 and 5.2.1 for details).

Only patients with normal renal function or mild renal impairment (CrCl >50 mL/min) will be recruited until completion of the early safety and PK review. If CrCl falls to ≤ 50 mL/min in one of these patients, the IV study therapy should be stopped and the patient followed up to the end of the study.

Provided the results of the early patient review confirm the eligibility of patients with CrCl of 31 – 50 mL/min, the IV study therapy should be stopped and the patient followed up to the end of the study if CrCl falls to ≤ 30 mL/min (see section 3.9).

6.7.3 Monitoring of liver-related laboratory parameters

For patients with significant elevations in liver-related laboratory parameters identified in study visit samples after enrolment, but not meeting individual discontinuation criteria, an intensified monitoring plan will be instigated as follows:

- If a patient reaches an ALT or AST ≥5 x ULN and has not met the discontinuation criteria, the following enhanced monitoring and patient follow-up will be instigated within a 48 hour period:
  - Collection of clinical and historical information to determine the cause of ALT and/or AST elevations;
  - If required, the daily assessment of AST, ALT, ALP, GGT and total bilirubin during treatment (see sections 4.1.3 and 5.2.1) will be continued after end of treatment until the peak value has been reached as documented by a decline in the values and the patient shows clinical improvement;
  - The frequency of testing will decrease to weekly or less if abnormalities stabilize after end of treatment, or if study drug has been discontinued and patient is asymptomatic. Patients will be followed, including laboratory testing, until resolution.
- Patients with ALT or AST ≥3 x ULN and total bilirubin >1.5 × ULN or with an ALP increase of 100% from baseline will qualify for intensified monitoring of detailed liver chemistry (including ALP, ALT, AST, gamma glutamyl transferase [GGT], and total bilirubin)

Sampling aimed at identifying the cause of changes observed during routine monitoring should be done for all patients fulfilling intensified monitoring criteria. Liver enzymes should be monitored at least every 24 hours until the elevated levels return to within the normal limits or are stable, as judged by the Principal Investigator.

For patient review of liver-related laboratory parameters, see section 5.2.5. For definition and handling of Hy's law cases, see section 6.3.7 and Appendix D.

6.8 Management of IMP related toxicities

For handling of patients having received an overdose and showing IMP related toxicities, see section 6.5.

6.9 Study governance and oversight

6.9.1 Scientific Advisory Committee

A Scientific Advisory Committee (SAC), including representatives of COMBACTE-CARE and the sponsor will review the safety and PK data and provide advice on all relevant scientific and safety issues during the study. The SAC will be responsible for reviewing the safety data and in particular the transaminase data from the safety and PK reviews for Cohorts 1 and 2 (see sections 5.2.5 and 5.3.3). The constitution of the SAC will include surgical representation to provide advice on safety related questions regarding surgical procedures and to advise on investigator assessments where required. Details on the tasks and operating procedures of the SAC and its members will be described in the SAC charter.

6.10 Medical emergencies, management and SAE contacts

The investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such, see section 6.4.

In the case of a medical emergency or other urgent medical concerns, the investigator should contact the country specific national study coordinator or sponsor's Medical Monitor as outlined in Table 6. Contact details of the respective national coordinators and the CTCC and sponsor medical contacts are also provided in appropriate site documents.

For questions regarding SAE reporting, the investigator should contact the CTCC pharmacovigilance centre. See Table 6 for contact details.

Table 6: Contacts for medical emergencies and SAE reporting

Country	**Role in the study**	Contact details for **medical emergencies**
All countries	Sponsor Medical Monitor	Pfizer 24/7 Medical Contact Line: France 1. PPD Germany 1. PPD Spain

Country	**Role in the study**	Contact details for **medical emergencies**
		1. PPD
Germany	PPD Medical Monitor	PPD PPD
France	PPD Medical Monitor	PPD
Spain	PPD Medical Monitor	PPD
SAE reporting (all countries)	PPD PPD	

7. INVESTIGATIONAL MEDICINAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational medicinal products (IMPs)

IMP	Dosage form and strength
Avibactam	Avibactam lyophilisate for concentrate for solution for infusion 600 mg
Aztreonam	Aztreonam powder for solution for infusion 2 g or 1 g
Metronidazole	Metronidazole 500 mg / 100 ml solution for infusion

The Investigational Medicinal Products (IMPs) ATM and AVI will be supplied in vials. The IMP ATM-AVI will be prepared using standard aseptic IV infusion preparation using saline. An IV infusion will be administered. The IMP Metronidazole will be supplied in infusion bags. For details please refer to IMP handling instructions.

7.2 Dose and treatment regimens

The duration of treatment with IV study therapy is 5 to 14 days where a full day is defined as a 24 hour period. From the study start, only patients with normal renal function or mild renal impairment (i.e. CrCl >50 mL/min; see Appendix E) will be eligible. The proposed administration of ATM-AVI for these patients (Cohort 1) is a loading dose (500 mg ATM plus 137 mg AVI by intravenous [IV] infusion over a 30 minute period), immediately followed by a dose of 1500 mg ATM plus 410 mg AVI by IV infusion over a 3 hour period every 6 hours (maintenance infusion). The targeted total dose on Day 1 will be 6500 mg ATM and 1777 mg AVI. For the following (full) days, this will be 6000 mg ATM / 1640 mg AVI.

In addition, anaerobic coverage for cIAI will be provided by administration of 500 mg metronidazole, infused over 1 hour. Metronidazole will be administered every 8 hours, starting after the first ATM-AVI maintenance infusion and maintained until end of IV study therapy.

The PK, safety and tolerability of the dosing regimen described above will be assessed in a first cohort of 10 patients (Cohort 1); i.e. recruitment into this initial cohort of patients will continue until 10 patients with CrCl >50mL/min have completed all scheduled PK and safety assessments.

In the event that a higher AVI dose will be administered in Cohort 2 (see section 1.4), all patients with normal renal function or mild renal impairment (CrCl > 50 mL/min) will receive a loading dose (500 mg ATM plus 167 mg AVI by intravenous [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 every 6 hours (maintenance infusion). Patients will also receive 500 mg metronidazole infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion.

Patients in Cohort 2 with moderate renal impairment (CrCl 31 - 50 mL/min) will receive either;

- A loading dose consistent with Cohort 1 (500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period), immediately followed by an extended loading infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period. The maintenance infusions (starting 3 hours after stop of the extended loading infusion) will be 750 mg ATM plus 205 mg AVI over a 3 hour period (to be administered every 6 hours). The targeted total dose on Day 1 will be 4250 mg ATM: 500 mg (loading dose) + 1500 mg (extended loading infusion) + 3x 750 mg = 2250 mg (maintenance infusion) and 1162 mg AVI: 137 mg (loading dose) + 410 mg (extended loading infusion) + 3x 205 mg (maintenance infusion). From Day 2 onwards, the targeted total daily dose will be 3000 mg ATM (4x 750 mg maintenance infusion)/ 820 mg AVI (4x 205 mg maintenance infusion).

Or

- A loading dose consistent with a higher AVI dose in Cohort 2 (500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period), immediately followed by an extended loading infusion of 1500 mg ATM plus 500 mg AVI over a 3 hour period. The maintenance infusions (starting 3 hours after stop of the extended loading infusion) will be 750 mg ATM plus 250 mg AVI over a 3 hour period (to be administered every 6 hours). The targeted total dose on Day 1 will be 4250 mg ATM: 500 mg (loading dose) + 1500 mg (extended loading infusion) + 3x 750 mg = 2250 mg (maintenance infusion) and 1417 mg AVI: 167 mg (loading dose) + 500 mg (extended loading infusion) + 3x 250 mg (maintenance infusion). From Day 2 onwards, the targeted total daily dose will be 3000 mg ATM (4x 750 mg maintenance infusion) / 1000 mg AVI (4x 250 mg maintenance infusion).

In the case that renal function recovers or deteriorates in Cohort 2 or 3 patients (i.e., local or central lab results show CrCl increases from 31 – 50 mL/min at baseline to >50 mL/min, or decreases from >50 mL/min at baseline to 31 – 50 mL/min) during the treatment period, the dose of ATM-AVI should be adjusted by the investigator to meet the applicable dose regimen (see above), based on the latest CrCl value.

In view of the primary objectives of this trial (assessment of ATM-AVI pharmacokinetics and patient safety), it is important that all IV study therapies are administered at a constant flow rate while strictly adhering to the dosing information given above.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling (European Commission GMP Guideline 2010). Label text will be translated into local language. The pharmacist at the study center will prepare and label the individual IV infusions according to the handling instructions.

7.4 Storage

All IV study therapy should be kept in a secure place under appropriate storage conditions. The storage conditions will be stated on the study drug labelling and in the pharmacy manual.

7.5 Compliance

Qualified study center personnel will administer the IV study therapy and assure treatment compliance. The dose, date, and exact start and stop time of administration of the IV study therapy will be recorded in the appropriate sections of the eCRF and checked by the monitor at monitoring visits.

7.6 Accountability

The IV study therapy provided for this study will be used only as directed in the study protocol.

Intravenous study therapy will be dispensed to the investigator or medically qualified personnel by the study center pharmacist. Intravenous study therapy will only be prepared / administered to patients by qualified pharmacy personnel / medically qualified personnel who have been appropriately trained to prepare / administer IV study therapy. Written authorization of study personnel to administer IMP must be documented on the Delegation of Authority Log in one of 2 ways:

- All study staff trained and authorized by the investigator to prepare / administer IV study therapy are listed on the Delegation of Authority Log,

  OR

- The nurse manager(s)/supervisor(s) and study pharmacists authorized by the investigator are listed on the Delegation of Authority Log as the person(s) responsible for ensuring that the nursing/pharmacy staff are appropriately trained on IV study therapy preparation/administration prior to preparing/administering it, and for maintaining current and complete training documentation at all times.

Written documentation of training of IV study therapy administration and pharmacy study center personnel will be kept current throughout the study, and ongoing training will be provided by study center personnel as assigned by the investigator on the Delegation of Authority Log. It is the investigator's responsibility to ensure that all documentation remains current and complete throughout the study. The investigator will document how he or she will ensure staff are adequately trained before they perform the infusion, and he or she will ensure that there is a system in place that will guarantee supervision of the study therapy administration process and patient safety (e.g., study therapy will only be administered to patients under supervision of an investigator). Source documentation should clearly indicate who administered the infusion. Records of IV study therapy usage should include the identification of the patient to whom the IV study therapy was administered, the quantity and date of administration, and a record of unused IV study therapy. The investigator/pharmacist is responsible for maintaining accurate IV study therapy accountability records throughout the study on the relevant forms provided by the sponsor/CTCC. Each administration of IV study therapy will be documented in the eCRF.

It is the investigator's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

- Deliveries of such products are correctly received by a responsible person (e.g., pharmacist).
- Deliveries are recorded.
- Intravenous study therapy is handled and stored safely and properly.
- Intravenous study therapy provided for this study is used only as directed in the study protocol.

- Study center personnel account for all study drugs received at the study center, dispensed for the patient, and returned to the pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved.

- The CTCC representative or delegate performs complete IV study therapy accountability during each monitoring visit, including verifying documentation of receipt, dispensing, return, and destruction of IV study therapy and consistency of this documentation with physical inventory.

- At the end of the study, study center personnel account for all unused IV study therapy and for appropriate destruction or return of all unused IV study therapy to a designated facility or the sponsor for destruction. Destruction procedures must be approved by the sponsor. It must be possible to reconcile delivery records with records of IV study therapy use and destroyed/returned stock. The investigator or pharmacist should sign certificates of delivery and return.

7.7 Concomitant and other treatments

Both ATM (Mattie 1994) and AVI (see IB) are predominantly eliminated by the kidney, partly by active tubular excretion. Probenecid and furosemide interfere with the active tubular excretion, resulting in increased plasma concentrations of the study drugs. While these increases are considered to be clinically insignificant (ER Squibb & Sons Limited 2014), concomitant administration of probenecid and/or furosemide should still be avoided if at all possible during IV study therapy. Patients being treated with probenecid are not eligible for this study (see Exclusion criteria). Based on current knowledge, further relevant drug-drug interactions with regard to ATM-AVI administration in this study are not to be expected (see section 1.3).

All prescription and over the counter medications being taken by the patient for the 2 weeks prior to study entry (considered prior treatment) and from enrolment through the LFU visit (considered concomitant treatments) must be documented on the appropriate pages of the eCRF. Systemic antibiotics should be documented for the entire duration of the study (from 2 weeks prior to enrolment through the LFU visit). Also application of topical antibacterial and antifungal agents and antibiotic peritoneal lavage need to be recorded in the eCRF.

If *Enterococcus* species or MRSA is one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy is indicated, then vancomycin, linezolid, or daptomycin may be added to the study regimens according to the usual practice of the investigator. Information on contraindications, special warnings and precautions and interactions with other medicinal products and other forms of interaction are available in the respective Summaries of Product Characteristics (SmPCs) for these products and investigators are recommended to refer to these for further prescribing information. If vancomycin, linezolid, or daptomycin are started empirically to cover MRSA or *Enterococcus* species, and if final culture results did not isolate MRSA or Enterococcus species, then the investigator should discontinue the additional Gram-positive coverage that was empirically added.

Other than vancomycin, linezolid, or daptomycin, which are permitted for treatment of suspected or isolated MRSA or Enterococcus species, the use of other systemic antimicrobials not specified by this protocol is not permitted during the study with the following exceptions: If a new infection develops at a remote site (i.e., outside of the abdomen) between the date and time of enrolment and the LFU visit, and the investigator considers addition of non-study antibiotics essential to the safety and wellbeing of the patient, additional antibiotics may be added (see also table below in this section).

Also it is anticipated that in instances of suspected clinical failure, alternative or additional antibiotic therapy to treat the cIAI may be required. Prior to administering additional or alternative antibiotics the investigator should contact the national coordinating investigator to confirm the clinical evaluation and microbiological identification of an isolate not covered by ATM-AVI and metronidazole. It is anticipated that in instances of suspected clinical failure, alternative or additional antibiotic therapy to treat the cIAI may be required, and where rescue therapy is provided the patient should be assessed as a clinical failure. An appropriate antibiotic should be selected, taking into account results of sensitivity testing (see also table below in this section).

Also antifungal therapy to treat the cIAI should be avoided unless clinically indicated.

All actions related to the administration of concomitant antibiotics should be documented in the eCRF.

Further medication (other than that described above), which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator without delay but should also be documented in the eCRF.

If analgesic medication is needed for pain, the use of analgesics without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after enrolment, the investigator should contact the sponsor's physician or delegate before initiating therapy. Continued patient study participation will be determined based upon assessment of the safety risk to the patient if he or she were to continue in the study. Patients who have already completed the IV study therapy should remain in the study until LFU assessment as they are not actively on study therapy but being followed up for outcomes.

Restricted Medication/Class of drug:	**Usage:**

Systemic anti-infective drugs* (antibiotics and antifungal drugs) *other than vancomycin, linezolid, or daptomycin which are permitted for treatment of suspected or isolated MRSA or *Enterococcus* species	Prior to administration: • contact national coordinating investigator • obtain a microbiological specimen from the infection site • confirm infection due to a pathogen not covered by ATM-AVI and metronidazole • review result of sensitivity testing • select appropriate antibiotic drug, taking the above into account as well as the corresponding Summary of Product Characteristics (SmPC) for further prescribing information
Analgesic medication	Drugs without antipyretic properties are preferred

Prohibited Medication/Class of drug:	
Probenecid	Prohibited from enrolment to end of IV study therapy

7.8 Post study access to study treatment

At the end of the study, the sponsor will not continue to supply study drug to subjects or investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

This is a prospective, open-label, multicenter study to determine the PK, safety and tolerability of aztreonam-avibactam (ATM-AVI) in the treatment of hospitalized patients. Analyses will be performed by the sponsor or its representatives. A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient included and any subsequent amendments will be documented, with final amendments completed prior to data base lock.

8.2 Sample size estimate

Up to 40 patients will be enrolled into the study in total. Although the study is not powered to perform statistical tests, assessment of safety and complete PK assessments from at least 30 patients with cIAI, is considered sufficient to adequately confirm the PK and safety profile of ATM-AVI in a population with a representative burden of disease. It is expected that 10 patients in Cohort 1 (and 10 patients in Cohort 2 if the higher AVI dose is used) having completed all safety assessments are sufficient for an initial review of key safety criteria of ATM-AVI, in order to progress with the continued treatment of patients.

8.3 Definitions of analysis sets

The modified intent to treat (MITT) population will include all enrolled patients who receive any amount of study drug.

The microbiologically modified intent-to treat (mMITT) population is a subset of the MITT population and includes all enrolled patients who have a diagnosis of cIAI and have an intra-abdominal pathogen at baseline (regardless of susceptibility to the study drug). For example, a reason for exclusion from the mMITT population may be (amongst others) lack of a pathogen collected from a surgical procedure at baseline, whether that be because the surgery was not performed, or was performed outside protocol time frame (as defined in inclusion criteria; see section 3.1).

The pharmacokinetic (PK) population includes all patients who have at least 1 plasma concentration data assessment available for ATM-AVI, no fundamental violations of the inclusion and exclusion criteria and no important protocol violations affecting assessment of PK as defined in the finalised Statistical Analysis Plan. The reason for exclusion will be listed for all subjects in question.

8.3.1 Efficacy analysis set

There are two efficacy analysis sets: the MITT and mMITT population (for definition see section 8.3).

8.3.2 Safety analysis set

The safety analysis set is the MITT population (for definition see section 8.3).

8.3.3 PK analysis set

The PK analysis set is the PK population (for definition see section 8.3).

8.4 Outcome measures for analyses

The primary outcome measures will be (see also section 2):

- ATM and AVI concentrations in plasma (samples to be collected for 6 hours after the start of an ATM-AVI 3 hour infusion). They will be analyzed in the PK analysis set.
- Derived PK parameters Cmax, tmax, AUC(0-6), AUC(0-last), tlast, t1/2, Vss, Vz and CL for the patients undergoing intensive sampling on day 4. They will be analyzed in the PK analysis set.
- Safety and tolerability as assessed by adverse events, physical examination, vital signs, ECGs, and laboratory assessments. They will be analyzed in the safety analysis set.

The secondary outcome measures will be:

- Proportion of patients with clinical cure at the TOC visit. This will be analyzed in the MITT and mMITT populations.

- Correlation of derived PK parameters for ATM-AVI and clinical cure at TOC. This will be analyzed in the mMITT population.

The exploratory outcome measures will be:

- Estimates of model parameters and their precision, goodness-of-fit, individual and mean predictions.

8.5 Methods for statistical analyses

The following characteristics will be summarised in the safety population: demographics (age, sex, and race), medical and surgical history, description of cIAI, baseline assessments of clinical signs and symptoms, microbiological assessment of primary infection site or blood, IV study therapy administration and baseline pathogens. MIC frequencies for each infecting species isolated from either the abdominal site or blood at baseline will be reported. Pathogens isolated from cultures obtained post-baseline will be listed.

No confirmatory interim analysis is planned. However, in the early patient review, the PK and safety aspects will be assessed as displayed in section 5.2.5 and 5.3.3.

8.5.1 Analysis of the primary variables

Descriptive statistical analyses will be performed. Number of observations, arithmetic mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum will be given for quantitative variables. If reasonable, geometric mean and coefficient of variation will also be given. Absolute and relative frequencies are given for qualitative variables. If variables are measured over time, each time point will be summarized. Summaries of the number and frequency of AEs will be presented. 95% confidence intervals will be given where reasonable. Full details of the PK analysis will be given in the Pharmacokinetic Analysis Plan.

Adverse events occurring from the first dose of IV study therapy up to the LFU visit will be summarized by preferred term, system organ class, relationship to IV study therapy and severity. Summaries and listings of death, AEs, SAEs, other significant AEs, and AEs that led to discontinuation or withdrawal will be presented.

8.5.2 Analysis of the secondary variables

The number and percentage of patients with clinical cure (shown with 80% and 95% confidence intervals) will be tabulated for the MITT and mMITT analysis set. Key patient subgroups (e.g. the group of patients with extended-spectrum β-lactamase [ESBL]-phenotype pathogens) will be summarised in the same way, and illustrated graphically as a forest plot.

The proportion of clinical cure at the TOC visit will be determined excluding any patients with concomitant antibiotics not administered for failure (mMITT). Refer to section 7.7 for rules relating to concomitant medication.

8.5.3 Exploratory analysis

The possible relationship between exposure to ATM-AVI and both efficacy and safety outcomes will be explored graphically. Moreover, complex PK/PD modelling (e.g. NONMEM) will be done to describe the general trend and variability in the observed data but also to better understand underlying mechanisms of drug action and the interaction with the physiologic system; to predict tested and untested doses and dosing regimens (Nielsen et al. 2013).

No inferential statistical tests will be implemented, given the small sample sizes with respect to any efficacy objective.

8.5.4 Evaluation of pharmacokinetics and of pharmacokinetic - pharmacodynamic relationships

The following section 8.5.4.1 describes the analysis of the first 25 patients undergoing intensive PK sampling. Section 8.5.4.2 describes the population PK/PD analysis that will include data from all patients in the study with one or more PK sample collected (see sections 5.3.1 and 8.3). The early safety and PK review (see section 5.3.3) will not be reported as part of the CSR.

8.5.4.1 Evaluation of the pharmacokinetics of ATM and AVI

The actual sampling times will be used in all final plasma PK parameter calculations. Pharmacokinetic parameters will be derived for the 25 patients with intensive plasma sampling using non-compartmental methods with Phoenix® WinNonlin 6.3, or higher (Certara L.P., St. Louis, Missouri); or SAS® Version 9.2, or higher (SAS Institute, Inc., Cary, North Carolina).

Key PK parameters and a non-compartmental PK report will be summarized in the Clinical Study Report (CSR) or in an appendix to CSR.

8.5.4.2 Population pharmacokinetic/pharmacodynamic analyses

The final data may be pooled with data from other studies to conduct population PK analysis (using NONMEM version VII or higher). Using these parameter estimates (mean PK parameters including inter-individual variance estimates) Monte-Carlo simulations will be undertaken and potential PK/PD relationships will be explored. A detailed population PK/PD analysis plan will be prepared prior to any such analysis/es, the results of which will be reported separately.

9. STUDY AND DATA MANAGEMENT

9.1 Pre-study activities

Before the first patient is entered into the study in an investigational study center, a Sponsor representative (or delegate) will

- Determine the adequacy of the facilities (including study personnel)
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) and other personnel involved in the study their responsibilities with regard to protocol adherence and study conduct and the role and responsibilities of the COMBACTE-CARE, the sponsor, the delegated Academic Research Organisation (CTCC) and further parties involved in the conduct of the study. This will be documented in a Clinical Study Agreement between the involved parties.

9.2 Training of study site personnel

Before the first subject is entered into the study, a sponsor and COMBACTE-CARE delegate will conduct an on-site initiation visit to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilized. The web based Electronic Data Capture (EDC) system TrialMaster (OmniComm Systems, Inc.) will be trained by eLearning.

The investigator will ensure that appropriate training relevant to the study is given to all of the study center personnel, and that any new information relevant to the performance of this study is forwarded to the study center personnel involved. The investigator will maintain a record of all individuals involved in the study (medical, nursing, and other study center personnel).

9.3 Monitoring of the study

The monitoring of this study will be coordinated by CTCC. All German trial sites will be monitored by CTCC. Trial sites outside of Germany will be monitored by local COMBACTE-CARE partners or delegates assigned by the sponsor, according to the monitoring manual developed by CTCC. Details will be defined in the study specific responsibility split and in the study-specific monitoring manual.

The trial sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the study subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the study is conducted in accordance with the study protocol, the principles of GCP and local legislation.

During the study, the monitor will have regular contacts with the study site, including telephone contacts and on-site visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the study center personnel is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts, laboratory printouts, electronic and paper-based medical records)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject (see section 5.6.4)

All investigators need to agree that a monitor will regularly visit the trial site and assure that the monitor will receive appropriate support in his/her activities during the monitoring visits. The monitor will be available between visits if the investigator(s) or other trial site personnel need information and advice about the study conduct. The informed consent form includes a statement that the monitor has the right – while observing the provisions of data protection legislation – to compare data of the case report forms with the trial subject's medical records.

A monitoring visit report will be prepared for each visit, describing the progress of the clinical study and any problems as well as proposed corrective and preventive actions.

Detailed information (e.g. frequency and duration of monitoring visits, source data verification etc.) will be described in the study specific monitoring manual.

9.3.1 Source data

Original records such as clinic charts, laboratory printouts as well as electronic and paper-based medical records are source documents which contain source data necessary for verification of the study data documented in the eCRF. The location of the source data will be documented trial site specific. Refer to the Clinical Study Agreement for location of source data.

9.3.2 Study agreements

The investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the

treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between COMBACTE-CARE/ sponsor /CTCC and the investigator should be in place before any study-related procedures can take place or patients are enrolled.

9.3.3 Archiving of study documents

The investigator will follow the principles outlined in the Clinical Study Agreement (CSA), ICH-GCP and local regulations.

9.4 Study timetable and end of study

The end of the study is defined as the last visit of the last patient participating in the study. This definition applies for the entire study, not for a specific region.

The study is expected to start in first quarter 2016 and to end by fourth quarter 2017. The investigators will be notified by the Sponsor when recruitment is complete.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP or if recruitment is slow. The sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ATM-AVI (see section 3.11).

9.4.1 Clinical Study Report

The Clinical Study Report or Synopsis will be submitted to competent authorities and ethics committees within 12 months after the end of the study (as defined above) as applicable, according to local requirements.

9.5 Data management

Data management will be performed by CTCC, according to the Data Management Manual. The data collected through third party sources will be obtained, imported into the study database and reconciled against study data, including the PK data. For the early patient review as described in section 5.3.3, PK data may additionally be sent directly to the sponsor.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the sponsor's Drug Dictionary. All coding will be performed by CTCC separate from the study database. The codes will be merged with the study data by the biometrician.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Validation Plan (manual checks) and the Database Specification (automatic checks). Quality control procedures will be applied to each

stage of data handling to ensure that all data are reliable and have been processed correctly. When all data have been coded, validated, reconciled, signed and locked, clean file will be declared and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, may be accompanied by a separate document that incorporates) wording that complies with relevant data protection and privacy legislation. All data collected for this study will be handled according to ICH-GCP and further applicable (e.g. local) regulations.

10.3 Ethics and regulatory review

An Ethics Committee (EC) or Institutional Review Board (IRB) should approve the final study protocol and amendments to protocol where applicable, including the final version of the Informed Consent Form and any other written information or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC or IRB, and to the study center personnel.

The opinion of the EC/IRB should be given in writing. The investigator should receive the written approval and send a copy thereof to the sponsor/CTCC prior to enrolment of any patient into the study. The EC should approve all advertising used to recruit patients for the study. If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

The sponsor should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

Before enrolment of any patient into the study, the final study protocol is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. The sponsor will handle the distribution of all documents requested by the national regulatory authorities.

The sponsor will provide regulatory authorities with safety updates/reports according to local requirements, including suspected and unexpected serious adverse reactions (SUSARs), where relevant. Reporting of such cases to the respective Ethics Committees and investigators will be done by CTCC.

10.4 Informed consent

The investigator(s) at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that patients who are unable to provide informed consent at Screening and who are entered into the study by the consent of a legally acceptable representative provide their own informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with national and local regulations.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the investigator's study file
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the investigator and the sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised clinical study protocol).

The amendment is to be approved by the relevant EC/IRB and, if applicable, also by the national regulatory authority before implementation. Local requirements are to be followed for revised protocols.

The sponsor/CTCC will distribute any subsequent amendments and new versions of the protocol to each investigator. For distribution to Ethics Committee see Section 10.1.

If a protocol amendment requires a change to a centre's Informed Consent Form, the sponsor/CTCC and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

The sponsor may change the ICF at any time to include extra safety information as deemed necessary. A patient will be re-consented if a new ICF is approved while the patient is still involved in study activities that are impacted by the changes to the ICF.

If local regulations require, any administrative change will be communicated to or approved by the competent EC/IRB.

10.6 Audits and inspections

Authorized representatives of the sponsor/CTCC, a regulatory authority, or an EC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the sponsor/CTCC immediately if contacted by a regulatory agency about an inspection at the center.

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