A PHASE 3 PROSPECTIVE, RANDOMIZED, MULTICENTER, OPEN-LABEL, CENTRAL ASSESSOR-BLINDED, PARALLEL GROUP, COMPARATIVE STUDY TO DETERMINE THE EFFICACY, SAFETY AND TOLERABILITY OF AZTREONAM-AVIBACTAM (ATM-AVI) ±METRONIDAZOLE (MTZ) VERSUS MEROPENEM ±COLISTIN (MER ±COL) FOR THE TREATMENT OF SERIOUS INFECTIONS DUE TO GRAM-NEGATIVE BACTERIA, INCLUDING METALLO-B-LACTAMASE (MBL) – PRODUCING MULTIDRUG RESISTANT PATHOGENS, FOR WHICH THERE ARE LIMITED OR NO TREATMENT OPTIONS

Investigational Product Number:	PF-06947387
Investigational Product Name:	Aztreonam -Avibactam
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trials Database (EudraCT) Number:	2017-002742-68
Protocol Number:	C3601002
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	18 May 2022	Increased sample size from "approximately 375 subjects" to "up to approximately 425 subjects". This change is reflected in the Protocol Summary, Section 3 (Study Design) and Section 9 (Data Analysis/Statistical Methods). This increase in patient numbers is in response to a slower than anticipated recruitment in another ATM-AVI Phase III protocol. The change will help ensure that there is a minimum of patients on the ATM-AVI treatment arm across the program. • Section 1.5 and Section 16: Updated Single Reference Safety Document and References list to reflect current and additional sources of study drugs or comparators (update as per PACLs dated 05-Aug-2020, 26-Mar-2021) • Section 1.6: Updated risk/benefit language to replace "Drug induced liver injury" with "Increased liver transaminases" to be consistent with Investigator Brochure (update as per PACL dated 09-Nov-2021) • Section 5.5.1: Clarification to the study drug characteristics (update as per PACL dated 05-Aug-2020) • Section 7.2.3: Clarification on when ECG should be performed for both treatment arms (update as per PACL dated 05-Aug-2020) • Section 11.1: Added a statement on deletion of data in line with the current Pfizer Protocol template Section 11.3: Added a new section on Data Protection from the current Pfizer Protocol template • Sections 12.1 and 12.2: Updated language based on the current Pfizer Protocol template • Appendix 8: Details on prior amendment to the

		protocol are now summarized in a new Appendix 8

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

The prevalence of multidrug 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. In particular, ongoing surveillance studies have demonstrated an increasing frequency of antibiotic resistance among MDR Gram-negative bacteria. Of particular concern is the spread of metallo β-lactamase (MBL) producing isolates, which are often MDR. The combination product aztreonam-avibactam (ATM-AVI) is being developed for intravenous (IV) treatment of serious infections caused by Gram-negative pathogens producing MBL in addition to other β-lactamases.

Study sites and number of subjects planned

The study is planned to be performed in approximately 170 sites in up to 30 countries in the Americas, Africa, Europe, and Asia, in regions with emerging and/or elevated incidence of carbapenem resistance, including resistance caused by MBLs.

Up to approximately 425 subjects with a diagnosis of complicated intra-abdominal infections or hospital-acquired pneumonia/ventilator-associated pneumonia will be randomized in this study, including approximately 283 randomized in the aztreonam-avibactam±metronidazole treatment arm and approximately 142 in the meropenem ±colistin treatment arm.

Objectives and Endpoints

Objectives

Based on differing regulatory requirements for European Medicines Agency and US Food and Drug Administration, the following objectives and outcome measures may differ for the United States and non United States countries analyses as noted below.

Primary Objective:	**Primary Endpoint:**
To evaluate the efficacy of aztreonam-avibactam ±metronidazole and meropenem ±colistin at Test of Cure visit for the treatment of serious infections due to Gram-negative bacteria, including those due to metallo-β-lactamase-producing multidrug resistant pathogens.	Proportion of subjects with clinical cure at Test of Cure visit in the Intent-To-Treat and Clinically Evaluable analysis sets (Note: For non-United States countries, the Intent-To-Treat and Clinically Evaluable are considered co-primary analysis sets. For the US, the Intent-To-Treat is considered the primary analysis set, while Clinically Evaluable is secondary).

Secondary Objectives:	**Secondary Endpoint(s):**
To evaluate efficacy of aztreonam-avibactam ±metronidazole and meropenem ±colistin at the Test of Cure visit in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.	Proportion of subjects with clinical cure at the Test of Cure visit in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.
To evaluate the efficacy of aztreonam-avibactam ±metronidazole and meropenem ±colistin at the Test of Cure visit in key sub populations.	• Proportion of subjects with clinical cure at the Test of Cure visit by infection type in the Intent-To-Treat and Clinically Evaluable analysis sets. • Proportion of subjects with clinical cure at the Test of Cure visit for subjects with metallo-β-lactamase-positive pathogens in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.
To assess the per-subject microbiological response to aztreonam-avibactam ±metronidazole and meropenem ±colistin at the Test of Cure visit.	Proportion of subjects with a favorable per-subject microbiological response at the Test of Cure visit in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.
To assess 28-day all-cause mortality.	Proportion of subjects who died on or before 28 days from randomization in the Intent-To-Treat and microbiological Intent-To-Treat analysis sets.
To evaluate the pharmacokinetics of aztreonam and avibactam in subjects with serious infections and to characterize the relationship between exposure and clinical and microbiological response for aztreonam-avibactam ±metronidazole utilization (listings to be provided in the Clinical Study Report, analysis to be reported outside of the Clinical Study Report).	• Pharmacokinetics of aztreonam and avibactam in subjects in the population pharmacokinetic analysis set. • Pharmacokinetic/pharmacodynamic relationship between exposure and clinical and microbiological response for aztreonam-avibactam ±metronidazole in the population pharmacokinetic analysis set.

Safety Objective:	**Safety Endpoint:**
To evaluate the safety and tolerability profile of aztreonam-avibactam ±metronidazole and meropenem ±colistin.	Safety and tolerability as assessed by adverse events, physical examination, vital signs, electrocardiograms, and laboratory assessments in the safety analysis set.

Tertiary Objectives:	**Tertiary Endpoint(s):**
To evaluate the efficacy of aztreonam-avibactam±metronidazole and meropenem ±colistin at the End of Treatment visit.	Proportion of subjects with clinical cure at the End of Treatment visit in the Intent-To-Treat, microbiological Intent-To-Treat, Clinically Evaluable and Microbiologically Evaluable analysis sets.
To evaluate the efficacy of aztreonam-avibactam ±metronidazole and meropenem ±colistin at the End of Treatment visit in key sub populations.	• Proportion of subjects with clinical cure at the End of Treatment visit by infection type in the Intent-To-Treat and Clinically Evaluable analysis sets. • Proportion of subjects with clinical cure at the End of Treatment visit for subjects with metallo-β-lactamase-positive pathogens in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.
To evaluate the efficacy of aztreonam-avibactam ±metronidazole and meropenem ±colistin at End of Treatment and Test of Cure visits by pathogen resistance types.	Proportion of subjects with clinical cure at End of Treatment and Test of Cure visits by Pathogen resistance type (eg, aztreonam-non-susceptible, extended-spectrum β-lactamase-positive, carbapenamase-positive, etc) in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.
To assess the per-subject microbiological response to aztreonam-avibactam ±metronidazole and meropenem ±colistin at End of Treatment visit.	Proportion of subjects with a favorable per-subject microbiological response at the End of Treatment in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.

Tertiary Objectives:	**Tertiary Endpoint(s):**
To assess the microbiological response by pathogen and by pathogen resistance type to aztreonam avibactam ±metronidazole and meropenem ±colistin at End of Treatment and Test of Cure visits.	• Proportion of subjects with a favorable per-pathogen microbiological response at the End of Treatment and Test of Cure visits in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets. • Proportion of subjects with a favorable per-subject microbiological response by pathogen resistance type (eg, aztreonam-non-susceptible, extended-spectrum β-lactamase-positive, carbapenamase-positive, metallo-β-lactamase positive) at the End of Treatment and Test of Cure visits in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets. • Proportion of subjects with a favorable per-pathogen microbiological response by pathogen resistance type (eg, aztreonam-non-susceptible, extended-spectrum β-lactamase-positive, carbapenamase-positive, metallo-β-lactamase-positive) at the End of Treatment and Test of Cure visits in the microbiological Intent-To-Treat and Microbiologically Evaluable analysis sets.

Exploratory Objectives:	Exploratory Endpoint(s):
To evaluate efficacy of aztreonam-avibactam ±metronidazole and meropenem ±colistin using objective clinical measures.	Composite endpoint including symptom-based objective clinical measures, to be defined in the Statistical Analysis Plan (Intent-To-Treat and clinically evaluable analysis sets).
To assess 14-day all-cause mortality.	Proportion of subjects who died on or before 14 days from randomization in the Intent-To-Treat analysis set.
To evaluate health resource utilization (listings to be provided in the Clinical Study Report, analysis to be reported outside of the Clinical Study Report).	• Length of hospital stay, including any readmissions up to Test of Cure (days). • Length of study treatment (days). • Length of intensive care unit stay (days). • Transferred to the intensive care unit (Yes/No). • Mechanical ventilation (Yes/No) for hospital-acquired. pneumonia/ventilator-associated pneumonia subjects. • Length of mechanical ventilation (days) for hospital-acquired. pneumonia/ventilator-associated pneumonia subjects. • Subsequent unplanned surgical intervention after treatment success versus failure (up to the Test of Cure visit) for complicated intra-abdominal infection subjects.

Supportive Analyses

Additional descriptive analyses of the primary endpoint (clinical cure rate) will be performed for the effect of protocol-allowed additional antibiotics (eg, Gram-positive antibiotics, aminoglycosides).

An additional descriptive analysis will be performed for clinical cure at Test of Cure using the modified Intent-To-Treat population which comprises subjects who were randomized and received any amount of intravenous study drug.

Additional descriptive analyses will also be performed for the secondary and tertiary outcomes of clinical cure rate and microbiological favourable response rate at End of Treatment and Test of Cure using the microbiological modified Intent-To-Treat which is a subset of the microbiological Intent-To-Treat comprising those subjects who received any amount of intravenous study drug.

CCI [redacted]

Study Design

This is a Phase 3 prospective, randomized, multicenter, open-label, central assessor-blinded, parallel group, comparative study to detennine the efficacy, safety, and tolerability of azti·eonam-avibactam ±meti·onidazole versus meropenem ±colistin in the ti·eatinent of hospitalized adults with complicated inti·a-abdominal infection or nosocomial pneumonia including hospital-acquired pneumonia and ventilator-associated pneumonia, in regions with endemic or emerging carbapenem resistance, and where metallo-j3-lactamase-producing multidrng resistant pathogens are suspected.

The study will consist of a Screening visit (Visit 1), a Baseline visit (Visit 2) on Day 1 of the study ti·eatinent, ongoing ti·eatinent visits (Visits 3 to 15) from Day 2 to Day 14, an End of Treatinent visit (Visit 16) within 24 hours after the last infusion, a Test of Cure visit (Visit 17) on Day 28 (±3 days) and a Late Follow-Up visit (Visit 18) on Day 45 (±3 days).

Subjects will be randomized in a 2:**1** ratio to the azti·eonam-avibactam±meti·onidazole ti·eatinent ann or the meropenem±colistin h'eatment aim. Randomization will be sti·atified based on infectious disease type (complicated inti·a-abdominal infection and hospital-acquired pneumonia/ventilator-associated pneumonia). For complicated inti-a-abdominal infection, subjects will also be sti·atified by Acute Physiology and Chronic Health Evaluation score (10 and>10) (Appendix 5). For hospital-acquired pneumonia/ventilator-associated pneumonia, subjects will also be sti·atified by mechanical ventilation status (YIN).

For subjects randomized to azti·eonam-avibactam±meh'onidazole, spai·se blood samples will be collected for population phannacokinetic assessments and phannacokinetic/phannacodynamic relationships will be evaluated in subjects where plasma samples and microbiological response data have been collected.

Each subject is expected to complete the study, including the Late Follow-Up visit. Paiiicipants in the study must be inpatients at the study site institution to receive study medication.

Target Subject Population

Adult hospitalized subjects with a confomed diagnosis of complicated inti-a-abdominal infection or hospital acquired pneumonia/ventilator associated pneumonia related to Gram-negative pathogens including, but not limited to, those infected with multidrng

resistant strains, and requiring administration of intravenous antibacterial treatment will be enrolled in this study.

The study will randomize up to approximately 425 subjects (at least 300 subjects with complicated intra-abdominal infection anticipated). The number of complicated intra-abdominal infection subjects with a perforated appendix or appendiceal abscess will be limited to approximately 40% of the study population with complicated intra-abdominal infections.

Study Treatments

Duration of Treatment

The recommended minimal duration of treatment in this study is 5 days for complicated intra-abdominal infections and 7 days for hospital acquired pneumonia/ventilator associated pneumonia. The maximal duration of treatment is 14 days.

Investigational Product, Dosage Form and Strength

Investigational product	Dosage form and strength
Test product	
Aztreonam-Avibactam	Aztreonam for injection, lyophilised powder for solution for infusion 2 g Avibactam lyophilisate for concentrate for infusion 600 mg
Comparators	
Meropenem	Meropenem 1 g powder for solution for infusion
Colistin	Colistin 2 million international units powder for solution for infusion
Co-administered drug	
Metronidazole	Metronidazole 500 mg/100 ml solution for infusion

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

Note: Comparators and co-administered drug are supplied centrally via the sponsor. In some instances, locally obtained commercial supplies will be utilized in accordance with local regulations.

Note: Aztreonam, Meropenem, Colistin and Metronidazole are commercial products over-labeled with the study clinical label.

All investigational products will be administered by intravenous infusion. Aztreonam and avibactam will be supplied as vials for reconstitution. The investigational aztreonam-avibactam will be prepared for co-administration in saline using standard aseptic intravenous infusion technique (see investigational product (IP) manual).

Aztreonam-avibactam±metronidazole treatment arm:

Subjects will be given a loading dose and then an extended loading dose before commencing on a maintenance dose (The loading dose and extended loading dose are only given once on Day 1 at the start of study treatment). All doses (loading, extended loading and maintenance), and the dosing frequency of the maintenance dose are dependent on renal function as per the table below and also Section 5.6.1.

Creatinine Clearance (mL/min)*	Loading dose of aztreonam-avibactam (by intravenous infusion over 30 minutes)	Extended loading dose of aztreonam-avibactam immediately following the loading dose (by intravenous infusion over 3 hours)	Time interval between end of extended loading dose and start of first maintenance dose	Maintenance dose of aztreonam-avibactam (by intravenous infusion over 3 hours)	Frequency of aztreonam-avibactam maintenance dose
>50	500 mg aztreonam plus 167 mg avibactam	1500 mg aztreonam plus 500 mg avibactam	3 hours	1500 mg aztreonam plus 500 mg avibactam	Every 6 hours
>30 to 50	500 mg aztreonam plus 167 mg avibactam	1500 mg aztreonam plus 500 mg avibactam	3 hours	750 mg aztreonam plus 250 mg avibactam	Every 6 hours
>15 to 30	675 mg aztreonam plus 225 mg avibactam	675 mg aztreonam plus 225 mg avibactam	5 hours	675 mg aztreonam plus 225 mg avibactam	Every 8 hours

*Estimated creatinine clearance using Cockcroft-Gault formula rounded to the nearest whole number (see Appendix 3).

Creatinine clearance should be monitored daily through the local laboratory from Day 1 to Day 4 (and Day 3 or 5 by the central laboratory, if PK samples are to be collected on Days 3 or 5) and then as clinically indicated. In the case that renal impairment recovers or deteriorates during the treatment period, the dose of aztreonam-avibactam should be adjusted by the investigator to meet the applicable dose regimen, based on the latest creatinine clearance value. If subsequent to randomization and while still on intravenous study treatment, a subject's estimated creatinine clearance falls below the threshold for study inclusion (ie, estimated creatinine clearance ≤15 mL/min) and there is a requirement to start renal replacement therapy, the Investigator should discontinue aztreonam-avibactam therapy.

In addition to aztreonam-avibactam, subjects with complicated intra-abdominal infection in this treatment arm will also receive intravenous metronidazole 500 mg every 8 hours (by

intravenous infusion over 60 minutes), starting after the extended loading dose of aztreonam-avibactam has completed and maintained until the end of the intravenous study treatment period. The Summary of Product Characteristics (Baxter Healthcare Ltd) does not indicate a dose reduction for metronidazole in subjects with renal impairment.

Subjects with hospital-acquired pneumonia/ventilator-associated pneumonia and proven or suspected co-infection with *Pseudomonas aeruginosa* may receive adjunctive therapy with an IV aminoglycoside (eg, amikacin, gentamicin or tobramycin, based upon local practice and epidemiology) at the Investigator's discretion. The need for adjunctive aminoglycoside therapy should be re-evaluated once culture and susceptibility results are available and the aminoglycoside should be discontinued if not needed.

Meropenem ±Colistin Treatment Arm:

Subjects will initially be given meropenem 1000 mg every 8 hours (given as an intravenous infusion over 30 minutes). If a meropenem-resistant pathogen is strongly suspected, a dose of meropenem 2000 mg every 8 hours can be used (given as an intravenous infusion over 3 hours). Colistin (colistimethate sodium) can also be initiated, at the Investigator's discretion. Colistin will be dosed based on guidance described by the European Medicines Agency (see Clinical Study Protocol Section 5.6.2).

If a meropenem-resistant Gram-negative pathogen is subsequently isolated, colistin (colistimethate sodium) can be added (if not already started), and/or the dose of meropenem can be increased to 2000 mg every 8 hours (given as an intravenous infusion over 3 hours), if this dose was not already used initially.

If a meropenem-susceptible Gram-negative pathogen is subsequently isolated and colistin (colistimethate sodium) had been initially started, the colistin (colistimethate sodium) should be discontinued and the dose of meropenem adjusted to the labeled dose regimen (1 g every 8 hours intravenously over 30 min, if a meropenem dose of 2000 mg every 8 hours was initially started).

Meropenem ±colistin doses will need to be adjusted for subjects with renal impairment. The dose of meropenem will need to be further adjusted once the susceptibility of the baseline Gram-negative pathogen(s) to meropenem is known.

Subjects with hospital-acquired pneumonia/ventilator-associated pneumonia and proven or suspected co-infection with *Pseudomonas aeruginosa* may receive adjunctive therapy with an intravenous aminoglycoside (eg, amikacin, gentamicin or tobramycin, based upon local practice and epidemiology) at the Investigator's discretion at any time during the treatment period. For subjects receiving colistin (colistimethate sodium), adjunctive aminoglycosides therapy should not be used concurrently; treatment with colistin (colistimethate sodium) should be discontinued prior to initiating aminoglycoside therapy. The need for adjunctive aminoglycoside therapy should be re-evaluated once culture and susceptibility results are available and the aminoglycoside should be discontinued if *Pseudomonas aeruginosa* is not

isolated or is no longer suspected, or susceptibility results indicate a carbapenem-susceptible strain.

If *Pseudomonas aeruginosa* is isolated and is non-susceptible to meropenem, an intravenous aminoglycoside may be added to meropenem if not originally commenced. Colistin should be discontinued if meropenem and aminoglycoside are being used together.

Statistical Methods

The study will randomize up to approximately 425 subjects in a 2:1 randomization ratio (approximately 283 subjects randomized to the aztreonam-avibactam ±metronidazole treatment arm and approximately 142 subjects to the meropenem ±colistin treatment arm).

As no formal hypothesis testing will be performed for this study, no power calculation was carried out to assess the number of subjects required for each treatment arm. The planned sample size is considered sufficient to estimate the overall clinical cure rates in each arm. The smaller numbers of subjects in these groups will be reflected in the precision of the estimate of clinical cure rate.

Definition of analysis sets

The all subjects analysis set will compromise all enrolled subjects for the study and will be used for reporting of disposition.

The Intent-To-Treat analysis set will include all randomized subjects regardless of receipt of study drug. Subjects in the Intent-To-Treat analysis set will be analyzed according to the treatment they are randomized to. The Intent-To-Treat analysis set will be used to evaluate the primary, secondary and tertiary objectives.

The safety analysis set will be used for reporting safety data and will include all subjects who received any amount of intravenous study treatment. Subjects in the safety analysis sets will be analyzed according to the treatment they receive.

The Clinically Evaluable analysis set is defined as all subjects who:

- Meet the definition of the Intent-To-Treat analyses.
- Meet disease criteria for diagnosis of complicated intra-abdominal infection or hospital-acquired pneumonia/ventilator-associated pneumonia.
- Received at least 48 hours of study treatment (aztreonam-avibactam±metronidazole or meropenem±colistin) or received <48 hours of study treatment before discontinuing study drug due to an adverse event.
- Did not receive concomitant antibiotic treatment with potential activity against any baseline pathogens between the time of first dose of study treatment and the time of Test of Cure. This does not include those subjects who have received protocol-allowed

antibiotics or have failed study treatment and require additional antibiotics to treat their infection.

- Had no important protocol deviations that may affect the assessment of efficacy (to be defined in the Statistical Analysis Plan).
- Did not have a clinical outcome of indeterminate at Test of Cure.
- Did not have monomicrobial infections due to non-eligible pathogens (eg, any *Acinetobacter spp., Pseudomonas aeruginosa*) and did not have only Gram-positive pathogens.

Subjects in the Clinically Evaluable analysis set will be analyzed according to the treatment they are randomized to. The Clinically Evaluable analysis set will be used to evaluate selected primary, secondary and tertiary objectives.

The microbiological Intent-To-Treat analysis set is a subset of the Intent-To-Treat analysis set and includes all subjects who have at least 1 Gram-negative pathogen in an adequate initial/prestudy culture. Subjects with monomicrobial infections due to any *Acinetobacter spp.*, and those subjects with only Gram-positive pathogens will be excluded from the microbiological Intent-To-Treat analysis set. The microbiological Intent-To-Treat analysis set will be used to evaluate selected secondary and tertiary objectives.

The Microbiologically Evaluable analysis set includes all subjects included in both microbiological Intent-To-Treat and Clinically Evaluable analysis sets, with at least 1 Gram-negative pathogen. The Microbiologically Evaluable analysis set will be used to evaluate selected secondary and tertiary objectives.

Sensitivity analyses will be performed using the modified Intent-To-Treat and microbiological modified Intent-To-Treat. The modified Intent-To-Treat and microbiological modified Intent-To-Treat are subsets of the Intent-To-Treat and microbiological Intent-To-Treat respectively and include all randomized subjects who receive any amount of intravenous study drug.

The population pharmacokinetic analysis set includes all subjects who have at least 1 plasma concentration data assessment available for aztreonam-avibactam±metronidazole and will be used to report all pharmacokinetic data.

Methods for statistical analysis

All data will be presented by treatment arm. Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

No formal hypothesis testing will be performed for this study; any comparisons between treatment arms will only be assessed as evidence of an effect, no formal statistical comparisons will be made.

Methodology for dealing with missing data will be specified in the Statistical Analysis Plan.

The primary descriptive efficacy analysis (for non-United States countries) will be the estimate of the clinical cure rate and 95% confidence interval in each treatment arm (aztreonam-avibactam±metronidazole and meropenem±colistin) in the Intent-To-Treat and Clinically Evaluable co-primary analysis sets. The estimate of the clinical cure rate and 95% confidence interval in each treatment arm in the Intent-To-Treat analysis set will be the primary analysis for the United States. Single arm confidence intervals will be computed using Jeffrey's method (Brown et al 2001; Cai 2005). The number and percentage of subjects who had a clinical response of clinical cure, clinical failure, and indeterminate in each treatment arm will be tabulated for the Intent-To-Treat and Clinically Evaluable analysis sets at the Test of Cure visit.

The primary analysis will be conducted using the clinical response assessment determined by a blinded independent adjudication committee. The Investigator's assessment of clinical response will also be summarized for the Intent-To-Treat and Clinically Evaluable analysis sets at the Test of Cure visit. In case of any discrepancy between the Investigator's and adjudication committee's clinical response assessment, the adjudication committee's assessment will prevail for the analysis.

Difference in clinical cure rate between treatment arms at Test of Cure visit (aztreonam-avibactam ±metronidazole minus meropenem ±colistin) and corresponding two-sided 95% confidence interval will be calculated for the Intent-To-Treat and Clinically Evaluable analysis sets. The two-sided 95% confidence interval for the observed difference in the cure rates (aztreonam-avibactam ±metronidazole group minus meropenem ±colistin group) will be computed using the method proposed for unstratified designs by Miettinen and Nurminen and an additional supporting descriptive analysis will be conducted using the stratified Miettinen and Nurminen method (Miettinen and Nurminen 1985), if each stratum has at least 3 subjects per each treatment group.

Clinical response summaries will be presented for the overall population, and also split by infection type (complicated intra-abdominal infection or hospital-acquired pneumonia/ ventilator-associated pneumonia), and by resistance group (eg, extended-spectrum β-lactamase status, carbapenemase status and metallo-β-lactamase status) as secondary/tertiary descriptive analysis.

Secondary and tertiary efficacy outcome measures will be presented using the same methods as the primary outcome measures. For descriptive secondary and tertiary outcome measures, number and percentage in each treatment arm will be tabulated.

The final pharmacokinetic data will be pooled with data from other studies to conduct a population pharmacokinetic analysis (using Nonlinear Mixed Effects Modelling). Using these parameter estimates (mean pharmacokinetic parameters including inter individual variance estimates), Monte-Carlo simulation will be undertaken and potential pharmacokinetic/pharmacodynamic relationships will be explored. Aztreonam and avibactam plasma concentrations versus time will be depicted graphically in the Clinical

Study Report (CSR). Full details of the pharmacokinetic and pharmacokinetic/pharmacodynamic analysis will be given in the Pharmacokinetic Modeling Analysis Plan. These results will be reported separately.

For exploratory efficacy variables, the proportion of subjects who died on or before 14 days after randomization will be presented by treatment arm. Further details on the analysis methods for response endpoint utilising objective measures of clinical response will be detailed in the Statistical Analysis Plan.

Regarding safety variables, adverse events will be summarized by means of counts summaries by Medical Dictionary for Regulatory Activities System Organ Class and preferred term separately for the study periods (treatment period [from first dose to End of Treatment] [treatment emergent adverse events], from End of Treatment to Late Follow-Up, and for the full study period [from first dose to Late Follow-Up]). All adverse events will be listed (including prior to first dose). Deaths, adverse events leading to discontinuation, and serious adverse events will be summarized.

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the Statistical Analysis Plan) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for all laboratory parameters.

The incidence of markedly abnormal values and changes from baseline in the electrocardiogram parameters will be summarized by treatment arm.

Subgroup analyses, which may include subject characteristics, disease severity, prior antibiotic use, infection type and pathogen resistance type, may be performed. More details on the subgroup analyses will be provided in the Statistical Analysis Plan. Additional descriptive analyses of the primary endpoint (clinical cure rate) will be performed for the effect of protocol-allowed additional antibiotics (eg, Gram-positive antibiotics, aminoglycosides).

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Please refer to Section 6 (Study Procedures) and Section 7 (Assessments) of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Table 1. Schedule of Activities

Visit Name	**Eligibility/ Screening[a]**	**Treatment period**		**EOT**	**TOC**	**LFU**
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**
Procedures and Assessments	**Days –1 to 1**	**Day 1 (Baseline[b])**	**Days 2 to 14**	**Within 24 hours after last infusion**	**Day 28 ±3 days**	**Day 45 ±3 days**
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical history	X					
APACHE II score (see Appendix 5)[c]	X					
Prior and concomitant medications (including prior antibiotic treatment)	X	X	Daily	X	X	X
Complete physical examination	X			X	X	
Assess infection-related signs and symptoms	X	X	Daily	X	X	
Perform focused physical examination	X	X	Daily	X	X	X[d]
Vital sign measurements[e]	X	X	Daily	X	X	
12-lead digital triplicate ECG		X	Day 3			

Table 1. Schedule of Activities

Visit Name	**Eligibility/ Screening[a]**	**Treatment period**		**EOT**	**TOC**	**LFU**
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**
Procedures and Assessments	**Days –1 to 1**	**Day 1 (Baseline[b])**	**Days 2 to 14**	**Within 24 hours after last infusion**	**Day 28 ±3 days**	**Day 45 ±3 days**
Chest X-ray or computed tomography scan (for HAP/VAP subjects only)	X[f]	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Collection of imaging and surgical report (for cIAI subjects only)	X	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Document whether subject is ventilated (for HAP/VAP subjects only)	X	X	Daily	X	X	
Serious and non-serious adverse event monitoring	X	X	Daily	X	X	X
Culture of abdominal site infection (for cIAI subjects only)[g]	At surgical intervention	At surgical intervention	As clinically indicated	As clinically indicated	As clinically indicated	
Respiratory specimen for Gram-stain/culture (for HAP/VAP subjects only)	X[h]	X[i]	As clinically indicated	X[j]	X	
Blood cultures[k]	X[k]	As clinically indicated[k]	As clinically indicated	As clinically indicated	As clinically indicated	

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Visit Name	**Eligibility/ Screening[a]**	**Treatment period**		**EOT**	**TOC**	**LFU**
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**
Procedures and Assessments	**Days –1 to 1**	**Day 1 (Baseline[b])**	**Days 2 to 14**	**Within 24 hours after last infusion**	**Day 28 ±3 days**	**Day 45 ±3 days**
Safety laboratories (chemistry, hematology, urinalysis)[l]	X	X	Central lab samples: Every 3 days, starting on Day 4; Local lab serum creatinine: Daily from Day 2 to Day 4, and as clinically indicated	X	X	
Collection of arterial blood gases	X[m]	As clinically indicated	As clinically indicated	As clinically indicated		
Blood for PK analysis[n]		X[o]	Day 4[p]			
Estimate CrCL[q]	X	X	Daily from Day 2 to Day 4 and as clinically indicated	As clinically indicated	As clinically indicated	
Serum or urine β-hCG for women of childbearing potential[r]	X					
Contraception check[s]	X	X	Daily	X	X	
Randomization		X				
Administer study treatment		X	Daily			

Table 1. Schedule of Activities

Visit Name	Eligibility/ Screening[a]	Treatment period		EOT	TOC	LFU
	Visit 1	Visit 2	Visits 3 to 15	Visit 16	Visit 17	Visit 18
Procedures and Assessments	**Days –1 to 1**	**Day 1 (Baseline[b])**	**Days 2 to 14**	**Within 24 hours after last infusion**	**Day 28 ±3 days**	**Day 45 ±3 days**
Clinical response assessment				X	X	
Mortality assessment		X	Daily	X	X	

Abbreviations: ABG=arterial blood gas; ALP=alkaline phosphatase; ALT=alanine aminotransferase; APACHE=Acute Physiology and Chronic Health Evaluation; AST=aspartate aminotransferase; ATM-AVI=aztreonam-avibactam; BAL=bronchoalveolar lavage; β-hCG=β-human chorionic gonadotropin; cIAI=complicated intra-abdominal infections; CrCL=creatinine clearance; ECG=electrocardiogram; EOT=end of treatment; HAP=hospital-acquired pneumonia; INR=international normalized ratio; LFU=late follow-up; MTZ=metronidazole; PSB=protected-specimen brush; PK=pharmacokinetics; TBili=total bilirubin; TOC=test of cure; ULN=upper limit of normal; VAP=ventilator-acquired pneumonia.

a. Study treatment should be started as soon as possible (within 24 hours) after a subject's eligibility has been confirmed and the subject has been randomized. Consequently, Day −1 and Day 1 may be the same calendar day, ie, all procedures scheduled for Day -1 and Day 1 could happen on the same day.

b. All procedures at Visit 2 are to be done before first dose of study therapy except for PK sampling. The repeat safety lab samples (including local lab for eligibility criteria confirmation) and clinically relevant cultures are only required if Visit 1 and Visit 2 are separated by surgery OR are >12 hours apart (see Section 6.2.1). Administration of the first dose of IV study therapy marks the beginning of study treatment Day 1.

c. Calculate APACHE using most recent local laboratory results available within the previous 24 hours prior to screening. Arterial blood gases are required for ventilated and recommended for non-ventilated HAP/VAP subjects, and for cIAI subjects as clinically indicated.

   Use of temperature obtained rectally in determining the APACHE II score is preferred but not mandatory. See Appendix 5. If an arterial blood gas is not clinically indicated, the APACHE score will be calculated using serum bicarbonate instead of arterial pH and assuming normal oxygenation (Variable score = 0).

d. If the subject has been discharged from hospital and is unable to return the physical examination will not be conducted at the LFU visit since the visit will be conducted by telephone.

e. Vital signs should be measured and documented at least once daily, preferably at a similar time each day. However, if any significant excursions occur during the study day, those measurements should also be captured. Body temperature will be measured using an automated thermometer. The subject'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 subject, the method of temperature measurement ideally should be consistent for the duration of the study. At the TOC visit only a single body temperature measurement is required. The actual time of body temperature collection will be

recorded. For subjects with HAP/VAP, respiratory rate (breath per minute) and peripheral O_2 saturation will be collected at Visit 1, at Visit 2, daily while the subject is receiving IV study treatment, at EOT and TOC visits.

f. Performing a chest X-ray or CT scan (if not available within 48 hours prior to randomization) in subjects with HAP/VAP.

g. Specimens must be obtained for culture at initial qualifying surgical procedure (performed within 24 hours before or after randomization). If additional surgical procedures are performed, additional abdominal site specimens should be obtained for microbiological culture (see Appendix 6).

h. Cultures from respiratory specimens obtained within 48 hours prior to randomization may be used, but subjects ventilated subsequently, regardless of whether they meet the criteria for VAP, must have a specimen obtained while ventilated.

i. Repeat of culture of respiratory specimens are not required, unless a Screening sample was obtained from a non-ventilated subject and the subject is subsequently ventilated (or the subject had a bronchoscopy). In this case, an appropriate respiratory specimen should be obtained via BAL, miniBAL, PSB sample or endotracheal aspirate at the Baseline visit (prior to the first dose of study treatment) (see Appendix 6).

j. If treatment is discontinued early, an attempt to obtain an appropriate respiratory specimen for culture should be made, ideally after stopping the study treatment and before the new treatment is administered.

k. All subjects must have had 2 sets of blood cultures obtained prior to randomization. Repeat samples for blood cultures are not required at Screening if available within 48 hours prior to randomization. Blood should be taken prior to the first dose of study treatment if not available within 48 hours prior to randomization. When obtaining samples for blood culture, blood should be collected from 2 sites (see Appendix 6). All subjects require 2 sets of blood cultures (1 anaerobic and 1 aerobic bottle from each site, ie, 4 bottles in total). For subjects who are bacteremic at any time during the study, repeat blood cultures should be performed at least every 3 days, until clearance of bacteremia is documented. Blood cultures should also be obtained as clinically indicated. See Section 7.3 and Appendix 6 for details of sample collection.

l. At Screening, the following assessments will be performed in the local laboratory for eligibility determination: serum creatinine (including calculation of CrCL), AST, ALT, ALP, TBili, and hematology as listed in Section 4.2.1. In addition, safety laboratory samples must be sent to the central reference laboratory for testing. During treatment period, if ALT or AST are >3 x ULN and the subject has not met the liver discontinuation criteria (Section 8.5.2), the frequency of liver laboratory testing collection, and INR, should be increased to daily monitoring (using local laboratory data and recorded as unscheduled visits) until the liver function tests recover to <3 x ULN.

m. For HAP/VAP subjects – obtaining arterial blood sample for ABG (required for ventilated subjects, recommended for non-ventilated subjects); for cIAI subjects- obtaining arterial blood sample for ABG as clinically indicated.

n. PK sampling is only relevant for subjects randomized to ATM-AVI ±MTZ.

o. 3 samples should be taken on Day 1 - see Table 13 and Figure 3 and Figure 4 for detailed guidance on schedule.

p. 3 samples have to be taken on Day 4±1 day - see Table 13 and Figure 3 and Figure 4 for detailed guidance on schedule.

q. Subjects must be frequently and closely monitored for rapidly changing CrCL through local laboratory measurement of serum creatinine. In case that renal function recovers or deteriorates during the treatment period, the dose of study treatment should be adjusted by the Investigator to meet the appropriate dose regimen, based on the latest CrCL value and in line with Section 5.6.5. In addition, to coincide with PK sample collection for patients randomized to the ATM-AVI treatment arm, CrCL will be estimated using central laboratory measurement of serum creatinine. PK samples should be collected on Day 4, but

can be collected on Days 3 or 5. CrCL will therefore also be estimated on Days 3 or 5 if PK blood samples are collected on Days 3 or 5. In this case, a blood sample for estimation of serum creatinine will also be collected on Days 3 or 5 and sent to the central laboratory. (See Appendix 3)

r. Serum or urine β-hCG for pregnancy test will performed in local laboratory for eligibility determination.

s. The contraception check is an opportunity to confirm that contraception is used consistently and correctly for the duration of the study and for at least 7 days after the last infusion of investigational product. Also, for studies enrolling adult subjects, it is the opportunity to assess changing potential to father/bear children and allows for altering contraception if new disease contraindicates a selected method of contraception or if nonchildbearing status is achieved.

1. INTRODUCTION

1.1. Background

The prevalence of multidrug 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 MDR Gram-negative bacteria. New antibiotics or combinations of existing antibiotics with resistance enzyme inhibitors are urgently needed to provide treatment options for patients with infections known or suspected to be caused by MDR Gram-negative pathogens (IMI; IMI 2015).

One of the most common resistance mechanisms in Gram-negative pathogens is the production of extended-spectrum β-lactamase (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 treatment. ESBL are found in a significant percentage of *Enterobacteriaceae* (including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp.*, *Citrobacter spp.*, *Proteus spp.*, *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* characterized by large heterogeneity in genotypes (with >20 reported resistance gene families, such as New Delhi Metallo-β-lactamase (NDM), *Klebsiella pneumonia* carbapenemase (KPC), Verona Integron encoded metallo-β-lactamase (VIM), and Oxacillinase (OXA)-48 (Nordmann and Poirel 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. 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, United Kingdom [UK]), including Australia, Singapore, Taiwan, and the United States (US). 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 (Johnson and Woodford 2013; Moellering 2010).

The spread of resistance leading to multi-drug resistant pathogens due to the ESBL cefotaximase -M (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).

1.2. Mechanism of Action/Indication

With more than 30 years of use worldwide, aztreonam (ATM) is an established injectable antibiotic indicated for the treatment of various infections caused by Gram-negative bacteria including but not limited to pneumonia and complicated intra abdominal infections (cIAIs) (see Summary of Product Characteristics [SmPC] of ATM and ATM prescribing information). 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. Activity against MBL (Class B) producing pathogens is possible, although potential inactivation by Class A, C, or D β-lactamases remains problematic.

Avibactam (AVI) is a novel, non β-lactam, β-lactamase inhibitor of a broad spectrum of enzymes, including Ambler Class A ESBLs, Class A KPC, and Class C (ampicillinase Class C [AmpC]) enzymes, and some Class D enzymes, notably OXA-48, a problematic carbapenemase in the European Union (EU) and Middle East. The inhibition of β-lactamase by AVI occurs through formation of a covalent bond between AVI and the 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.

1.3. Rationale for Conducting This Study

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 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 treatment is the fact that ATM-AVI has shown excellent activity in pre-clinical studies against a broad range of Gram-negative pathogens thereby restoring ATM activity against ATM-resistant pathogens, including several of the most problematic MDR pathogens, but excluding *A. baumannii* as listed above (see Investigator's Brochure (IB) for further details).

To date, 92 healthy volunteers have been dosed with the investigational product (IP) (ie, ATM-AVI, placebo or ATM/AVI separately), in a single Phase 1 study (Please see Section 1.4 for further details). Additional details can be found in the ATM-AVI IB.

A prospective, open-label, multicenter Phase 2a study to determine the pharmacokinetics (PK), safety and tolerability of ATM-AVI for the treatment of cIAI in hospitalized adults, and to provide dose confirmation for Phase 3 clinical studies has completed enrolment and the CSR is pending. The PK/pharmacodynamic (PD) data generated will contribute to a robust package of data, supported by prior experience with ATM and AVI, and will be validated by qualitative data for the combination from the ATM-AVI Phase 3 program.

This ATM-AVI Phase 3 study is part of the Work Package 2B (WP2B) in the Innovative Medicines Initiative (IMI) supported COMBACTE-CARE project. IMI is a joint undertaking between the EU and the pharmaceutical industry association European Federation of Pharmaceutical Industries and Associations (EFPIA) (see IMI). COMBACTE-CARE (Combatting Bacterial Resistance in Europe – Carbapenem-resistence) is a consortium of 19 academic and 3 pharmaceutical partners focusing on carbapenem resistance in Europe. The study is registered in the EudraCT database with the number 2017-002742-68.

1.4. Rationale for Study Design, Doses and Control Groups

In patients with hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) and cIAIs, Gram-negative pathogens, including those producing ESBLs and AmpC β-lactamases, are important causative pathogens.

Most intra-abdominal infections are polymicrobial and caused by organisms residing in the gastrointestinal tract, including aerobes and facultative and obligate anaerobes. In patients with cIAI, MTZ 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 MTZ is well suited to treatment of pathogens commonly responsible for cIAIs. In patients with HAP/VAP, anaerobic organisms are not common causative pathogens; therefore ATM-AVI is considered to provide efficient coverage for the pathogens causing HAP/VAP.

Meropenem (MER) has been selected as the comparator because of its established efficacy against resistant Gram-negative pathogens isolated in cIAI and HAP/VAP, for which is it approved and widely used in these indications due to the spectrum of activity including efficacy against ESBL- and AmpC- producing *Enterbacteriaceae* causing cIAI and HAP/VAP (MERREM®, 2016; MERONEM® SmPC, 2017). It is amongst the treatment options recommended as a first-line agent for the treatment of serious bacterial infections due to MDR Gram-negative pathogens (Kalil et al. 2016).

The option to add concomitant therapy with colistin (COL) (colistimethate sodium) is based on current standard of care for proven or suspected carbapenem-resistant *Enterobacteriaceae* (CRE) (Nation et al. 2015). Both COL and tigecycline are frequently used in the treatment of CRE infections based on demonstrated activity against CRE, yet both agents are associated with significant tolerability and safety concerns. Optional COL was chosen for use in the comparator arm because it shows more consistent in vitro activity against MBL pathogens than tigecycline (Morill et al. 2015; Narayabab et al. 2016; Tängden et al. 2015).

The decision to select MER ±COL rather than COL monotherapy as the starting treatment regimen was based on current standard of care for serious infections due to Gram-negative bacteria, including MBL-producing MDR pathogens (IDSA 2016, Hopkins 2015-2016 and Solomkin et al. 2010). Since only a relatively small proportion of sites are likely to have a high prevalence of MBLs, many investigators may be reluctant to initiate a patient on COL unless they suspect the involvement of an MBL pathogen in the patient's infection. Mandating COL therapy for all patients could expose patients who have only a MER-susceptible Gram-negative pathogen to unnecessary risks. Considering the safety concerns that are associated with COL, compared with the better-tolerated standard of care agents for Gram-negative pathogens, such as high dose MER, the use of COL will be optional and at the investigator's discretion (Jaruratanasirikul et al. 2005, Keel et al. 2011, and Li et al. 2006).

1.4.1. Study Design and Control Group

This is a Phase 3 prospective, randomized, open-label, central assessor-blinded, parallel group, multicenter comparative study to determine the efficacy, safety and tolerability of aztreonam-avibactam ±metronidazole (ATM-AVI ±MTZ) versus meropenem ±colistin (MER ±COL) in the treatment of serious infections due to Gram-negative bacteria, including MBL-producing MDR pathogens for which there are limited or no treatment options.

The comparative, 2-arm study design is sufficient to provide descriptive estimates of efficacy, safety and tolerability for ATM-AVI and comparator in the treatment of patients with cIAI or HAP/VAP. The study is open-label due to the complicated dosing regimens of the investigational product. The Investigators, site personnel, and patients will not be blinded in this open-label study. The independent adjudication committee (central assessor) will be blinded with the aim of unbiased adjudication of the primary objective measure. The 2:1 ratio for randomization (to ATM-AVI ±MTZ versus MER ±COL, respectively) is chosen in order to enrich the safety and efficacy data for patients treated with ATM-AVI ±MTZ and increase the number of potential MBL-producing Gram-negative pathogens in that group. Due to the excessive fluid burden that would be expected in the case of a double-blinded study, for patients with different infection types (cIAI or HAP/VAP) and for a range of renal functions, it was not considered feasible to use placebo infusions to create a double-blinded study. Volume overload is associated with the development of serious medical complications and increased mortality; a recent study in 3147 patients in the Sepsis Occurrence in Acutely Ill Patients (SOAP) study in 24 European countries found that a 1 L positive fluid balance per 24 hours was associated with an approximate 20% increase in mortality risk (Payen et al. 2008). Instead, a study design with a blinded central adjudication committee is considered to be most appropriate for the proposed ATM-AVI ±MTZ study in order to reduce risk to patients and reduce the risk for bias.

Clinical efficacy for the study population will be estimated using a clinical response endpoint applicable to all patients. Secondary endpoints include microbiological response in microbiological analysis sets, and 28 day mortality.

The duration of study drug treatment (5 to 14 days for cIAI and 7 to 14 days for HAP/VAP) takes into account the current US Food and Drug Administration (FDA) recommendations for the development of drugs for treatment of cIAI (FDA 2015). The study is approximately 45 days in duration. It will consist of a Screening visit (Visit 1), a Baseline visit (Visit 2) on Day 1 of the study treatment, ongoing treatment visits (Visits 3 to 15) from Day 2 to Day 14, an End of Treatment (EOT) visit (Visit 16) within 24 hours after the last infusion, a Test of Cure (TOC) visit (Visit 17) on Day 28 (±3 days) and a Late Follow Up (LFU) visit (Visit 18) on Day 45 (±3 days).

The study is planned to be performed in approximately 170 sites in up to 30 countries in the Americas, Africa, Europe, and Asia, in regions with emerging and/or elevated incidence of carbapenem resistance, including resistance caused by MBLs.The chosen study design as described below takes into account the joint scientific advice received from the European Medicines Agency (EMA) and the FDA in October 2012 and April 2015 and further scientific advice from the FDA in December 2016 alongside the current regulatory guidelines, ie, the EMA "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections" (EMA 2011), EMA "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections" (EMA 2013), the US FDA Guidance for Industry "Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases" (FDA 2017), the US FDA Guidance for Industry "Complicated Intra-Abdominal Infections: Developing Drugs for Treatment" (FDA 2015), and the US FDA Guidance for Industry "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment" (FDA 2014).

1.4.2. Dose Selection for 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 3 study have been selected based on pre-clinical and clinical data on ATM-AVI, using PK data for ATM, AVI and ATM-AVI and including covariate information collected in healthy volunteers and patients to construct a robust population PK model. Furthermore, AVI PK and safety data together with PK/PD modelling results obtained during development of the new ceftazidime-avibactam (CAZ-AVI) combination product Avycaz™ in the US (Zavicefta® in Europe) have been taken into account (FDA prescribing information: AVYCAZ 2017, European Commission: Product information Zavicefta 2016).

Patients will be monitored frequently and closely for rapidly changing creatinine clearance (CrCL), and the Investigator will adjust the study drug dose promptly if needed. (See Appendix 3)

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 while prolonging time above the minimum inhibitory concentration (MIC) with extended infusion time and shorter dosing intervals. The rationale for the selected dose regimen is based on the objective of obtaining optimal exposure to achieve a >90% probability of target attainment (PTA) against PK/PD targets for both ATM and AVI which have been identified from non-clinical data. The PK/PD targets are:

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

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

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

In Cohort 1 of the Phase 2a study in patients with cIAI (and CrCL >50 mL/min) the dosing regimen was selected based on the Phase 1 safety data and PK/PD modeling above, ie, a loading dose (500 mg ATM plus 137 mg AVI by IV infusion) over a 30 minute period, was immediately followed by a maintenance infusion of 1500 mg ATM plus 410 mg AVI over a 3 hour period [q6h]). Patients also receive 500 mg MTZ infused over 1 hour every 8 hours (q8h), starting after the first ATM-AVI maintenance infusion.

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

In this Phase 3 study, the dosing regimen is the same as that administered in Cohorts 2 and 3 of the Phase 2a study. The loading dose for patients with normal renal function or mild renal impairment (CrCL >50 mL/min) is 500 mg ATM plus 167 mg AVI infused over a 30 minute period, immediately followed by an extending loading dose of 1500 mg ATM plus 500 mg AVI over a three hour period. Three hours after the extended loading dose is completed, a maintenance dose of 1500 mg ATM and 500 mg AVI is infused over 3 hours and administered (q6h). The targeted total daily dose on Day 1 is 6500 mg ATM/2167 mg AVI. From Day 2 onwards, this will be 6000 mg ATM/2000 mg AVI.

Dose selection (ATM-AVI) for patients with moderate renal impairment (CrCL >30 mL/min to ≤50 mL/min) and severe renal impairment (CrCL >15 mL/min to ≤30 mL/min)

As both ATM and AVI are eliminated primarily as unchanged substances by the kidney, dosing regimens for patients with moderate to severe renal impairment (CrCL >15 mL/min to ≤50 mL/min) require adjustment. Doses are based on PK modeling and simulation.

The review and approval of data from the Phase 2a Cohort 1 by the SAC also led to the approval that Cohort 2 could recruit patients with moderate renal impairment (CrCL >30 mL/min to ≤50 mL/min). The population PK models for both ATM and AVI included data from patients with renal impairment which allowed the use of modeling and simulation for dose selection in Phase 2a and 3. The dose selection for patients with moderate renal impairment was based on the following criteria: matching the predicted ATM steady state area under the curve between time zero and 24 hours after dose ($AUC_{(0\text{-}24,ss)}$) in patients with moderate renal impairment, to the predicted $AUC_{(0\text{-}24,ss)}$ in patients with normal renal function (CrCL >80 mL/min) receiving ATM 1500 mg/AVI 500 mg; maintaining the same dosing ratio between ATM and AVI; and maintaining >90% PTA. Furthermore, since the dosing ratio between ATM and AVI is fixed, and given the differential impact of renal impairment on the clearance of ATM and AVI, it was accepted that matching an area under the plasma concentration versus time curve (AUC) target for ATM would result in exceeding the exposure targets for AVI in patients with normal renal function, but should not appreciably exceed the exposure in patients with mild renal impairment with the standard dose. As patients can have fluctuating renal function, in order to ensure sufficient exposure on the first day of dosing, the loading and first maintenance dose for patients with moderate renal impairment (CrCL >30 to 50 mL/min) will be the same as for patients with normal renal function. Thus in this Phase 3 study, the dose for patients with moderate renal impairment is a loading dose of 500 mg ATM plus 167 mg AVI by IV infusion over a 30 minute period, immediately followed by an extended loading dose of 1500 mg ATM plus 500 mg AVI by IV infusion over a 3 hour period, and then following a 3 hour gap, a reduced maintenance doses of 750 mg ATM plus 250 mg AVI by infusion over a 3 hour period q6h.

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

1.4.3. Dose Selection for Metronidazole

MTZ will be co-administered with ATM-AVI in patients with cIAI for the entire duration of study drug treatment (5 to 14 days) to provide coverage for anaerobic pathogens. The dose to be administered (500 mg MTZ IV over 1 hour q8h starting after the extended loading dose [second dose] of ATM-AVI) was chosen based on the current Guidelines of the Infectious Diseases Society of America for management of cIAI (Solomkin et al. 2010). This dose selection for MTZ is also in line with nationally approved SmPCs in Europe (Baxter Healthcare Ltd.) which do not indicate a need for dose adjustments in renal impairment.

1.4.4. Dose Selection for Meropenem

The dose of MER selected for this study (1 g IV q8h over 30 minutes) is consistent with the currently labeled recommendations for adult patients with cIAI (MERONEM® SmPC 2017, MERREM® 2016) and HAP/VAP (MERONEM® SmPC 2017). The protocol allows for the option to use an increased dose of MER (2 g IV q8h) in the case of proven or suspected CRE. Prolonged infusion (over 3 hours) may be used if this is the standard of care or in the case of proven or suspected CRE. The use of increased dose MER and prolonged infusion time is an evolving standard of care for patients with presumed MDR Gram-negative infections, based on extensive PK/PD analyses indicating improved target attainment for certain high-MIC pathogens otherwise classified as MER-resistant, including MBL- and KPC-producing strains (Jaruratanasirikul et al. 2011; Roberts et al. 2009; Tsala et al. 2016). Doses are to be adjusted for patients with renal impairment based on frequent monitoring of CrCL.

1.4.5. Dose Selection for Colistin

The COL dosing regimen specified by the study protocol is consistent with recent guidance issued by EMA (EMA 2014a and EMA 2014b), which indicates that COL should be dosed and monitored as follows: a loading dose of 9 million international units (IU) over 30 to 60 minutes, followed by 9 million IU daily in 2 or 3 divided doses as a slow IV infusion. Doses are to be adjusted for patients with renal impairment based on frequent monitoring of CrCL. Recent clinical studies indicate this dose regimen to be generally well tolerated and efficacious in the treatment of patients with serious blood stream infections and patients with ventilator-associated bacterial pneumonia (Dalfino et al. 2012; Dewan and Shoukat 2014).

1.5. Single Reference Safety Document

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

The SRSD for co- administered drug MTZ is MTZ United Kingdom (UK) SmPCs (Baxter Healthcare Ltd.) and Metronidazole, CHINA; Metronidazole, USA. The SRSD for comparator Meropenem is United Kingdom (UK) MERONEM® SmPC 2017, and for comparator Colistin is Colomycin® United Kingdom (UK) SmPC 2016 and Colistimethate sodium, USA.

1.6. Benefits/Risk and Ethical Assessment

Patients enrolled into this clinical study will have cIAIs requiring surgical intervention (including open laparotomy, percutaneous drainage of an abscess and laparoscopic surgery) or nosocomial pneumonia (NP) including HAP and VAP that are of sufficient severity to require hospitalization and treatment with IV antibiotics.

The potential benefit to patients participating in this study is that they will receive effective antibiotic treatment for their infection. ATM-AVI is covering Gram-negative pathogens in cIAI and HAP/VAP patients, and other suspected pathogens are covered by the administration of allowed concomitant antibiotics while MTZ will be covering anaerobic pathogens in cIAI, see details in Section 5.10. Microbiology data reported for ATM-AVI to date shows it has potent in vitro activity against *Enterobacteriaceae*, including activity against MDR isolates that carry MBLs (see IB for further details). In addition, AVI has been shown to restore the effectiveness of ceftazidime in clinical studies in patients with cIAI and HAP/VAP (see IB of ATM-AVI), and restoration of activity of aztreonam is also expected when combined with AVI. Thus ATM-AVI warrants further study in difficult to treat, serious infections where MDR *Enterobacteriaceae* may occur. 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 which results in limited or no current treatment options (see Section 1.1). It is possible that ATM-AVI will not prove to be as effective as the comparator regimens which represent current standard of care for a cIAI and/or NP. In order to mitigate this risk, the study patients will be closely monitored and managed with appropriate therapies as determined by the Investigator who is providing treatment, based on the clinical response of the patient. In addition, protocol-allowed specified concomitant antibiotics to cover non-susceptible pathogens, are permitted according to local microbiological results (see Section 5.10).

ATM-AVI is not approved for marketing in any country. However, ATM has been marketed for over 30 years and has an established safety profile. Extensive data in over 2000 patients from the CAZ-AVI program indicates that AVI does not alter the established safety profile of its β-lactam partner in the combination, thus the same could be reasonably expected for ATM in combination with AVI.

All adverse drug reactions (ADRs) expected for the ATM monoproduct are considered ADRs for ATM-AVI, and to date no unique risks have been identified for the combination of ATM-AVI compared with ATM alone.

ATM solution for injection (Azactam™) was first approved by the US FDA in 1986 and is indicated for intra-abdominal infections. The most frequent ADR for ATM comprise gastrointestinal disorders (diarrhea, nausea, vomiting: common according to Council for International Organizations of Medical Science (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 (CAZ or ceftaroline). As part of the CAZ-AVI 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 AVI alone or in combination with ceftaroline, CAZ or ATM. CAZ-AVI was approved by the FDA on 25 February 2015 (Trademark: Avycaz) and by the EMA on 28 April 2016 (Trademark: Zavicefta). No ADRs are currently expected for the AVI monoproduct. More than 2000 patients across the indications of cIAI, complicated urinary tract infections, and HAP/VAP have been exposured to CAZ-AVI and no significant differences in the safety profile for CAZ-AVI were found compared to ceftazidime (CAZ) only.

To date on the ATM-AVI clinical development program, data are available from 1 completed Phase I study in healthy volunteers (Study C3601005), and an ongoing Phase 2a study in patients with cIAI (Study C3601001). In completed Study C3601005, the most common adverse events (AEs) reported in the ATM-AVI treatment arms were headache, liver function test abnormal, diarrhoea and infusion/cannula site pain/reaction, which are expected events for the ATM monoproduct (ER Squibb & Sons Limited 2014).

Increases in transaminase levels are expected for ATM-AVI on the basis of the ATM labelling and are listed in Section 4.8 ("Undesirable effects") of the UK ATM SmPC where they are considered to be "usually reversing during therapy and without overt signs or symptoms of hepatobiliary dysfunction" (ER Squibb & Sons Limited 2014). Although data are limited at this stage of development, the transaminase elevations observed in the completed ATM-AVI Study C3601005 and preliminary unvalidated data from ongoing Study C3601001 show a similar pattern to that expected with ATM monotherapy, ie, generally asymptomatic, mild and reversible. Preliminary post-hoc exposure-response analyses for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations in study C3601005 suggest that AVI does not contribute to the expected effect of ATM on AST and ALT (in-house data). Increased liver transaminases are considered an important potential risk for ATM-AVI (see IB for further details). Liver related AEs and increases in serum transaminases will continue to be kept under close surveillance in ATM-AVI clinical studies and managed appropriately, including the use of individual patient liver specific withdrawal criteria in line with guidance from the Regulatory Agencies.

Data from the Phase I study did not show evidence of a drug-drug interaction (DDI) between ATM and AVI after single doses. 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) PK, undergo limited metabolism and are eliminated primarily as unchanged substances by the kidney. In addition, neither shows significant inhibition or induction of cytochrome P450 (CYP) enzymes in vitro and/or in vivo. Both ATM and AVI have low binding to human plasma proteins (ATM: approximately 43% [Colomycin® SmPC 2016; Crandon and Nicolau 2013; Vinks et al. 2007]; AVI: 5.7% to 8.2% [FDA prescribing information: AVYCAZ 2017]). Furthermore, data from the Phase I study suggest that there is no clinically relevant influence of sex or age on the PK of AVI (Tarral and Merdjan). As

only renal function influences PK of ATM and AVI, reduced doses in the regimens for moderate and severe renal impairment patients were included in this study.

In addition to the identified and potential risks for ATM-AVI described above, there are also general study related risks that encompass puncture of a vein 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 107 to 154 mL; 18 mL thereof will be used for PK analysis (see Table 14). The results of safety laboratory sampling (clinical chemistry, hematology) will be made available to the investigators. Similarly, the results of specimen 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 electrocardiograms (ECGs). These procedures however are not considered as risks for the patients that would affect the benefit-risk assessment.

In summary, the known and potential risks of receiving ATM-AVI are expected to be similar to those seen with ATM. To date, no unique risks have been identified for the AVI component or the combination of ATM and AVI. Thus, the benefit/risk of ATM-AVI remains acceptable in this population of patients with life-threatening serious infections caused by Gram-negative pathogens producing MBLs and other β-lactamases implicated in the development of MDR for whom only limited alternative treatment options are available. The potential risks and discomforts to the individual patients in this study are well balanced by providing best practice medical monitoring and clinical care for each patient. 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 (ie, medically and ethically justified).

Detailed information on identified and important risks for ATM-AVI is located in the ATM-AVI IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

Based on differing regulatory requirements for EMA and FDA, the following objectives and outcome measures may differ for the US and non-US countries analyses as noted below.

Primary Objective:	**Primary Endpoint:**
To evaluate the efficacy of ATM-AVI ±MTZ and MER ±COL at the Test of Cure (TOC) visit for the treatment of serious infections due to Gram-negative bacteria, including those due to MBL-producing MDR pathogens.	Proportion of subjects with clinical cure at the TOC visit in the Intent-To-Treat (ITT) and Clinically Evaluable (CE) analysis sets (Note: non-US countries, the ITT and CE are considered co-primary analysis sets. For the US, the ITT is considered the primary analysis set, while CE is secondary).

This protocol will use an independent adjudication committee (central blinded assessor) to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria (see Section 9.7).

2.2. Secondary Objectives

Secondary Objectives:	Secondary Endpoint(s):
To evaluate efficacy of ATM-AVI ±MTZ and MER ±COL at the TOC visit in the microbiological ITT (micro-ITT) and Microbiologically Evaluable (ME) analysis sets.	Proportion of subjects with clinical cure at the TOC visit in the micro-ITT and ME analysis sets.
To evaluate the efficacy of ATM-AVI ±MTZ and MER ±COL at the TOC visit in key sub populations.	• Proportion of subjects with clinical cure at the TOC visit by infection type in the ITT and CE analysis sets. • Proportion of subjects with clinical cure at the TOC visit for subjects with MBL-positive pathogens in the micro-ITT and ME analysis sets.
To assess the per-subject microbiological response to ATM-AVI ±MTZ and MER ±COL at the TOC visit.	Proportion of subjects with a favorable per-subject microbiological response at the TOC visit in the micro-ITT and ME analysis sets.
To assess 28-day all-cause mortality.	Proportion of subjects who died on or before 28 days from randomization in the ITT and micro-ITT analysis sets.
To evaluate the pharmacokinetics (PK) of ATM and AVI in subjects with serious infections and to characterize the relationship between exposure and clinical and microbiological response for ATM-AVI ±MTZ utilization (listings to be provided in the Clinical Study Report (CSR), analysis to be reported outside of the CSR.	• PK of ATM and AVI in subjects in the popPK analysis set. • PK/ Pharmacodynamic (PD) relationship between exposure and clinical and microbiological response for ATM-AVI ±MTZ in the popPK analysis set.

2.3. Safety Objectives

Safety Objective:	**Safety Endpoint:**
To evaluate the safety and tolerability profile of ATM-AVI ±MTZ and MER ±COL.	Safety and tolerability as assessed by adverse events (AEs), physical examination, vital signs, electrocardiograms (ECGs), and laboratory assessments in the safety analysis set.

2.4. Tertiary Objectives

Tertiary Objective:	Tertiary Endpoint(s):
To evaluate the efficacy of ATM-AVI ±MTZ and MER ±COL at the End of Treatment (EOT) visit.	Proportion of subjects with clinical cure at the EOT visit in the ITT, micro-ITT, CE and ME analysis sets.
To evaluate the efficacy of ATM-AVI ±MTZ and MER ±COL at the EOT visit in key sub populations.	• Proportion of subjects with clinical cure at the EOT visit by infection type in the ITT and CE analysis sets. • Proportion of subjects with clinical cure at the EOT visit for subjects with MBL-positive pathogens in the micro-ITT and ME analysis sets.
To evaluate the efficacy of ATM-AVI ±MTZ and MER ±COL at EOT and TOC visits by pathogen resistance type.	Proportion of subjects with clinical cure at EOT and TOC visit by pathogen resistance type (eg, ATM-non-susceptible, ESBL-positive, carbapenamase-positive, etc) in the micro-ITT and ME analysis sets.
To assess the per-subject microbiological response to ATM-AVI ±MTZ and MER ±COL at the EOT visit.	Proportion of subjects with a favorable per-subject microbiological response at the EOT in the the micro- ITT and ME analysis sets.
To assess the microbiological response by pathogen and by pathogen resistance type to aztreonam avibactam ±metronidazole and meropenem ±colistin at the EOT and TOC visits.	• Proportion of subjects with a favorable per-pathogen microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets. • Proportion of subjects with a favorable per-subject microbiological response by pathogen resistance type (eg, ATM-non-susceptible, ESBL-positive, carbapenamase-positive, MBL- positive) at the EOT and TOC visits in the micro-ITT and ME analysis sets. • Proportion of subjects with a favorable per-pathogen microbiological response by pathogen resistance type (eg, ATM-non-susceptible, ESBL-positive, carbapenamase-positive, MBL-positive) at the EOT and TOC visits in the micro-ITT and ME analysis sets.

2.5. Exploratory Objectives

Exploratory Objectives:	Exploratory Endpoint(s):
To evaluate efficacy of ATM-AVI ±MTZ and MER ±COL using objective clinical measures.	Composite endpoint including symptom-based objective clinical measures, to be defined in the Statistical Analysis Plan (SAP) (ITT and CE analysis sets).
To assess 14-day all-cause m01iality.	Proportion of subjects who died on or before 14 days from randomization in the ITT analysis set.
To evaluate health resource utilization (listings to be provided in the CSR, analysis to be repo1ied outside of the CSR).	• Length of hospital stay, including any readmissions up to TOC (days). • Length of study treatment (days). • Length of intensive care unit (ICU) stay (days). • Transfened to the ICU (Yes/No). • Mechanical ventilation (Yes/No) for *HAPN* AP subjects. • Length of mechanical ventilation (days) for *HAPN* AP subjects. • Subsequent unplanned surgical intervention after treatment success vs failure (up to the TOC visit) for cIAI subjects.

CCI [redacted]

3. STUDY DESIGN

This is a Phase 3, prospective, randomized, multicenter, open-label, central assessor-blinded (see Section 9.7), parallel group, comparative study to detennine the efficacy, safety, and tolerability of ATM-AVI ±MTZ versus MER ±COL in the treatment of hospitalized adults with cIAI or NP (including HAP and VAP) in regions with endemic or emerging carbapenem resistance, and where MBL-producing MDR pathogens are suspected.

The study outline is provided in Figure 1, the study treatment is provided in Figure 2.

Adult hospitalized subjects with a confirmed diagnosis of complicated intra-abdominal infection or hospital acquired pneumonia/ventilator associated pneumonia related to Gram-negative pathogens including, but not limited to, those infected with multidrug resistant strains, and requiring administration of intravenous antibacterial treatment will be enrolled in this study.

The study will randomize up to approximately 425 subjects (at least 300 subjects with cIAI anticipated) in regions with emerging and/or elevated incidence of carbapenem resistance, including MBL-producing pathogens. The number of subjects with a perforated appendix or appendiceal abscess will be limited to approximately 40% of the study population with cIAI. It is estimated that approximately 8-10% of subjects will be identified with MBL-producing Gram-negative pathogens.

The study will consist of a Screening visit (Visit 1), a Baseline visit (Visit 2) on Day 1 of the study treatment, ongoing treatment visits (Visits 3 to 15) from Day 2 to Day 14, an EOT visit (Visit 16) within 24 hours after the last infusion, a TOC visit (Visit 17) on Day 28 (±3 days) and a LFU visit (Visit 18) on Day 45 (±3 days).

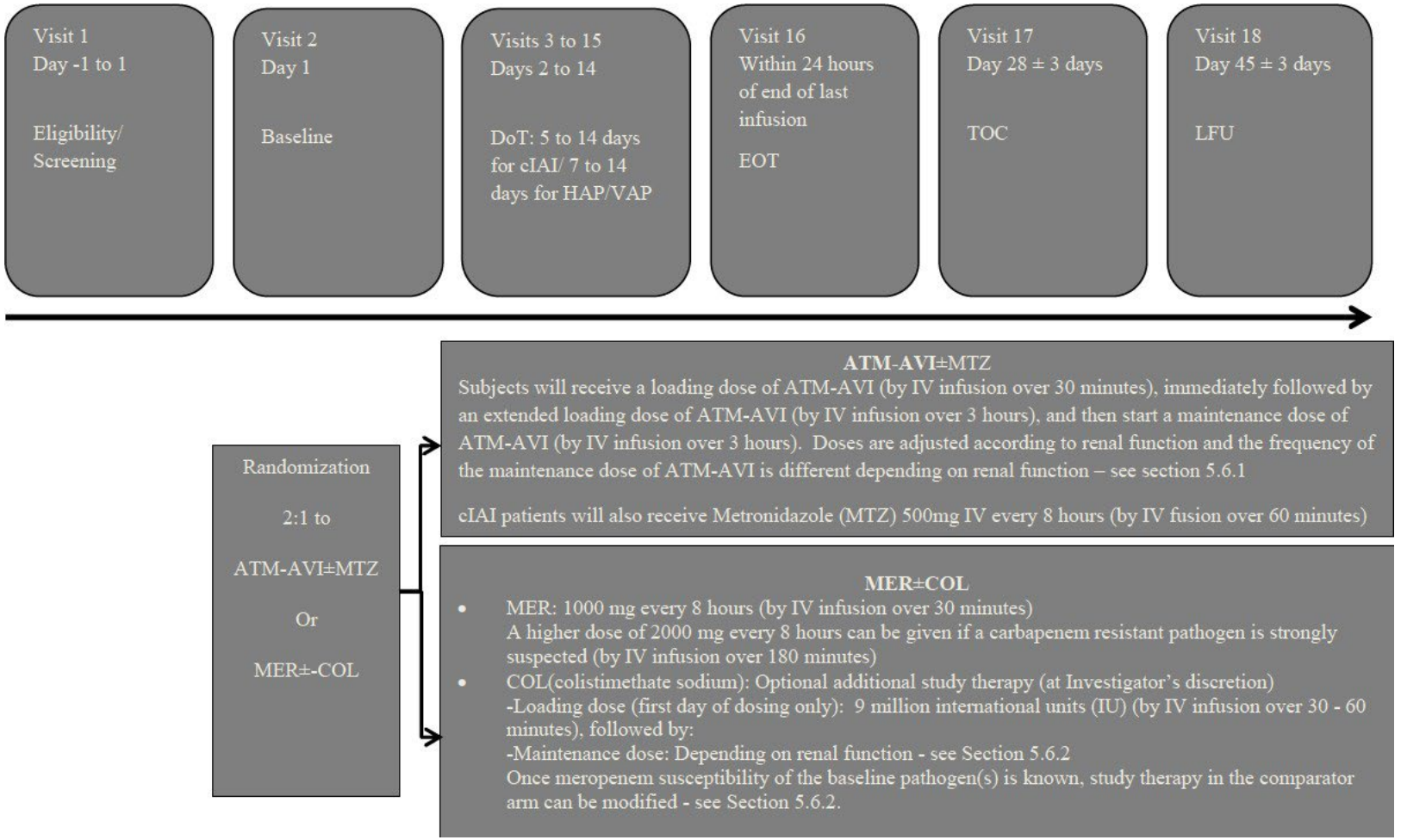
After obtaining written informed consent and confirming eligibility, subjects will be randomized in a 2:1 ratio to the ATM-AVI ±MTZ treatment arm or the MER ±COL treatment arm according to a central randomization schedule (approximately 283 subjects to ATM-AVI ±MTZ and approximately 142 subjects to MER ±COL per group). Please refer to Section 5.6, for more details with regard to treatment arms, dosage and mode of administration and duration of treatment. Subjects will be stratified at randomization based on infectious disease type (cIAI and HAP/VAP). For cIAI, subjects will also be stratified by Acute Physiology and Chronic Health Evaluation (APACHE) II score (≤10 and >10) (see Appendix 5). For HAP/VAP, subjects will also be stratified by mechanical ventilation status (Y/N).

The recommended minimal duration of treatment is 5 days for cIAI and 7 days for HAP/VAP. The maximal duration of treatment is 14 days.

For subjects randomized to ATM-AVI ±MTZ, sparse blood samples will be collected for PK assessments by population pharmacokinetic (popPK) analysis, and PK/PD relationships will be evaluated in subjects where plasma samples and microbiological response data have been collected.

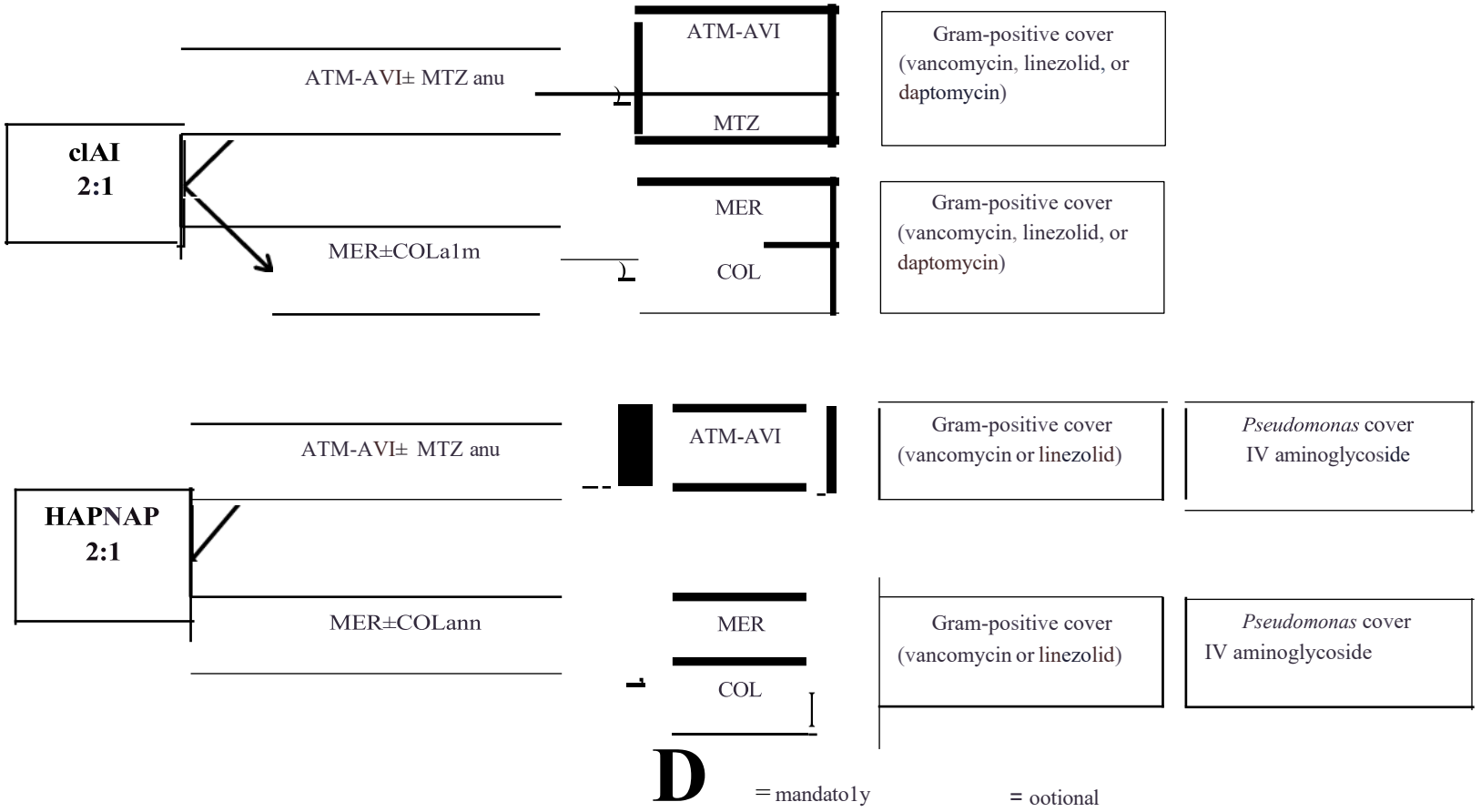
Each subject is expected to complete the study, including the LFU visit. Subjects will receive their study treatment by study center personnel while in the hospital.

Figure 1 Study Outline



Abbreviations: ATM-AVI=aztreonam-avibactam; ATM-AVI ±MTZ=ATM-AVI ±metronidazole; cIAI=complicated intra-abdominal infections; COL=colistin (colistimethate sodium); DoT=duration of treatment; EOT=end of treatment; *HAPN* AP=hospital-acquired pneumonia/ventilator-associated pneumonia; IU=intemational units; IV=intravenous(ly); LFU=late follow-up; MER=meropenem; MER ±COL=MER±colistin; MTZ= metronidazole: TOC=test of cure.
Note: Administration of the first dose of IV study therapy marks the beginning of study treatment Day 1.

Figure 2 Study Treatment



Abbreviations: ATM-AVI=aztreonam-avibactam; cIAI=complicated intra-abdominal infections; COL=colistin (colistimethate sodium); *HAPN* AP=hospital-acquired pneumonia/ ventilator-associated pneumonia; IV=intravenous(ly); MER=meropenem; MER±COL=meropenem±colistin; MTZ=metronidazole.

For details of study treatment see Section 5.6, and for details of allowed concomitant medication see Section 5.10.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

The target population is hospitalized subjects with a diagnosis of cIAI or HAP/VAP.

For subjects with cIAI, a presumed diagnosis is necessary for enrolment. The diagnosis of cIAI will be based on the subject's clinical syndrome or will be supported by intra-operative findings, including intra-operative culture of specimens. Operative intervention must be required and includes open laparotomy, laparoscopic surgery, and percutaneous drainage of an abscess. All subjects will undergo a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study treatment. The exact clinical diagnoses and brief descriptions that define the population of subjects with cIAI eligible for this study are given in Sections 4.1.1 and 4.1.2 and for subjects with HAP/VAP in Sections 4.1.1 and 4.1.3.

For subjects with HAP/VAP, an established diagnosis of NP is required, as detailed in Section 4.1.3.

The inclusion and exclusion criteria will be assessed by a site Investigator before enrolment of the subject to the study. Clinically indicated antibiotic treatment must not be delayed because subject is being considered for clinical study participation.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1. Inclusion Criteria

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

4.1.1. All Subjects

1. Subject must be ≥18 years of age.

2. Evidence of a personally signed and dated informed consent document indicating that the subject or a legally acceptable representative has been informed of all pertinent aspects of the study. If a subject is unable to consent for themselves at Screening, the subject's legally acceptable representative may provide written consent, in accordance with the country-specific regulations. Those subjects who are unconscious or considered by the Investigator clinically unable to consent at Screening and who are entered into the study 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 local regulations.

3. Subjects must have a confirmed diagnosis of HAP/VAP, or presumed diagnosis of cIAI requiring administration of IV antibacterial treatment (see additional Inclusion Criteria on cIAI and HAP/VAP for minimum disease criteria).

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

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

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

   c. Have medically confirmed ovarian failure.

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

5. Female subject of childbearing potential must have a negative serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL.

6. Subject must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.1.2. Additional Inclusion Criteria - cIAI Subjects

1. Diagnosis of cIAI 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. Subjects who undergo a surgical procedure with complete fascial closure are appropriate for the study. The skin incision may be left open for purposes of wound management as long as complete fascial closure is accomplished. The subject 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. Other secondary peritonitis (not primary/ spontaneous bacterial peritonitis associated with cirrhosis or chronic ascites);

g. Intra-abdominal abscess (including of the liver and spleen provided that there is extension beyond the organ with evidence of intra-peritoneal involvement).

OR

Pre-operative enrollment where the following clinical criteria are met with confirmation of infection by surgical intervention within 24 hours (before or after) of randomization:

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:

- Documented fever (defined as body temperature ≥38°C) or hypothermia (with a rectal core body temperature ≤35°C);
- Elevated white blood cells (WBC) (>12000 cells/µL);
- Systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) <70 mmHg, or a SBP decrease of >40 mmHg;
- Increased heart rate (>90 beats per minute [bpm]) and respiratory rate (>20 breaths/min);
- Hypoxemia (defined as oxygen [O_2] 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.

2. Subject must have had or will have a surgical intervention within 24 hours (before or after) of randomization. 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.

4.1.3. Additional Inclusion Criteria – HAP/VAP Subjects

1. Onset of symptoms >48 hours after admission or <7 days after discharge from an inpatient care facility (for which the duration of admission was >3 days).

2. New or worsening infiltrate on chest X-ray (or computerized tomography [CT] scan) obtained within 48 hours prior to randomization.

3. At least 1 of the following:

   - Documented fever (temperature ≥38°C) or hypothermia (rectal/core temperature ≤35°C);

   - WBC ≥10,000 cells/mm^3, leukopenia with total WBC ≤4500 cells/mm^3, or >15% immature neutrophils (bands) noted on peripheral blood smear.

4. At least 2 of the following:

   - A new cough (or worsening of cough at baseline);

   - Production of purulent sputum or purulent endotracheal secretions;

   - Auscultatory finding consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds, dullness on percussion, egophony);

   - Dyspnea, tachypnea, or hypoxemia (O_2 saturation <90% or partial pressure of O_2 [pO_2]<60 mmHg while breathing room air);

   - Need for acute changes in the ventilator support status/system to enhance oxygenation, as determined by worsening oxygenation (arterial blood gas [ABG] or pO_2 in arterial blood [PaO_2]/fraction of inspired O_2 [FiO_2]) or needed changes in the amount of positive end-expiratory pressure.

5. Subjects must have a respirato1y specimen obtained for Gram- stain and culture after the onset of signs and symptoms for *HAPN* AP and 48h prior to randomization. This includes culture of either expectorated sputum or a specimen of respirato1y secretions obtained by endotracheal aspiration in intubated subjects, or by bronchoscopy with bronchoalveolar lavage (BAL), mini-BAL or protected-specimen brnsh (PSB) sampling. See Appendix 6 for details on appropriate specimen collection for ventilated and non-ventilated subjects.

4.2. Exclusion Criteria

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

4.2.1. All Subjects

1. Subject has an APACHE II score >30.

2. At Screening the subject is found to have/or strongly suspected to have an infection caused by a Gram-negative species not expected to respond to either ATM-AVI and/or MER (eg, *Acinetobacter baumannii),* or an infection caused by only Gram-positive species. The subject is allowed to paiiicipate in the study if the Investigator considers that the species is a colonizer which does not waiTant specific treatment.

3. Subject has received more than one day (>24 hours) of any systemic antibiotic within 48 hours prior to randomization. This is inclusive of all doses of any systemic antibiotic initiated in this time period (but not counting overlapping periods of antibiotics), eg, a subject who receives 4 doses of an 8 hourly regimen with the last dose given just before randomization is calculated as 32 hours of prior antibiotic.

The exception to this is a subject who is a failure of prior systemic antibiotic treatment as evident by either documented worsening of objective signs and symptoms of infection or lack of improvement in at least one objective sign or symptom of infection despite a minimum of 48 hours antibiotic treatment.

For cIAI subjects, who received less than one day (<24 hours) of any systemic antibiotic within 48 hours prior to randomization, one dose of antibiotic may be received postoperatively within 6 hours of the surgical procedure (defined as 6 hours from the time of skin closure or, if skin closure is not performed, 6 hours from the time the wound dressing is applied).

4. Subject has a history of serious allergy such as anaphylaxis, angioedema and bronchospasm, hypersensitivity or any serious reactions to any systemic antibacterial which is allowed per protocol including ATM, carbapenem, monobactam or other β-lactam antibiotics, AVI, colistimethate or polymixin B, nitroimidazoles or MTZ, vancomycin, linezolid, daptomycin, aminoglycosides (eg, amikacin, gentamicin, tobramycin), or any of the excipients of the respective (investigational) medicinal products to be administered during the study.

5. Subject is unlikely to respond to up to 14 days of study treatment.

6. Clinical judgment by the Investigator that the subject has a high likelihood of dying within the specified study treatment period despite delivery of adequate antibiotics for treatment of the index infection.

7. Subject has a concurrent infection that may interfere with the evaluation of response to the study antibiotics.

8. Subject has known *Clostridium difficile* associated diarrhea.

9. Subject has a need for effective concomitant systemic antibacterials in addition to those allowed per protocol, and/or systemic antifungals, and/or any prohibited medication (eg, probenecid) (see Section 5.10).

10. Subjects receiving hemodialysis or peritoneal dialysis.

11. Subject has an estimated CrCL ≤15 mL/min by Cockcroft-Gault formula (Cockcroft and Gault 1976) or expected to require peritoneal dialysis, hemodialysis or hemofiltration during the study.

12. Subject has acute hepatitis or acute hepatic failure, cirrhosis or chronic hepatic failure (any Child-Pugh class).

13. Presence of hepatic disease as indicated by ALT or AST >3 x upper limit of normal (ULN) at Screening. However, subjects with AST and/or ALT up to 5 x ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.

14. Subject has a total bilirubin (TBili) >2 x ULN, unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease. This must be documented.

15. Alkaline phosphatase (ALP) >3 x ULN. However, subjects with values >3 x ULN and <5 x ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

16. Subject has a perinephric infection.

17. Subject has an absolute neutrophil count <500/mm^3.

18. Subject has previously been treated with the ATM-AVI.

19. Subject has been previously enrolled in this study.

20. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study treatment and for at least 7 days after the last infusion of investigational product (see Section 4.6.1).

21. Subject is participating in or has participated in other investigational interventional studies (drug) within the last 30 days (or 5 times the half-life of the previously administered investigational compound, whichever is longer) prior to screening and/or during study participation.

22. Subject has other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study (eg, in HAP/VAP subjects with pulmonary disease such as lung cancer, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary disease or recent pulmonary embolism).

23. Subject is unlikely to comply with protocol, eg, uncooperative attitude and unlikelihood of completing the study.

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

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

4.2.2. Additional Exclusion Criteria – cIAI Subjects

1. Subject was diagnosed with traumatic bowel perforation undergoing surgery within 12 hours; perforation of gastroduodenal ulcers undergoing surgery within ≤24 hours. Other intra-abdominal processes in which the primary etiology is not likely to be infectious.

2. Subject has infections limited to the hollow viscous, such as simple cholecystitis, gangrenous cholecystitis without rupture, and simple appendicitis, or has acute suppurative cholangitis, infected necrotizing pancreatitis, or pancreatic abscess.

3. Subject has abdominal wall abscess or small-bowel obstruction without perforation or ischemic bowel without perforation.

4. Subject has a prior liver, pancreas, or small-bowel transplant.

5. Subject whose surgery will include staged abdominal repair, or "open abdomen" technique, or marsupialization. This criterion is intended to exclude subjects in whom the abdomen is left open, particularly those for whom re-operation is planned.

4.2.3. Additional Exclusion Criteria – HAP/VAP Subjects

1. APACHE II score <10.

2. HAP/VAP subject has a known or high likelihood (based on any available microbiological results at the time of enrollment) of monomicrobial infection with a Gram-positive organism.

3. Subjects with lung abscess, pleural empyema, or post-obstructive pneumonia.

4. Subject is a recipient of a lung or heart transplant.

5. Subjects with myasthenia gravis.

For procedures for withdrawal of incorrectly enrolled subjects see Section 4.5.

4.3. Subject Enrolment and Randomization

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator will:

1. Obtain signed informed consent from the potential subject or their legally acceptable representative before any study specific procedures are performed. The subject is considered enrolled when the ICF is signed and the enrolment call is done in the interactive response technology (IRT) system.

2. IRT system will assign the subject with a unique enrolment number ie, subject identifier (ID) at the screening visit (sites will have to enter the subject ID into the IRT system to retrieve subject data).

3. Determine subject eligibility. See Section 4.1 and 4.2.

4. At Baseline, the Investigator will confirm that all eligibility criteria still are fulfilled and will then perform the randomization transaction in the IRT system.

5. At randomization the IRT system will assign eligible subjects a unique randomization code and IP kit number(s).

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization.

4.4. Randomization Criteria

All subjects being enrolled and fulfilling all eligibility criteria will be randomized in a 2:1 ratio to receive 1 of the 2 IV dosing regimens of either the ATM-AVI ±MTZ treatment arm (ie, test product) or the MER±COL treatment arm (ie, comparator).

4.5. Procedures for Handling Incorrectly Enrolled or Randomized Subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Medical Monitor immediately, and a discussion should occur between the Medical Monitor and the Investigator regarding whether to continue or discontinue the subject from treatment. The Medical Monitor must ensure all decisions are appropriately documented.

4.6. Lifestyle Requirements

4.6.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 7 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct

use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subject needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

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

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

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

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

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

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

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

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 7 days after the last dose of investigational product.

4.7. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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

5. STUDY TREATMENTS

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

For this study, the investigational products are test product Aztreonam- Avibactam (ATM-AVI), co-administered drug Metronidazole (MTZ), and comparators Meropenem (MER) and Colistin (COL).

5.1. Allocation to Treatment

All subjects being enrolled and fulfilling all eligibility criteria will be randomized.

Randomization will be performed using an IRT system. Specific information concerning the use of the IRT system will be provided in a separate user manual.

Block randomization using an IRT system will be used to randomize subjects in a 2:1 ratio to receive 1 of the 2 IV dosing regimens of either the ATM-AVI ±MTZ treatment arm (ie, test product) or the MER ±COL treatment arm (ie, comparator). The randomization scheme for this study will be generated using the Sponsor randomization system.

Randomization will be stratified as follows:

- Infectious disease type (cIAI versus HAP/VAP)
    - For cIAI subjects, they will be further stratified by APACHE II score category (≤10 versus >10) (see Appendix 5);

- For HAP/VAP subjects, they will be further stratified by mechanical ventilation status (yes versus no).

The IP (ATM-AVI ±MTZ or MER ±COL) should, if possible, be administered as soon as possible after the IP kit number is assigned.

5.2. Methods for Ensuring Blinding

This is an open-label study. The Investigators, site personnel, and subjects will not be blinded in this open-label study; however, reasonable attempts by investigators and site personnel should be made to minimize bias wherever possible.

Clinical response outcome recorded at scheduled visits will be assessed by an independent adjudication committee (central assessor) in a blinded fashion with the aim of unbiased adjudication of the primary objective measure. Data will be provided relating to the subject's clinical response (eg, death status, disease progression, AEs, surgical procedures) without disclosing treatment arm. Details on the central independent adjudication committee will be provided in a separate charter.

No interim analysis is planned, and no analysis of data according to treatment arm assignment will be made prior to database lock, except for the interim E-DMC reviews (See Section 9.5).

Programming and statistical personnel separate from the Sponsor study team will be responsible for producing the data outputs and will help limit access by the study team to individual subject and group treatment assignment until database lock has occurred.

5.3. Methods for Unblinding

Only the independent adjudication committee members will be blinded during the study. They will not require unblinding.

5.4. Subject Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the CRF.

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

Subject compliance with dosing administration will be verified by accounting doses administered. The subject dosing compliance should be within the range of 80% and 120% of expected doses during treatment period. Subject noncompliance cases should be discussed with medical monitors.

5.5. Investigational Product Supplies

5.5.1. Dosage Forms and Packaging

The identity of the IP is provided in Table 2.

Table 2. Identity of Investigational Product

Investigational product	Dosage form and strength
Test product	
Aztreonam -Avibactam	Aztreonam 2 g powder for concentrate for solution for infusion Avibactam 600 mg powder for concentrate for solution for infusion
Comparators	
Meropenem	Meropenem 1 g powder for solution for infusion
Colistin	Colistin 2 million IU powder for solution for infusion. Colistimethate sodium equivalent to 150 mg colistin base activity per vial.
Co-administered drug	
Metronidazole	Metronidazole 500 mg/100 mL solution for infusion

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

Note: Comparators and co-administered drug are supplied centrally via the sponsor. In some instances, locally obtained commercial supplies will be utilized in accordance with local regulations.

Note: Aztreonam, Meropenem, Colistin and Metronidazole are commercial products over-labeled with the study clinical label.

Central supply or locally obtained commercial supplies of these drugs will be used in accordance with local regulations.

All IPs will be administered by IV infusion. Aztreonam and AVI will be supplied as vials for reconstitution. The IP ATM-AVI will be prepared for co-administration in saline using standard aseptic IV infusion technique (see IP Manual).

5.5.2. 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.

Labels will be provided as either a single panel label or as multi-language booklet labels.

5.5.3. Preparation and Dispensing

See the IP manual and package insert for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.6. Administration (Dose and Treatment Regimen)

The recommended minimal duration of treatment with IV study treatment is 5 days for cIAI and 7 days for HAP/VAP. The maximal duration of treatment is 14 days.

5.6.1. ATM-AVI ±MTZ Treatment Arm

ATM-AVI: Subjects will be given a loading dose and then an extended loading dose before commencing on a maintenance dose. All doses (loading, extended loading and maintenance), and the dosing frequency of the maintenance dose are dependent on renal function according to Table 3 below.

Table 3. ATM-AVI Doses in Relationship to CrCL

CrCL (mL/min)*	Loading dose of ATM-AVI (by IV infusion over 30 minutes)	Extended loading dose of ATM-AVI immediately following the loading dose (by IV infusion over 3 hours)	Time interval between end of extended loading dose and start of first maintenance dose	Maintenance dose of ATM-AVI (by IV infusion over 3 hours)	Frequency of ATM-AVI maintenance dose
>50	500 mg ATM plus 167 mg AVI	1500 mg ATM plus 500 mg AVI	3 hours	1500 mg ATM plus 500 mg AVI	q6h
>30 to 50	500 mg ATM plus 167 mg AVI	1500 mg ATM plus 500 mg AVI	3 hours	750 mg ATM plus 250 mg AVI	q6h
>15 to 30	675 mg ATM plus 225 mg AVI	675 mg ATM plus 225 mg AVI	5 hours	675 mg ATM plus 225 mg AVI	q8h

Abbreviations: ATM-AVI= aztreonam-avibactam; CrCL=creatinine clearance; IV=intravenous(ly); q6h=every 6 hours; q8h=every 8 hours.

*Estimated creatinine clearance using Cockcroft-Gault formula rounded to the nearest whole number (see Appendix 3).

MTZ: Subjects with cIAI will also receive MTZ 500 mg IV q8h (by IV infusion over 60 minutes). The first dose of MTZ will be started immediately after the extended loading dose of ATM-AVI has completed and treatment will be continued until the end of the treatment period. The SmPC (Baxter Healthcare Ltd.) does not indicate a dose reduction for MTZ in subjects with renal impairment. However, a dose reduction may be necessary in end stage renal disease (ESRD) subjects (see Section 5.6.5).

5.6.2. MER ±COL Treatment Arm

Subjects will initially be given IV MER 1000 mg q8 h (with or without COL). However, if an MER-resistant pathogen is strongly suspected, COL (ie, colistimethate sodium) can also be initiated, and/or a dose of MER 2000 mg q8h can be used (given as an IV infusion over 3 hours), at the Investigator's discretion (Jaruratanasirikul et al. 2005; Keel et al. 2011; Li et al. 2006).

If a MER-resistant Gram-negative pathogen is subsequently isolated, COL can be added (if not already started), and/or the dose of MER can be increased to 2000 mg q8h (given as an IV infusion over 3 hours, if this dose was not already used initially).

If a MER-susceptible Gram-negative pathogen is subsequently isolated and COL had been initially started, the COL should be discontinued and the dose of MER adjusted to the labeled dose regimen (1 g q8h IV over 30 minutes) (if a MER dose of 2000 mg q8h was initially started) (Table 4).

Meropenem (MER) (MERONEM® SmPC):

- First day of dosing (or until the MER susceptibility of the baseline Gram-negative pathogen(s) is known):

Table 4. MER Doses in Relationship to CrCL

CrCl (mL/min)*	Baseline Gram-negative pathogen not initially suspected to be MER-resistant Dose of MER (by IV infusion over 30 minutes)	Baseline Gram-negative pathogen strongly suspected to be MER-resistant ** Dose of MER (by IV infusion over 180 minutes)
>50	1000 mg q8h	2000 mg q8h
>25 to 50	1000 mg q12h	2000 mg q12h
>15 to 25	500 mg q12h	1000 mg q12h

Abbreviations: CrCL=creatinine clearance; IV=intravenous(ly); MER=meropenem; q8h=every 8 hours; q12h=every 12 hours.

*Estimated creatinine clearance using Cockcroft-Gault formula rounded to the nearest whole number (see Appendix 3).

** Note the infusion time over 180 minutes recommended for the higher doses of meropenem is based on usual clinical practice for subjects with infections due to resistant pathogens (Jaruratanasirikul et al. 2005; Keel et al. 2011; Li et al. 2006).

Meropenem ±colistin doses will need to be adjusted for subjects with renal impairment (Section 5.6.5). The dose of MER will need to be further adjusted once the susceptibility of the baseline Gram-negative pathogen(s) to MER is known (see notes above).

Colistin (COL) (colistimethate sodium):

This is optional study therapy that can be added to MER, at the Investigator's discretion. Doses of COL are expressed as colistimethate sodium in IU, as described by EMA 2014a and EMA 2014b. For colistimethate sodium (IU and mg) and COL base activity (CBA) mg conversion table see Appendix 7 and Table 5.

Polymyxin B may be used as an alternative to COL where COL is not available or readily accessible. Polymyxin B will be sourced locally and administered per local label.

Table 5. COL Doses in Relationship to CrCL

CrCl (mL/min)*	**Loading dose of colistin (colistimethate sodium) (First dose) for subjects ≥60 kg****	**Time interval between end of loading dose and start of maintenance dose**	**Maintenance dose of COL**
	(by IV infusion over 30 to 60 minutes)		**(by IV infusion over 30 to 60 minutes)**
>50	9 million IU	12 hours	9 million IU daily in 2 or 3 divided doses
>30 to 50	9 million IU	24 hours	6 million IU daily in 2 divided doses
>20 to 30	9 million IU	24 hours	5 million IU daily in 2 divided doses
>15 to 20	9 million IU	24 hours	4 million IU daily in 2 divided doses.

Abbreviations: COL=colistin (colistimethate sodium); CrCL=creatinine clearance; IU=international units; IV=intravenous(ly).

*Estimated creatinine clearance using Cockcroft-Gault formula rounded to the nearest whole number (see Appendix 3).

**Dose of colistin should be reduced to 6 million IU for subjects below 60 kg.

5.6.3. Optional Aminoglycosides

Subjects with HAP/VAP and proven or suspected co-infection with *Pseudomonas aeruginosa* may receive an optional IV aminoglycoside (eg, amikacin, gentamicin or tobramycin, based upon local practice and epidemiology) at the Investigators discretion to allow coverage for suspected or proven *Pseudomonas aeruginosa* infection. For subjects receiving colistin (colistimethate sodium), adjunctive aminoglycosides therapy should not be used concurrently; treatment with colistin (colistimethate sodium) should be discontinued prior to initiating aminoglycoside therapy. The need for adjunctive aminoglycoside therapy should be re-evaluated once culture and susceptibility results are available and the aminoglycoside should be discontinued if *Pseudomonas aeruginosa* is not isolated or is no longer suspected, or susceptibility results indicate a carbapenem susceptible strain.

If *Pseudomonas aeruginosa* is isolated and is non-susceptible to meropenem, an intravenous aminoglycoside may be added to meropenem if not originally commenced. Colistin should be discontinued if meropenem and aminoglycoside are being used together.

The need for continued dosing with an aminoglycoside should be reviewed at least after 72 hours to mitigate potential nephrotoxic effect.

5.6.4. Optional Gram-positive Antibiotics

Subjects with HAP/VAP may receive optional vancomycin or linezolid and subjects with cIAI may receive optional vancomycin, linezolid or daptomycin at the investigators discretion to provide antibiotic cover for a Gram-positive infection. The need for an adjunctive Gram-positive antibiotic should be re-evaluated once culture and susceptibility results are available and the Gram-positive agent should be discontinued if a Gram-positive species is not isolated or is no longer suspected.

5.6.5. Changes in Renal Function during Study Treatment

In some subjects, the CrCL estimated from serum creatinine can rapidly recover (or deteriorate), especially early in the course of treatment for the infection. There is potential for accumulation of MTZ metabolites in ESRDsubjects, and therefore enhanced monitoring for MTZ associated AEs is recommended, and a dose reduction may be necessary. Renal function should therefore be closely monitored throughout the treatment period (as clinically indicated) and the dose of study treatment adjusted by the Investigator according to the CrCL value calculated by the Cockcroft-Gault formula (Appendix 3).

Creatinine clearance should be monitored daily through the local laboratory from Day 1 to Day 4 (and Day 3 or 5 by the central laboratory, if PK samples are to be collected on Days 3 or 5) and then as clinically indicated. If subsequent to randomization and while still on IV study treatment, a subject's estimated CrCL falls below the threshold for study inclusion (ie, estimated CrCL ≤15 mL/min) and/or there is a requirement to start renal replacement therapy, the Investigator should discontinue ATM-AVI or MER ±COL investigational therapies.

5.7. Investigational Product Storage

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

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

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

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

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

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

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

5.8. Investigational Product Accountability

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

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

The study personnel at the investigational site will account for all drugs supplied, purchased, dispensed and returned for appropriate destruction. Certificates of delivery, destruction and return must be signed.

Study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

IV study treatment will be dispensed to the Investigator or medically qualified personnel by the study center pharmacist. IV study treatment will only be prepared/administered to subjects by qualified pharmacy personnel/medically qualified personnel who have been appropriately trained to prepare/administer IV study treatment. Written authorization of study personnel to administer IP 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 treatment 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 treatment 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 treatment 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 treatment administration process and subject safety (eg, study treatment will only be administered to subjects under supervision of an Investigator). Source documentation should clearly indicate who administered the infusion. Records of IV study treatment usage should include the identification of the subject to whom the IV study treatment was administered, the quantity and date of administration, and a record of unused IV study treatment. The Investigator/pharmacist is responsible for maintaining accurate IV study treatment accountability records throughout the study on the relevant forms provided by Pfizer. Each administration of IV study treatment will be documented in the CRF.

It is the Investigator's responsibility to establish a system for handling study treatments, including IPs, to ensure that:

- Deliveries of such products are correctly received by a responsible person (eg, pharmacist).
- Deliveries are recorded.
- IV study treatment is handled and stored safely and properly.
- IV study treatment 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 subject, and returned to the pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved.
- The monitor performs complete IV study treatment accountability during each monitoring visit, including verifying documentation of receipt, dispensing, return, and destruction of IV study treatment and consistency of this documentation with physical inventory.

5.8.1. Destruction of Investigational Product Supplies

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

5.9. 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.

5.10. Concomitant Treatment(s)

All prescription and over the counter medications being taken by the subject for the 2 weeks prior to the first dose of study medication (considered prior treatment) and from the first dose of study medication through the LFU visit (considered concomitant treatments) must be documented on the appropriate pages of the CRF. Systemic antibiotics should be documented for the entire duration of the study (from 2 weeks prior to the first dose of study medication through the LFU visit). Application of topical antibacterial and antifungal agents, and peritoneal lavage for cIAI subjects, also need to be recorded in the CRF. All actions related to the administration of concomitant antibiotics should be documented in the CRF.

Concomitant medications which are allowed per protocol, restricted and prohibited are detailed in Table 6, Table 7, and Table 8, respectively:

Table 6. Allowed Concomitant Medications

Allowed Procedure/Medication/Class of drug:	**Subjects with cIAI:**	**Subjects with HAP/VAP:**
MTZ	Subjects in the ATM-AVI±MTZ arm will all receive MTZ as part of study therapy (see Section 5.6.1).	N/A
Vancomycin, linezolid or daptomycin	If a Gram-positive pathogen is suspected then **vancomycin, linezolid or daptomycin** may be added to the study regimen according to the usual practice of the Investigator. If a Gram-positive pathogen is not isolated, then the Gram-positive agent should be stopped, at the Investigator's discretion, and subjects should continue in the study.	If a Gram-positive pathogen is suspected then **vancomycin or linezolid** may be added to the study regimen according to the usual practice of the Investigator. If a Gram-positive pathogen is not isolated, then the Gram-positive agent should be stopped, at the Investigator's discretion, and subjects should continue in the study.

Table 6. Allowed Concomitant Medications

Allowed Procedure/Medication/Class of drug:	Subjects with cIAI:	Subjects with HAP/VAP:
IV aminoglycoside (eg, amikacin, gentamicin or tobramycin based upon local practice and epidemiology)	N/A	In the ATM-AVI ±MTZ arm, an IV aminoglycoside may be added if Pseudomonas aeruginosa is suspected. In the MER ±COL arm; if *Pseudomonas aeruginosa* is suspected, an IV aminoglycoside may be added to MER. In this case COL should not be commenced. If *Pseudomonas aeruginosa* is isolated and is susceptible to MER, the Investigator may stop COL (if this had been started) and an IV aminoglycoside may be added to the subject's regimen. COL and an IV aminoglycoside should **not** be used together. The need for continued dosing with an aminoglycoside should be reviewed after 72 hours to mitigate potential nephrotoxic effects.
Peritoneal lavage with saline or other non-antibacterial-containing solution	Permitted (note that antibiotic peritoneal lavage is not allowed).	N/A
Topical antibacterial and antifungals (or any oral antibiotic that has very poor absorption systemically, eg, oral vancomycin)	Permitted except that they may not be applied to the surgical site.	Permitted

Abbreviations: ATM-AVI ±MTZ =aztreonam-avibactam±metronidazole; cIAI=complicated intra-abdominal infection; COL=colistin (colistimethate sodium); HAP/VAP=hospital-acquired pneumonia/ventilator-associated pneumonia; IV=intravenous (ly); MER=meropenem; MER ±COL=meropenem±colistin; MTZ=metronidazole; N/A=not applicable.

Table 7. Restricted Concomitant Medications

Restricted Procedure/Medication /Class of drug:	**Subjects with cIAI:**	**Subjects with HAP/VAP**
Systemic antibiotics	Concomitant systemic antibiotics are not allowed (except those specified as allowed per the protocol), unless the subject is considered to have failed study treatment and requires additional antibiotics to treat their infection. OR The subject develops a new infection at a remote site and the Investigator considers addition of non-study antibiotics essential for the safety and well-being of the subject.	
Systemic antifungals	Antifungal treatment to treat the cIAI should be avoided unless clinically indicated.	Antifungal treatment to treat the HAP/VAP should be avoided unless clinically indicated.

Abbreviations: cIAI=complicated intra-abdominal infection; HAP/VAP=hospital-acquired pneumonia/ ventilator-associated pneumonia.

Table 8. Prohibited Concomitant Medications

Prohibited Procedure/Medication /Class of drug:	**Subjects with cIAI:**	**Subjects with HAP/VAP**
Probenecid	To be avoided from informed consent to end of IV study treatment	
Antibiotic peritoneal lavage	Not permitted (note that peritoneal lavage with saline or other non-antibacterial-containing solution is allowed).	N/A
Inhaled antibiotics	N/A	Should be avoided from the start to the end of IV study treatment for subjects in either treatment arm.

Abbreviations: ATM-AVI±MTZ =aztreonam-avibactam±metronidazole; cIAI=complicated intra-abdominal infection; HAP/VAP=hospital-acquired pneumonia/ventilator-associated pneumonia; IV=intravenous(ly); N/A=not applicable.

Both ATM (Mattie 1994) and AVI (see IB) are predominantly eliminated by the kidney, partly by active tubular excretion. In vitro studies have shown probenecid and furosemide interfere with the active tubular excretion, resulting in increased plasma concentrations of the study drugs, however, these increases are considered to be clinically insignificant (ER Squibb & Sons Limited 2014). Concomitant administration of probenecid should be avoided during IV study treatment. Furosemide should be used with caution in the setting of potentially nephrotoxic drugs, eg, aminoglycosides and COL. Based on current knowledge, further relevant DDIs with regard to ATM-AVI administration in this study are not to be expected (see Section 5.11.1).

The use of other systemic antimicrobials not specified by this protocol is not permitted during the study. However, if a new infection develops at a remote site (ie, outside of the abdomen for cIAI subjects or outside of the lung for HAP/VAP subjects) between the date and time of the first dose of study treatment and the LFU visit, and the Investigator considers addition of non-study antibiotics essential to the safety and well-being of the subject, additional antibiotics may be added. If possible, the Investigator should first discuss this with the Medical Monitor and attempt to choose antibiotics (guided by local microbiology and sensitivity testing) that will not have antibacterial activity against the subject's baseline pathogens to avoid confounding the assessment of the effect of study therapy.

It is anticipated that in instances of suspected clinical failure, alternative or additional antibiotic treatment to treat the index infection (cIAI or HAP/VAP) may be required, and where rescue antibiotic treatment is provided the subject should be assessed as a clinical failure. An appropriate antibiotic should be selected, taking into account results of sensitivity testing. If possible, the Investigator should first discuss this with the Medical Monitor.

Information on contraindications, special warnings and precautions and interactions with other medicinal products and other forms of interaction for protocol-allowed antibiotics are available in the respective SmPCs for these products and Investigators are recommended to refer to these for further prescribing information. For ATM-AVI DDI see Section 5.11.1.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF. If analgesic medications are needed for pain, the use of analgesic medication without antipyretic properties is preferred. Should a subject require a biologic immunosuppressive agent or chemotherapy treatment after enrollment, the Investigator should contact the Medical Monitor before initiating treatment. Continued subject study participation will be determined based upon assessment of the safety risk to the subject if he or she were to continue on study treatment. Subjects who have already completed the IV study treatment should remain in the study until LFU assessment as they are not actively on study treatment but being followed up for outcomes.

5.10.1. Other Concomitant Treatment

Concomitant medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

5.11. Drug-drug Interaction

5.11.1. Aztreonam-avibactam

Drug-drug interactions with AVI are unlikely. The binding of AVI to human plasma proteins is very low and concentration-independent. AVI had negligible or no direct inhibitory effect on CYP isoenzymes in vitro; the negligible inhibition observed was at high concentration of AVI that exceed any clinically relevant exposure. AVI showed no potential for in vitro induction of CYP1A2, 2B6, 2C9 and 3A4 isoenzymes in human hepatocytes. Against CYP2E1, AVI showed a slight induction potential at very high concentrations (1326 μg/mL) that exceed any clinically relevant exposure. Neither AVI nor ATM is an inhibitor of any major renal or hepatic transporters in the clinically relevant exposure range. In vitro, AVI is a potential substrate of human organic anion transporter (OAT)1 and OAT3 renal transporters and ATM dose-dependently inhibited the OAT1-mediated uptake of AVI, with maximum inhibition of 78% at 1000 μM. However, considering the in vitro half maximal inhibitory concentration (IC50) values (~ 700 μM for OAT1 and > 1000 μM for OAT2) relative to the maximum likely clinical plasma concentrations (187 μM) suggests that any interaction would probably be minimal.

The lack of an interaction between ATM and AVI was confirmed clinically. The PK and statistical comparison results indicated no DDI between ATM (2000 mg) and AVI (600 mg) when each drug was administered alone or in combination as a single 1-hour IV infusion in healthy young subjects. In addition, following 10 days multiple dosing of the combination, PK parameters at steady state for both ATM and AVI were comparable to Day 1.

Concomitant administration of probenecid or furosemide and ATM cause clinically insignificant increases in the serum levels of ATM.

Due to the induction of β lactamases, certain antibiotics (eg, cefoxitin, imipenem) have been found to cause antagonism with many β-lactams, including ATM, for certain Gram-negative aerobes, such as *Enterobacter* species and *Pseudomonas* species.

Prolongation of prothrombin time has been reported rarely in subjects receiving ATM. In addition, numerous cases of increased activity of oral anticoagulants have been reported in subjects receiving antibiotics, including β-lactams. Severe infection or inflammation, and the age and general condition of the subject appear to be risk factors.

Single-dose PK studies have not shown any significant interaction between ATM and gentamicin, cephradine, clindamycin or MTZ.

Unlike broad spectrum antibiotics, ATM produces no effects on the normal anaerobic intestinal flora. No disulfiram-like reactions with alcohol ingestion have been reported.

5.11.2. Coagulation and Concomitant Use of Anticoagulants

Appropriate monitoring (according to applicable medical guidelines and institutional standard of care) should be unde1iaken when anticoagulants are prescribed conc01nitantly with antibiotics. Adjustments in the dose of oral anticoagulants may be necessaiy to maintain the desired level of anticoagulation.

5.11.3. Other Investigational Products

fufo1mation on DDis with other medicinal products and other fo1ms of interaction for protocol allowed antibiotics are available in the respective SmPCs for these products and fuvestigators ai·e recommended to refer to these for fmiher prescribing info1mation.

6. STUDY PROCEDURES

Study periods are defined in Figure 1. Details of the study plan and timing of procedures are provided in Schedule of Activities (Table 1).

Eve1y effo1i 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 Schedule of Activities (Table 1) detailing the procedures and discussed by visit in the following sections.

6.1. Screening and Enrollment

Prior to any study specific procedures, subjects (or their legally acceptable representative if applicable) must provide written info1med consent. Enrollment/Screening procedures will be perfo1med according to the Schedule of Activities (Table 1). At Screening, subjects will be assessed regai·ding eligibility criteria. Subjects who do not meet all of these criteria must not be enrolled in the study (see Section 4.3).

CCI [redacted]

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

At Eligibility/Screening (Day -1 to 1), each potential subject (or his/her legally acceptable representative) will provide written info1med consent prior to staiiing any study-specific procedures.

Each subject will undergo Screening assessment procedures less than 24 hours prior to randoinization. Exceptions to this ai·e for respirato1y specimen for cultures and chest X-ray/CT scan for *HAPN*AP subjects which are valid if collected within 48 hours prior to randoinization and blood cultures which are valid if collected within 48 hours prior to randoinization in all subjects. Local laborato1y test results will be used to qualify subjects for inclusion. To this end, the following assessments need to be perfo1med in the local laborato1y and entered in the CRF: sernm creatinine (including calculation of CrCL), sennn or urine-hCG for pregnancy test, AST, ALT, ALP, TBili, and hematology as listed in Section 4.2. For eligibility assessment, CrCL needs to be calculated at the study site, based

on the creatinine value determined at local laboratory (see Appendix 3). In addition, safety laboratory samples must be sent to the central reference laboratory for testing (see Section 7.2.1).

Eligibility/Screening assessments will consist of:

1. Obtaining informed consent.
2. Reviewing of the inclusion and exclusion criteria.
3. Collecting demographics.
4. Collecting medical history.
5. Reviewing and recording prior medications (including prior antibiotic treatment).
6. Performing complete physical examination as defined in Section 7.2.2.
7. Assessing infection-related signs and symptoms.
8. Performing focused physical examination (see Section 7.2.2).
9. Measuring vital signs including blood pressure (BP), heart rate and body temperature as defined in Section 7.2.4. For subjects with HAP/VAP, collecting respiratory rate (breath per minute) and peripheral O_2 saturation.
10. Performing a chest X-ray or CT scan (if not available within 48 hours prior to randomization) in subjects with HAP/VAP.
11. Completing the APACHE II score (Appendix 5).
12. Completing the ventilation device status in subjects with HAP/VAP.
13. Collecting imaging and surgical report in subjects with cIAI.
14. Collecting AEs.
15. Collecting specimen of abdominal site infection and sending to local laboratory for microbiology culture, and sending isolates to central laboratory (for subjects with cIAI only) (see Appendix 6).
16. Obtaining an appropriate respiratory specimen for Gram- stain and culture (Cultures from respiratory specimens obtained within 48 hours prior to randomization may be used, but subjects ventilated subsequently, regardless of whether they meet the criteria for VAP, must have a specimen obtained while ventilated). Specimens will be sent to local laboratory for microbiological culture and isolates and unstained Gram-stain slides (for induced sputum and expectorated sputums only) will be sent to central laboratory (for subjects with HAP/VAP only) (see Appendix 6).

17. Obtaining blood samples and sending to local laboratory for microbiological culture, and sending isolates to central laboratory (see Appendix 6). Repeat blood cultures do not need to be performed at Screening if available within 48 hours prior to randomization.

18. Obtaining blood and urine samples for safety analysis. Blood is to be sent to the local laboratory (for testing laboratory eligibility criteria as listed in Section 4.2.1) and blood and urine to the central laboratory.

19. Collection of ABGs (ABGs are required for ventilated and recommended for non-ventilated HAP/VAP subjects, and for cIAI subjects as clinically indicated).

20. Estimating CrCL using the serum creatinine results from the local laboratory. See Appendix 3 for CrCL calculation.

21. Obtaining blood or urine sample for serum β-hCG for women of childbearing potential (local laboratory reference laboratory).

22. Confirming highly effective contraception is being used.

6.2. Study Period

6.2.1. Visit 2: Baseline Procedures and Day 1 of Treatment (Day 1)

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 in subjects with cIAI.

Local laboratory test results obtained at Visit 1 will be used to qualify subjects for inclusion (see Section 6.1.1). At Visit 2, safety lab samples (including local lab for eligibility criteria confirmation) and clinically relevant cultures (and further assessments as listed in points 3, 11, 13 to 16 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 and clinically relevant cultures are required, they should be collected prior to dosing (exception: if Visit 2 occurs pre-operatively, study drug may be administered before collecting abdominal specimen for culture; see below 11).

Study treatment should be started as soon as possible (within 24 hours) after a subject's eligibility has been confirmed and the subject has been randomized. Consequently, Day -1 and Day 1 may be the same calendar day, ie, all procedures scheduled for Day -1 and Day 1 could happen on the same day. All procedures at Visit 2 are to be done before first dose of study therapy except for PK sampling.

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

1. Reviewing of the inclusion and exclusion criteria.
2. Reviewing and recording prior and concomitant medications (including prior antibiotic treatment).

3. Assessing infection-related signs and symptoms.
4. Performing focused physical examination (see Section 7.2.2).
5. Measuring vital signs including BP, heart rate and body temperature as defined in Section 7.2.4. For subjects with HAP/VAP, collecting respiratory rate (breath per minute) and peripheral O_2 saturation.
6. Performing a 12-lead digital triplicate ECG. The subject should be resting in a supine position for at least 10 minutes prior to the evaluation (see Section 7.2.3).
7. Performing a chest X-ray or CT scan (as clinically indicated) in subjects with HAP/VAP.
8. Completing the ventilation device status in subjects with HAP/VAP.
9. Collecting imaging and surgical report (as clinically indicated) in subjects with cIAI.
10. Collecting new AEs and reviewing ongoing AEs.
11. Collecting specimen of abdominal site infection (if not already collected at Visit 1 [Note: if Visit 2 occurs pre-operatively, study drug may be administered before collecting abdominal specimens; however, they must be collected during the surgery]) and sending to local laboratory for microbiology culture, and sending isolates to central laboratory (for subjects with cIAI only) (see Appendix 6).
12. Collecting respiratory specimen for Gram-stain/culture (except where an adequate specimen was previously collected within 48 hours prior to randomization) and sending to local laboratory (for subjects with HAP/VAP only) if not collected at Screening. For subjects who were not ventilated at Screening but were intubated subsequently (or subjects who had a bronchoscopy performed): obtaining an appropriate respiratory specimen for Gram- stain and culture. Specimens will be sent to local laboratory for microbiological culture and isolates and unstained Gram-stain slides (for induced sputum and expectorated sputums only) will be sent to central laboratory (for subjects with HAP/VAP only) (see Appendix 6).
13. Obtaining blood samples as clinically indicated and sending to local laboratory for microbiological culture, and sending isolates to central laboratory (see Appendix 6).
14. Obtaining blood and urine samples for safety analysis. Blood is to be sent to local laboratory and blood and urine to the central laboratory.
15. Collection of ABGs as clinically indicated.
16. Estimating CrCL using the serum creatinine results from the local laboratory. See Appendix 3 for CrCL calculation.
17. Confirming highly effective contraception is being used.

18. Collecting mortality assessment.

19. Randomization.

20. Commence dosing according to the randomization schedule.

21. Following the initiation of the IV infusion of study treatment, blood samples for PK analysis for subjects randomized to ATM-AVI will be obtained as according to Table 13 and Figure 3 and Figure 4.

6.2.2. Visit 3 to 15: Ongoing Treatment (Days 2 to 14)

The recommended minimal duration of treatment in this study will be 5 days for cIAI and 7 days for HAP/VAP. The maximal duration of treatment will be 14 days. Subjects, who require continuation of IV study treatment after 5 days (cIAI) or 7 days (HAP/VAP), will continue to receive their IV study treatment by study center personnel in the hospital.

The following assessment procedures will be performed during treatment with IV study treatment:

1. Daily reviewing prior and concomitant medications (including prior and concomitant antibiotic treatment).

2. Daily assessing infection-related signs and symptoms.

3. Daily performing focused physical examination (see Section 7.2.2).

4. Daily measuring vital signs including BP, heart rate and body temperature as defined in Section 7.2.4. For subjects with HAP/VAP, daily collecting respiratory rate (breath per minute) and peripheral O_2 saturation.

5. Performing a 12-lead digital triplicate ECG on Day 3 immediately following the end of the study drug infusion. The subject should be resting in a supine position for at least 10 minutes prior to the evaluation (see Section 7.2.3).

6. Performing a chest X-ray or CT scan (as clinically indicated) in subjects with HAP/VAP.

7. Daily completing the ventilation device status in subjects with HAP/VAP daily.

8. Collecting imaging and surgical report (as clinically indicated) in subjects with cIAI.

9. Daily collecting new AEs and reviewing ongoing AEs.

10. Collecting specimen as clinically indicated of abdominal site infection and sending to local laboratory for microbiology culture, and sending isolates to central laboratory (for subjects with cIAI only) (see Appendix 6).

11. Collecting respiratory specimen for Gram-stain/culture as clinically indicated and sending to local laboratory for microbiology culture, and sending isolates and unstained Gram-stain slides (for induced sputum and expectorated sputums only) to central laboratory (for subjects with HAP/VAP only) (see Appendix 6).

12. Obtaining blood samples for subjects who are bacteremic at least every 3 days until clearance of bacteremia and sending to local laboratory for microbiological culture, and sending isolates to central laboratory (see Appendix 6). Blood cultures should also be obtained as clinically indicated.

13. Obtaining blood and urine samples every 3 days starting on Day 4 and sending to the central laboratory for safety analysis. Blood samples are to be sent to local laboratory daily between Days 2 and 4 (and as clinically indicated) for measurement of serum creatinine.

14. Collection of ABGs as clinically indicated.

15. Obtaining blood samples for PK analysis on Day 4 (Subjects randomized to ATM-AVI ±MTZ only) (Day 4 PK samples can be collected on Day 4 ±1 day, see Table 13 and Figure 3 and Figure 4 for schedule).

16. Estimating CrCL daily from Day 2 to Day 4, and as clinically indicated, using the serum creatinine results from the local laboratory. See Appendix 3 for CrCL calculation.

17. Confirming daily that highly effective contraception is being used.

18. Collecting mortality assessment daily.

19. Daily dosing according to the randomization schedule.

6.2.3. Post-Treatment Period

6.2.3.1. Visit 16: End of Treatment (Within 24 Hours after Last Infusion)

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

1. Reviewing prior and concomitant medications (including prior and concomitant antibiotic treatment).

2. Performing complete physical examination as defined in Section 7.2.2.

3. Assessing infection-related signs and symptoms.

4. Performing focused physical examination (see Section 7.2.2).

5. Measuring vital signs including BP, heart rate and body temperature as defined in Section 7.2.4. For subjects with HAP/VAP, collecting respiratory rate (breath per minute) and peripheral O_2 saturation.

6. Performing a chest X-ray or CT scan in subjects with HAP/VAP as clinically indicated.

7. Completing the ventilation device status in subjects with HAP/VAP.

8. Collecting imaging and surgical report (as clinically indicated) in subjects with cIAI.

9. Collecting new AEs and reviewing ongoing AEs.

10. Collecting specimen as clinically indicated of abdominal site infection and sending to local laboratory for microbiology culture, and sending isolates to central laboratory (for subjects with cIAI only) (see Appendix 6).

11. Collecting respiratory specimen for Gram-stain/culture if at all possible and sending to local laboratory for microbiology culture, and sending isolates and unstained Gram-stain slides (for induced sputum and expectorated sputums only) to central laboratory (for subjects with HAP/VAP only) (see Appendix 6).

12. Obtaining blood samples for subjects who are bacteremic as clinically indicated until clearance of bacteremia and sending to local laboratory for microbiological culture, and sending isolates to central laboratory (see Appendix 6).

13. Obtaining blood and urine samples for safety analysis and sending to central laboratory. Blood samples should be sent to the local laboratory as clinically indicated for measurement of serum creatinine.

14. Collection of ABGs as clinically indicated.

15. Estimating CrCL as clinically indicated, using the serum creatinine results from the local laboratory. See Appendix 3 for CrCL calculation.

16. Confirming highly effective contraception is being used.

17. Assessing clinical response.

18. Collecting mortality assessment.

6.2.3.2. Visit 17: Test of Cure (Day 28 ±3 days)

If it is not possible to perform the TOC on study Day 28, then the allowed visit window is Day 25 to 31.

The following assessment procedures will be performed at TOC:

1. Reviewing prior and concomitant medications (including antibiotic treatment).
2. Performing complete physical examination as defined in Section 7.2.2.
3. Assessing infection-related signs and symptoms.
4. Performing focused physical examination (see Section 7.2.2).
5. Measuring vital signs including BP, heart rate and body temperature as defined in Section 7.2.4. For subjects with HAP/VAP, collecting respiratory rate (breath per minute) and peripheral O_2 saturation.
6. Performing a chest X-ray or CT scan (as clinically indicated) in subjects with HAP/VAP.
7. Completing the ventilation device status in subjects with HAP/VAP.
8. Collecting imaging and surgical report (as clinically indicated) in subjects with cIAI.
9. Collecting new AEs and reviewing ongoing AEs.
10. Collecting specimen as clinically indicated of abdominal site infection and sending to local laboratory for microbiology culture, and sending isolates to central laboratory (for subjects with cIAI only) (see Appendix 6).
11. Collecting respiratory specimen for Gram-stain/culture if at all possible and sending to local laboratory, and sending isolates and unstained Gram-stain slides (for induced sputum and expectorated sputums only) to central laboratory (for subjects with HAP/VAP only) (see Appendix 6).
12. Obtaining blood samples for subjects who are bacteremic as clinically indicated until clearance of bacteremia and sending to local laboratory for microbiological culture, and sending isolates to central laboratory (see Appendix 6).
13. Obtaining blood and urine samples for safety analysis and sending to central laboratory. Blood samples should be sent to the local laboratory as clinically indicated for measurement of serum creatinine.
14. Estimating CrCL as clinically indicated, using the serum creatinine results from the local laboratory. See Appendix 3 for CrCL calculation.
15. Confirming highly effective contraception is being used.
16. Assessing clinical response.
17. Collecting mortality assessment.

6.2.3.3. Visit 18: Late Follow-up (Day 45±3 days)

If it is not possible to perform the LFU on study Day 45, then the allowed visit window is Day 42 to 48. If the subject has been discharged from hospital and is unable to return, the LFU visit can be conducted by telephone (with the permitted omission of the physical examination).

The LFU visit assessment procedures include:

1. Performing focused physical examination (see Section 7.2.2).
2. Collecting new AEs and reviewing ongoing AEs.
3. Reviewing prior and concomitant medications (including prior and concomitant antibiotic treatment).

6.3. Discontinuation of Investigational Product

Subjects may be discontinued from IP in the following situations:

- Condition under investigation resolved prior to minimum treatment period.
- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Occurrence of an AE or any other condition posing a risk to a subject or jeopardizing a safe continuation of the study treatment for the respective subject (as judged by the investigator, and/or the national coordinators, and/or the Medical Monitor and the Study Sponsor).
- Positive pregnancy test at any time during the treatment period.
- In the absence of any alternative explanation for the increase in the following abnormalities, individual subjects should be withdrawn if the following criteria are met (see also Section 8.5.2):
    - ALT or AST >8 x ULN;
    - ALT or AST >3 x ULN and TBili >2 x ULN or international normalized ratio (INR) > 1.5;
    - ALT or AST >3 × ULN and with appearance of symptoms and signs suggestive of new or progressive liver disease (eg, new or worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [eosinophils >2 x ULN]);
    - A subject meeting Hy's Law (HL) criteria (see Section 8.4.5 and Appendix 4).

- If CrCL falls ≤15 mL/min, or there is a requirement to start renal replacement therapy, ATM-AVI should be discontinued. It is at the Investigator's discretion to either discontinue MER ±COL or whether an immediate dose change or a short period of continued observation is required.

- Treatment failure (refer to Table 9).

- In the opinion of the Investigator, it is not in the best interest of the subject to continue the study treatment or at the request of the Sponsor or delegates that the subject stops participation in the study.

- Severe non-compliance with the CSP.

6.3.1. Procedures for Discontinuation of a Subject from Investigational Product

At any time, subjects are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 6.4), without prejudice to further treatment. A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (See Section 8).

The subject should be scheduled for the EOT visit within 24 hours after IV study treatment discontinuation. For subjects who discontinue study treatment but wish to continue in the study, their follow-up assessments should be collected (EOT, TOC and LFU visits). Data from these visits should be captured in the electronic case report form (CRF).

Adverse events (AEs) and serious adverse events (SAEs) will be followed up as described in Section 8.1.4.

If a subject is withdrawn from study, see Section 6.4.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events Section 8.1.3) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

6.4.1. Screen Failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as 'Screen failure' (the potential subject who does not meet one or more criteria required for participation in a study, this reason for study withdrawal is only valid for not randomized subjects).

6.4.2. Withdrawal of Consent

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

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.4.3. Lost to Follow-up

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

7. ASSESSMENTS

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

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

The electronic data capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the CRFs as specified in the CSP and in accordance with the instructions provided.

For studies conducted at US (investigational new drug [IND]) sites and non-US (non-IND) sites, data from IND and non-IND study sites will be pooled together for analysis.

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 (CSA). The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

7.1. Efficacy Assessments

7.1.1. Clinical Response Assessment

Clinical response will be determined at the EOT and TOC visits as either cure, failure or indeterminate. The clinical response at each visit will be assessed by the Investigator, and subsequently validated by an independent adjudication committee that will be blinded to study treatment (see Section 9.7). Reason for failure will be indicated according to the clinical response definitions as follows (Table 9):

Table 9. Definition of Clinical Response Categories at the EOT and TOC visits

Clinical response	Definition
Cure	Baseline signs and symptoms have improved such that after study treatment, no further antimicrobial treatment for the index infection (ie, cIAI or HAP/VAP) is required.[a] In addition, none of the failure criteria listed below should be met. **Additionally for cIAI subjects:** No unplanned drainage or surgical intervention is necessary since the initial procedure.
Failure	Subjects who meet any of the following criteria will be considered a treatment failure: Death (after receiving at least 48 hours of study treatment). Subject who received treatment with further antibiotics for the index infectiona. This includes subjects prematurely discontinued from study treatment due to an AE who require further antibiotics for the index infection. **Additionally for cIAI subjects:** Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively in situation of adequate infection source control at the time of initial surgical procedure. Postsurgical wound infections (eg, signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care).
Indeterminate	Death (after receiving less than 48 hours of study treatment). Subject lost to follow-up. **Additionally for cIAI subjects:** Inadequate infection source control at time of initial surgical procedure.

Abbreviations: AE=adverse event; cIAI=complicated intra-abdominal infection; EOT=end of treatment; HAP=hospital-acquired pneumonia; TOC=test of cure; VAP=ventilator-acquired pneumonia.

a. Further antibiotics for the index infection should only be initiated for ongoing or worsening signs and symptoms of the infection.

If a subject is assessed as a clinical failure at the EOT visit, this assessment will be carried forward to the TOC visit.

In addition, an exploratory assessment of clinical response based on objective measures of signs and symptoms of infection will be collected.

7.1.2. Microbiological Response

For each pathogen identified at Baseline, microbiological outcome at EOT and TOC will be determined as shown in Table 10.

Table 10. Definition of Microbiological Response Categories at the EOT and TOC Visits, for Each Pathogen Identified at Initial/Pre Study (Study Qualifying) Culture

Microbiological response	Definition
Eradication	Absence of causative pathogen from an appropriately obtained specimen[a] at the site of infection.
Presumed eradication	Repeat culture of specimens were not performed/clinically indicated in a subject who had a clinical response of cure.
Persistence	Causative organism is still present from an appropriately obtained specimen at the site of infection. If the causative organism displays ≥4-fold higher MIC to study therapy after treatment with IV study therapy, the response will also be categorized as "Persistence with increasing MIC".
Presumed persistence	Subject was assessed as a clinical failure and repeat culture of specimens were not performed/clinically indicated.
Indeterminate microbiological response	Death (after receiving less than 48 hours of study treatment). Subject lost to follow-up. **Additionally for cIAI subjects:** Inadequate infection source control at time of initial surgical procedure.

Abbreviations: BAL=bronchoalveolar lavage; cIAI=complicated intra-abdominal infection; EOT=end of treatment; IV=intravenous(ly); MIC=minimum inhibitory concentration; PSB=protected-specimen brush; TOC=test of cure.

a. A definition of an appropriately obtained specimen for each infection site will be included in the study microbiology manual (see Appendix 6). For subjects with cIAI, an appropriately obtained specimen for determination of microbiological response is defined as a specimen obtained using an adequate technique (eg, surgical procedure (laparotomy or laproscopic), percutaneous drainage (where in place for less than 24 hours) or wounds where the subject has a superficial or deep surgical wound reported at any point during the follow-up period). From expectorated or induced sputum, an adequate specimen is one with ≤10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Low Power Field (LPF) upon a Gram-stain; throat secretions are considered to be inadequate; other specimens such as endotracheal aspirate, BAL, mini-BAL, and PSB are considered to be adequate. For blood, two sets of blood cultures should be collected (ie, 4 bottles) from 2 different sites for aerobic and anaerobic incubation. One set of blood cultures must be obtained through a venipuncture. Collect samples, ideally over a period of 2 hours at least 10 to 20 minutes apart from separate sites.

If a pathogen is assessed as persistence or persistence with increasing MIC at the EOT visit, this assessment will be carried forward to the TOC visit.

7.1.2.1. Microbiological Response Assessment

The per-subject and per-pathogen microbiological response at the EOT and TOC visits will be assessed based on the pathogen(s) isolated from the study qualifying baseline and post-baseline cultures per the definitions outlined below.

Per-pathogen Microbiological Assessments after Completion of All Follow Up Visits

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 10. Microbiological responses other than "indeterminate" will be classified as "favorable" or "unfavorable." Favorable microbiological response assessments include "eradication" and "presumed eradication." Unfavorable microbiological response assessments include "persistence", "persistence with increasing MIC", and "presumed persistence." Subjects with a microbiological response assessment of "indeterminate" will be considered to be non-evaluable for the micro-ITT and ME analysis sets. Classifications such as "superinfection" and "new infection" will be considered separately (see "emergent infections" below).

Per-subject (Overall) Microbiological Response Assessments

Overall microbiological response will also be assessed as "favorable" or "unfavorable" for each subject. Subjects will be determined to have a favorable microbiological response if all baseline pathogens for that subject have a favorable outcome (eradicated or presumed eradicated) at the appropriate time point (EOT, TOC). If the outcome for any pathogen is unfavorable (persistence, persistence with increasing MIC, or presumed persistence), the subject will be considered to have an unfavorable microbiological response.

Per-resistance Type Microbiological Response Assessments

Microbiological response (per subject and per pathogen) will be presented for the subgroup of subjects with a pathogen in the given resistance group (eg, ATM-non-susceptible, ESBL-positive, carbapenamase-positive, and MBL-positive). Per-pathogen microbiological response will be presented separately for ATM-non-susceptible, ESBL-positive, carbapenamase-positive, and MBL-positive pathogens.

Emergent Infections

New pathogens that appear after Baseline are categorized in Table 11 and will be summarized separately.

Table 11. Definition of Emergent Infection Categories

Emergent infection	Definition
Superinfection	Emergence of a new pathogen(s) associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics during the period up to and including the EOT visit.
New infection	Emergence of new pathogen(s) associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics in the time period after the EOT visit.

Abbreviations: cIAI=complicated intra-abdominal infection; EOT=end of treatment; HAP=hospital-acquired pneumonia; VAP=ventilator-acquired pneumonia.

7.2. Safety Assessments

Safety and tolerability assessment will be undertaken on individual subject and cohort basis through a determination of SAEs and AEs based on signs and symptoms, examinations and laboratory tests. If deterioration in a laboratory value is associated with clinical signs and symptoms, the clinical diagnosis (or sign or symptom) will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. For details on AE definition and reporting see Section 8. If the findings meet the criteria for an SAE, procedures for reporting such events should be followed (refer to Section 8.1.4.1).

7.2.1. Laboratory Safety Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Schedule of Activities (see Table 1 and Section 6).

Blood and urine samples collected for safety analyses will be sent to the central laboratory for analysis. The results of safety laboratory sampling will be made available to the investigators. Investigators are to review central laboratory results and to confirm and document any significant results. The laboratory safety variables to be measured at the central laboratory are displayed in Table 12.

Local laboratory results, including safety parameters will be used for eligibility determination (ie, serum creatinine for calculation of CrCL, serum or urine β-hCG for pregnancy test, AST, ALT, ALP, TBili, and hematology as listed in Section 4.2) and subject management throughout the study. Local laboratory test results will be entered in the CRF (see Section 6.1.1).

For HAP/VAP subjects, arterial blood gases are required for ventilated subjects, recommended for non ventilated subjects at Screening visit to calculate APACHE II score; for cIAI subjects, arterial blood gases are to be collected as clinically indicated at Screening visit to calculate APACHE II score. Where ABGs are not available at screening, serum bicarbonate is to be used to calculate APACHE II score as per Appendix 5. For all subjects,

arterial blood gases are also collected as clinically indicated at Baseline, during treatment period and at EOT.

Liver function tests and CrCL must be closely monitored throughout the study. Further details for the monitoring of liver function tests are described in Section 8.5.2. Further details regarding the calculation of the CrCL are described in Appendix 3.

Further safety samples may be collected if clinically indicated at the discretion of the Investigator and analyzed in the local laboratory of the study site. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The following safety laboratory variables will be measured:

Table 12. Laboratory Safety Variables

Clinical chemistry	Hematology	Arterial blood gases[b]	Urinalysis
Albumin		Partial pressure of oxygen (PaO_2)	
Total protein	Hematocrit	Partial pressure of carbon dioxide ($PaCO_2$)	Appearance (color, clarity)
ALT	Hemoglobin	pH	Bilirubin
AST	INR (at baseline and as clinically indicated)	Oxygen saturation	Glucose
ALP	Platelet count	Bicarbonate (HCO_3)	Ketones
Bilirubin (total, direct and indirect)	Red blood cell count		Leukocyte esterase
Bicarbonate	WBC count (total and differential)		Nitrite
Blood urea nitrogen			pH
Calcium, total			Protein
Chloride			Specific gravity
Serum creatinine[a]			Urobilinogen
Glucose (nonfasting)			
Inorganic phosphorus			
Potassium			
Sodium			

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCL=creatinine clearance; INR=international normalized ratio; WBC=white blood cells.

a. Following each determination of serum creatinine until TOC (inclusive), also the estimate CrCL will be calculated.

b. For HAP/VAP subjects, arterial blood gases are required for ventilated subjects, recommended for non ventilated subjects at Screening visit to calculate APACHE II score; for cIAI subjects, arterial blood gases are only collected as clinically indicated to calculate APACHE II score at Screening visit. For all subjects, arterial blood gases are collected as clinically indicated at Baseline, during treatment period and at EOT.

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 Section 6.3 and 8.5.2). The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.4.3.

7.2.2. Physical Examination

A complete physical examination will be performed as scheduled in the Schedule of Activities (Table 1) and 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 (CV), abdomen including wound examination, musculoskeletal, and neurological systems.

If clinically abnormal findings emerge or there is worsening of any condition compared to the physical examination at Screening, these findings should be documented as AEs on the respective page of the CRF.

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 subject's clinical condition, they may be done later (as soon as possible). After the Screening visit, weight should be measured as clinically indicated. If these assessments cannot be performed due to the subject's clinical condition, they may be done later (as soon as possible). For the purpose of assessing eligibility, a subject's weight obtained during the current or most recent hospitalization may be used if the subject's clinical condition at the time of screening does not allow this assessment to be performed.

A detailed focused (infection-related abdominal or respiratory signs and symptoms per indication) assessment will be performed at Screening, at Baseline, daily during treatment with IV study treatment, at the EOT, TOC and LFU visits (see Table 1).

The following infection-related focused physical examinations will be conducted:

- For HAP/VAP subjects, a pulmonary assessment, which includes auscultation, will be performed.
- For cIAI subjects, abdominal signs and symptoms will be assessed and postoperative abdominal and wound examinations will be performed. Surgical wound examination should occur daily even if inspection is limited by the presence of a negative pressure wound therapy device. A thorough wound evaluation should occur when a full dressing change is performed.

7.2.3. ECG

Standard 12-lead ECGs (triplicates for each recording time point) will be recorded and assessed at Baseline and Day 3 during the treatment period (see Table 1). The ECG on Day 3 should be performed at maximum plasma concentration (C_{max}) which is immediately (within 30 minutes) after an infusionis completed.

The date of ECG must be recorded in the CRF.

The ECGs should be standard 12-lead ECGs with a lead II rhythm strip with the subject in the supine position after the subject 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.

7.2.4. Vital Signs

Vital sign measurements (including BP, heart rate and body temperature) should be assessed at Screening, Baseline, daily (twice daily for body temperature) while the subject is receiving IV study treatment, at EOT and at TOC visits; for subjects with HAP/VAP, respiratory rate (breath per minute) and peripheral O_2 saturation will be collected at Screening, Baseline, daily while the subject is receiving IV study treatment, at EOT and TOC visits (see Table 1). Vital signs should be measured and documented at least once daily, preferably at a similar time each day. However, if any significant excursions occur, those measurements should also be captured.

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 center as source data. For information on how AEs based on vital signs should be recorded and reported, see Section 8.4.3.

7.2.4.1. Pulse and Blood Pressure

Supine BP and heart rate should be measured using a semiautomatic BP recording device with an appropriate cuff size or by direct measurement via arterial catheter. The subjects will be required to rest in a supine position for at least 10 minutes prior to heart rate and BP measurements.

7.2.4.2. Body Temperature

Body temperature will be measured using an automated thermometer. The subject'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 subject, the method of temperature measurement ideally should be consistent for the duration of the study. At the TOC visit only a single body temperature measurement is required. The actual time of body temperature collection will be recorded.

7.2.5. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL for β-hCG will be performed locally at screening (Visit 1).

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL for β-hCG and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. An indeterminate or positive urine pregnancy test will be confirmed by a serum pregnancy test performed either locally or by the central laboratory.

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

7.2.6. Other Safety Assessments

7.2.6.1. Chest X-ray/ CT Scan

For HAP/VAP subjects only, a chest X-ray or a CT scan will be taken at Screening (if not available within 48 hours prior to randomization), and as clinically indicated during the study (see Table 1).

7.2.6.2. Acute Physiology and Chronic Health Evaluation

At Screening, cIAI and HAP/VAP subjects will be assessed by using the Acute Physiology and Chronic Health Evaluation (APACHE) II score (see Appendix 5). Subjects with cIAI will also be stratified at randomization based on APACHE score. ABGs will be collected at Screening to calculate APACHE II score (see Table 1) as required for ventilated subjects, recommended for non-ventilated subjects with HAP/VAP and as clinically indicated for subjects with cIAI. Where ABGs are not available at screening, serum bicarbonate is to be used to calculate APACHE II score.

7.3. Microbiology

Cultures of abdominal site infections (for cIAI subjects only)

Specimens must be obtained for culture from an initial qualifying surgical procedure performed within 24 hours before or after randomization and sent to the local laboratory for microbiological culture. This will be treated as the baseline culture.

Additional specimens will be collected for culture, as clinically appropriate at the time of repeat surgical procedures or from the wound, during the treatment period, and at EOT and TOC (see Table 1), if surgical procedure/intervention permits.

All specimens will be sent to the local laboratory for microbiological culture, and isolates will be sent to the central laboratory.

Respiratory specimen for Gram-stain/culture (for HAP/VAP subjects only)

Cultures from respiratory specimens obtained within 48 hours prior to randomization may be used. Repeat respiratory specimens at Baseline are not required, unless a Screening sample was obtained from a non-ventilated subject and the subject is subsequently ventilated (or has bronchoscopy). In this case, an appropriate respiratory specimen should be obtained via BAL, miniBAL, PSB sample or endotracheal aspirate prior to the first dose of study treatment.

Respiratory specimens will also be collected during the treatment period if clinically indicated and at EOT and TOC (see Table 1) if at all possible. If treatment is discontinued early, an attempt to obtain an appropriate respiratory specimen for culture should be made, ideally after stopping the study treatment and before the new treatment is administered.

All specimens will be sent to the local laboratory for microbiological culture, and isolates will be sent to the central laboratory. A Gram-stain needs to be performed and an unstained Gram-stain slide (dried glass mount) of each respiratory specimen (expectorated and induced sputum only) must also be sent to the central reference laboratory.

Collection of Blood for Culture (for all subjects)

All subjects require 2 sets of blood cultures (1 anaerobic and 1 aerobic bottle in each set) within 48 hours prior to randomization. Blood cultures should be performed at Baseline prior to first dose of study treatment if blood cultures are not available within 48 hours prior to randomization. For subjects who are found to be bacteremic, blood cultures should be repeated at least every 3 days until clearance of bacteremia is documented. If a negative culture report has not been achieved by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit. Blood cultures should also be obtained as clinically indicated (see Table 1).

All specimens will be sent to the local laboratory for microbiological culture, and isolates will be sent to the central laboratory.

Further details are provided in Appendix 6.

7.4. Pharmacokinetics

PK sampling will be employed to achieve further information on the PK of ATM-AVI in the subject population.

7.4.1. Collection of Plasma Samples for Analysis of Aztreonam-Avibactam

A total of 6 blood samples (2 mL/sample to provide approximately 1.0 mL of plasma) for PK and/or PK/PD evaluation should be collected into appropriately labeled tubes containing sodium fluoride/potassium oxalate (gray top) from subjects assigned to the ATM-AVI ±MTZ treatment arm. Samples will be collected from the subject's arm opposite to that into which study drugs (ATM-AVI) are infused and/or via use of a concurrent multi-lumen central line, and will be labelled, stored and shipped as detailed in the Laboratory Manual. Three samples

should be taken on both Day 1 and Day 4 of study treatment. To provide greater flexibility, Day 4 PK samples can be collected on Day 4 ±1 day [Note: A blood sample (5 mL) for estimation of serum creatinine will also be collected on Days 3 or 5 and sent to the central laboratory if PK samples are collected on Days 3 or 5].

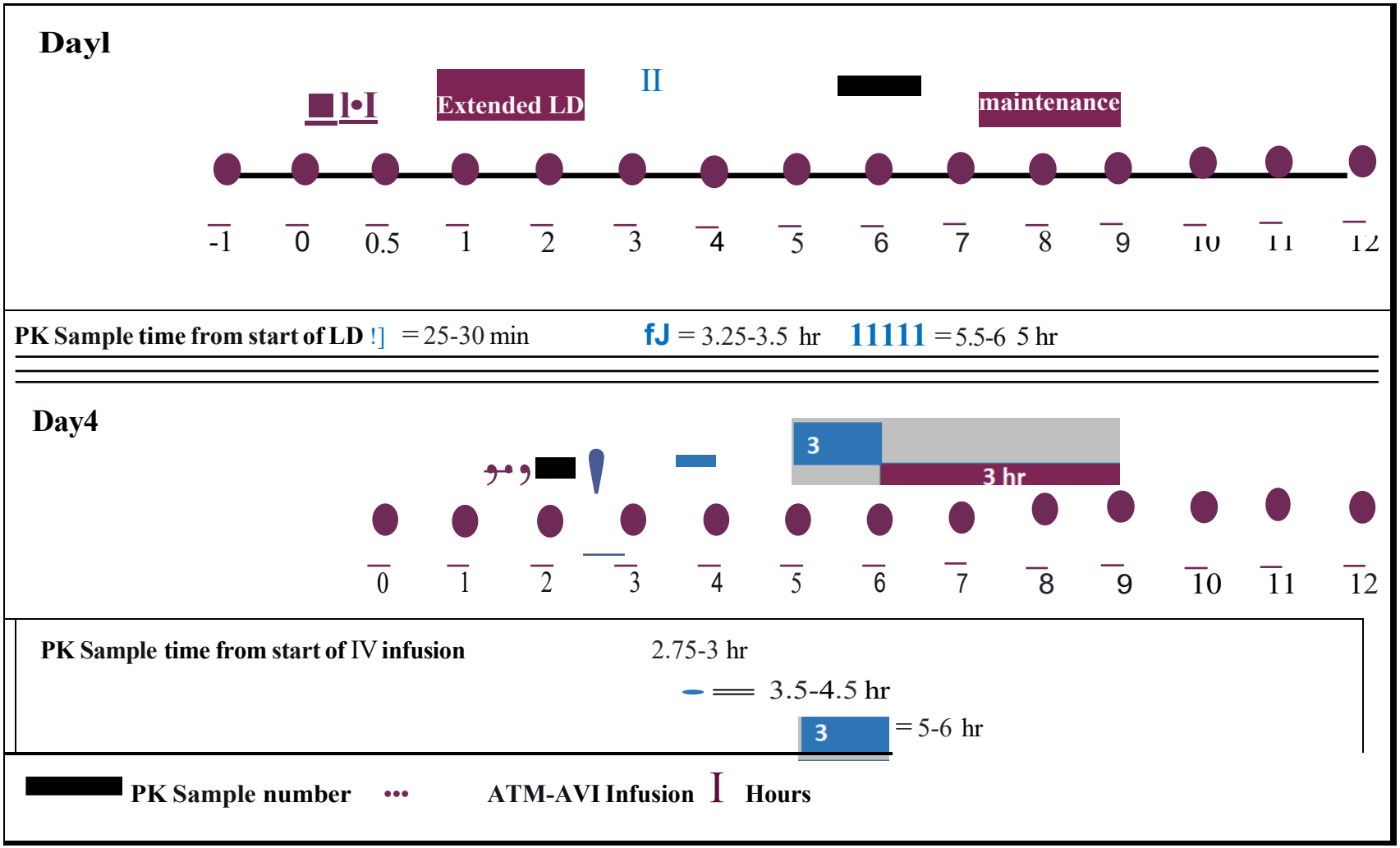
All subjects randomized to ATM-AVI will have 3 blood samples collected for determination of study drug in plasma for both Day 1 and Day 4 (a total of 6 samples per subject). These samples will be taken as scheduled in the Schedule of Activities (Table 1) and at the times presented in Table 13 as well as in Figure 3 and Figure 4 below. Where this presents difficulty to the site, priority should be given to collection of sample 2 on Day 1 and all 3 samples on Day 4. Where possible, Day 1 samples 1 and/or 3 should also be collected. The time of sample collection for sample 3 on both Days 1 and 4 is different depending on the CrCL value of either >30 mL/min or >15 mL/min to ≤30 mL/min, ie, whether the subject is receiving q6h or q8h maintenance dosing (see Table 13).

Table 13. Pharmacokinetic ATM-AVI Sample Collection Time Points

Day	Sample time
Day 1	All subjects randomized to ATM-AVI: (3 samples/subject) Sample 1: Within 5 minutes before the end of the loading dose infusion (25 to 30 min after the start of the loading dose infusion). Sample 2: Within 15 minutes before the end of the extended loading dose infusion (3.25 to 3.5 hours after the start of the loading dose infusion). Sample 3: Within 1 hour before the start of the first maintenance infusion: For subjects on q6h dosing: 2 to 3 hours after stopping the extended loading dose (5.5 to 6.5 hours after the start of the loading dose infusion). For subjects on q8h dosing: 4 to 5 hours after stopping the extended loading dose (7.5 to 8.5 hours after the start of the loading dose infusion).
Day 4	All subjects randomized to ATM-AVI: (3 samples/subject) Sample 1: Within 15 minutes before the end of the IV infusion (2.75 to 3 hours after the start of the IV infusion). Sample 2: 30 to 90 minutes after stopping the IV infusion (3.5 to 4.5 hours after the start of the IV infusion). Sample 3: Within 1 hour before the start of the next maintenance infusion: For subjects on q6h dosing: 2 to 3 hours after stopping the IV infusion (5 to 6 hours after the start of the IV infusion). For subjects on q8h dosing: 4 to 5 hours after stopping the IV infusion (7 to 8 hours after the start of the IV infusion).

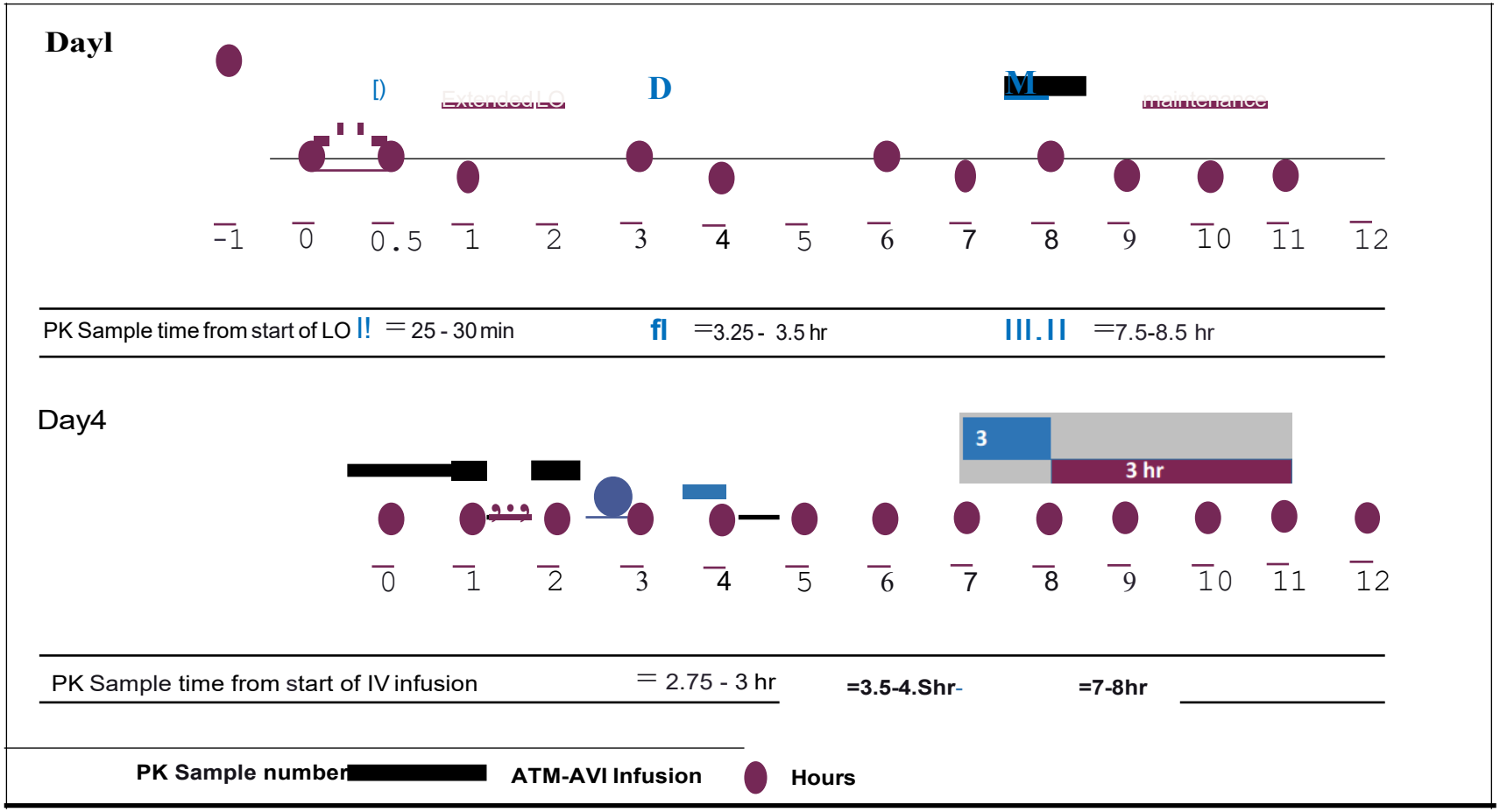
Abbreviations: ATM-AVI=aztreonam-avibactam; IV=intravenous(ly); q6h = every 6 hours; q8h = every 8 hours.

Figure 3 ATM-AVI Pharmacokinetic Sample Collection Time-Points for Subjects with CrCL >30mL/min (Q6h Maintenance Dose)



Abbreviations: ATM-AVI= aztreonam-avibactam; CrCL = creatinine clearance; IV= intravenous(ly); LD = loading dose; PK= pharmacokinetics; q6h = every 6 how-s.

Figure 4 ATM-AVI Pharmacokinetic Sample Collection Time-Points for Subjects with CrCL >15 to30 mL/min (Q8h Maintenance Dose)



Abbreviations: ATM-AVI= aztreonam-avibactam; CrCL = creatinine clearance; IV= intravenous(ly); LD = loading dose; PK= pharmacokinetics; q8h = every 8 how-s.

The date, starting and stop time of infusion and exact time of sample collection must be recorded in the CRF for each sample. If a deviation from the protocol is experienced due to technical difficulties, eg, with the administration of the infusion or PK sampling, the details of the deviation have to be recorded in the CRF.

The plasma samples will be analyzed, and the resulting data will be used in PK analysis. A PK/PD analysis will be performed if adequate microbiological response data are collected. PK/PD analyses will be reported separately.

7.4.2. Determination of Drug Concentration

Samples for determination of ATM and AVI concentration in plasma will be analyzed using an appropriate validated bioanalytical method in compliance with Pfizer & vendor standard operating procedures (SOPs). Full details of the bioanalytical methods used will be described in a separate bioanalytical report.

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

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis 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 and validate the analytical method. Results from such analyses may be reported separately from the CSR.

7.4.3. Storage and Destruction of Pharmacokinetic Samples

PK samples will be disposed of 12 months after the Bioanalytical Report finalization unless requested for future analyses.

Any residual back-up PK samples may be used for future CCI [redacted] (in this case, residual back-up PK samples will be shipped to Sponsor assigned biostorage; see details in the Laboratory Manual). This is optional and will require additional informed consent from subjects (See Section 7.6).

7.5. Pharmacogenomics: not applicable

Pharmacogenomics samples will not be taken during the study.

7.6. Biological Samples

The subject's consent to the use of donated biological samples is mandatory. Optional CCI [redacted] samples will utilize the PK samples, so no additional draw of blood is needed.

Samples for safety, microbiological and PK analyses will be collected as per the inclusion criteria, Schedule of Activities (Table 1) and PK sampling schedule (Table 13). The volume of blood to be drawn from each subject is displayed in Table 14. All samples will be processed and analyzed 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. Aspects of the subject management may require additional samples, which might also increase the volume of blood drawn.

Table 14. Volume of Blood to Be Drawn from Each Subject

Assessment		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	Minimum 8, maximum 11[a]	Minimum 40, maximum 55
	Hematology	2.5	Minimum 6, maximum 9[a]	Minimum 15, maximum 22.5
Pregnancy test[b]		2.5	Minimum 0, maximum 1	Minimum 0, maximum 2.5
Pharmacokinetic sampling		2	6	12
Blood culture		10 - 15	Minimum 4	40 - 60
Arterial blood gases		2	Minimum 0, maximum 1	Minimum 0, maximum 2
Total[c]				107 – 154

Abbreviation: β-hCG=β-human chorionic gonadotropin; CrCL=creatinine clearance; EOT=end of treatment; TOC=test of cure.

a. Number of samples depends on clinical response (duration of treatment: 5 – 14 days). Sampling time points: Screening (local lab and central lab), Baseline, study Days 4, 7, 10, and 13; EOT, within 24 hours after end of last infusion); TOC, Day 28 ±3 days. In addition samples on clinical chemistry panel are required on Day 2 and Day 3 for serum creatinine for estimation of CrCL.
b. Determination of urine or serum β-hCG for women of childbearing potential at Screening (Visit 1) only.
c. If the subject is found to be bacteremic, the total volume required for blood culture will increase by a further 60 mL for each follow up sample being drawn.

7.6.1. Storage, Re-use and Destruction of Biological Samples

Samples will be stored until the end of the study and then destroyed; unused PK samples (with consent) will be stored for up to 15 years for CCI analysis; microbiology isolates will be kept at least five years after the study drug is submitted to the regulatory authorities for marketing approval.

7.6.2. Labelling and Shipment of Biological Samples

The Principal Investigator ensures 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 2 'International Airline Transportation Association (IATA) 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with Pfizer and appropriate labelling, shipment and containment provisions are approved.

Samples must be collected, labelled, processed, analyzed, 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 CRF.

An isolate ID number will be allocated to all pathogen isolates obtained. Samples of all isolates will be sent to the central reference laboratory (see Section 7.3). PK samples will be shipped periodically from the study centers to the responsible (Pfizer-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, center number, enrollment number, date of sample collection, and a unique ID for each of the samples in the shipment.

7.6.3. Chain of Custody of Biological Samples

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

The Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the center until shipment or disposal (where appropriate) and keeps 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.

Pfizer 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 assigned biostorage during the entire life cycle.

CCI

[redacted]

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for repo1iing safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Repo1i Fo1m to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be repo1ied as described in the following paragraphs.

Events listed in the table above that require repo1iing to Pfizer Safety on the CT SAE Repo1i Fonn within 24 hours of awareness of the event by the investigator are to be repo1ied regardless of whether the event is dete1mined by the investigator to be related to an investigational product under study. In paiiicular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, i1Tespective of the extent of available event info1mation. This time frame also applies to additional new (follow-up) info1mation on previously fo1wai·ded repo1is. In the rare situation that the investigator does not become immediately aware of the occmTence of an event, the investigator must report the event within 24 hours after leaining of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate info1mation both to dete1mine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events Section 8.2.3 below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up info1mation in an expedited fashion. This infonnation is more detailed than that recorded on the CRF. In general, this will include

a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal Section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through the treatment period and including the LFU visit.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

Any AEs/SAEs that are unresolved at the subject's last AE/SAE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Definitions of Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study personnel: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to 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.

8.4.3. Adverse Events Based on Examinations and Tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to Baseline in protocol-mandated laboratory values, vital signs and ECG should therefore only be reported as AEs if they fulfil any of the AE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the clinical diagnosis (or sign or symptom) will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin 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/SAE.

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

8.4.4. Exceptions from Standard Adverse Events Collection

Where there is deterioration in the condition for which the IV study treatment 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 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 8.4.4.1) or disease progression (Section 8.4.4.2) and not an AE.

8.4.4.1. Lack of Effect

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

8.4.4.2. Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study 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 subject'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 (ie, not by way of insufficient therapeutic effect). Events, which are unequivocally due to disease progression, should not be reported as an AE/SAE during the study unless the outcome is fatal within the active collection period. If disease under study has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an SAE on the AE CRF, and SAE Report Form.

8.4.5. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

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

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

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

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

8.4.6.1. Exposure During Pregnancy

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.4.6.2. Exposure During Breastfeeding

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

8.4.6.3. Occupational Exposure

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

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

8.4.7. Medication Errors

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

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

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

Medication errors include:

- Medication errors involving subject exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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

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

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

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

8.4.7.1. Overdose

Overdose is defined as a dose of study drug administered to a subject in excess of that specified in Section 5.6. Overdose does not automatically make an AE/SAE but if the consequences of the overdose are accompanied by an AE or serious for example death or hospitalization, the event is AE or SAE and should be reported as such.

Avibactam alone and in combination with another β-lactam partner antibiotic CAZ (CAZ-AVI) was studied in healthy volunteers at doses up to 2000 mg of AVI in single and multiple dose regimens in Phase 1 clinical pharmacology studies, including a thorough QT study, with no safety signals or trends identified for AVI (see IB).

If an overdose or intoxication on the IV study treatment occurs in the course of the study, then the Investigator or other site personnel will inform Pfizer immediately when he or she becomes aware of it.

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

Recording an overdose will be done according to the following:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the medication error CRF module. Relevant information regarding any corresponding SAE(s) related to the overdose must be forwarded to Pfizer safety in CT SAE Report Form for data entry in the safety database.

- An overdose without associated symptoms is only reported on the medication error CRF module.

8.5. Management of Laboratory Safety

If necessary, ATM may be cleared from the serum by hemodialysis and/or peritoneal dialysis. ATM has been shown to be cleared from the serum by continuous arteriovenous hemofiltration. AVI may also be cleared from the serum by hemodialysis (55% of the AVI dose was removed in 4 hours in a group of subjects with ESRD).

8.5.1. Renal Function

CrCL will be monitored at Screening, Baseline, Day 2 through Day 4 (daily) (and Day 5 if PK sample collected on Day 5) and as clinically indicated and dose of study drug will be adjusted accordingly throughout the study. Determination of creatinine will be part of each safety laboratory until TOC inclusive, ie, every 3 days until end of IV study treatment (as defined in Table 1), followed by calculation of CrCL at the central laboratory. For eligibility assessment at Screening and renal function monitoring for dose adjustment of study drug at subsequent visits, CrCL needs to be calculated at the study site, based on the creatinine value determined at local laboratory (see Section 6 and Appendix 3).

If subsequent to randomization and while still on IV study treatment, a subject's estimated CrCL falls below the threshold for study inclusion (ie, estimated CrCL ≤15 mL/min) and/or there is a requirement to start renal replacement therapy, the Investigator should discontinue ATM-AVI or MER±COL investigational therapies.

8.5.2. Monitoring of Liver-related Laboratory Parameters

If a subject reaches an ALT or AST >3 x ULN and has not met the discontinuation criteria, the following enhanced monitoring and subject follow-up will be instigated:

- Collection of clinical and historical information to determine the cause of ALT and/or AST elevations (and completing the relevant CRFs modules);
- Frequency of liver function tests, and INR, should be increased to daily monitoring (using local laboratory data and recorded as unscheduled visits) until the liver function tests recover to ≤3 x ULN.

In the absence of any alternative explanation for an increase in the following abnormalities, individual subjects of both treatment arms should be discontinued from study treatment if any of the following criteria are met (also see Section 8.4.5):

- ALT or AST >8 x ULN;
- ALT or AST >3 x ULN and either TBili >2 x ULN or INR > 1.5;
- ALT or AST >3 × ULN and with appearance of symptoms and signs suggestive of new or progressive liver disease (eg, new or worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [eosinophils >2 x ULN]).

With regards to any cases of Potential Hy's Law (PHL) (occurrences of AST or ALT >3 x ULN together with TBili >2 x ULN), the Pfizer medical monitor will initially review the case (as described in Appendix 4) and then the case will be referred for independent clinical hepatologist review. The independent clinical hepatology review will be unblinded to study treatment allocation.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The study will randomize up to approximately 425 subjects in a 2:1 randomization ratio (approximately 283 subjects to ATM-AVI ±MTZ and approximately 142 subjects to MER ±COL) with serious infections proven or strongly suspected to be caused by MDR pathogens, including those producing MBLs. Current literature indicates that the prevalence of infections caused by pathogens producing MBLs could range from 17% to 31% (Azim et al. 2010; De et al. 2010; Lascols et al. 2011; Mouloudi et al. 2010 and Walsh et al. 2011), but we anticipate a more conservative estimate for prevalence of 8-10% in the study.

As no formal hypothesis testing will be performed for this study, no power calculation was carried out to assess the number of subjects required for each treatment arm. The planned sample size is considered sufficient to estimate the overall clinical cure rates in each arm. The smaller numbers of subjects in these groups will be reflected in the precision of the estimate of clinical cure rate.

9.2. Definitions of Analysis Sets

9.2.1. Efficacy Analysis Set

9.2.1.1. Intent-To-Treat (ITT) Analysis Set

The ITT analysis set will include all randomized subjects regardless of receipt of study drug. Subjects in the ITT analysis set will be analyzed according to the treatment they are randomized to. The ITT analysis set will be used to evaluate the primary, secondary and tertiary objectives.

9.2.1.2. Clinically Evaluable (CE) Analysis Set

The CE analysis set is defined as all subjects who:

- Meet the definition of the ITT analyses.
- Meet disease criteria for diagnosis of cIAI, or HAP/VAP.

- Received at least 48 hours of study treatment (ATM-AVI ±MTZ or MER ±COL) or received <48 hours of study treatment before discontinuing study drug due to an AE.

- Did not receive concomitant antibiotic treatment with potential activity against any baseline pathogens between the time of the first dose of study treatment and the time of TOC. This does not include those subjects who have received protocol-allowed antibiotics, or have failed study treatment and require additional antibiotics to treat their infection.

- Had no important protocol deviations that may affect the assessment of efficacy (to be defined in the SAP).

- Did not have a clinical outcome of indeterminate at TOC.

- Do not have monomicrobial infections due to non-eligible pathogens (any *Acinetobacter spp*., *Pseudomonas aeruginosa*) and do not have only Gram-positive pathogens.

Subjects in the CE analysis set will be analyzed according to the treatment they are randomized to. The CE analysis set will be used to evaluate selected primary, secondary and tertiary objectives.

9.2.1.3. Microbiological Intent-To-Treat (micro-ITT) Analysis Set

The microbiological Intent-To-Treat (micro-ITT) analysis set is a subset of the ITT analysis set and includes all subjects who have at least 1 Gram-negative pathogen in an adequate initial/prestudy culture. Subjects with inherently resistant pathogens (monomicrobial infections due to any *Acinetobacter* spp.), and those subjects with only Gram-positive pathogens will be excluded from the micro-ITT analysis set. The micro-ITT analysis set will be used to evaluate selected secondary and tertiary objectives.

9.2.1.4. Microbiologically Evaluable (ME) Analysis Set

The ME analysis set includes all subjects included in both micro-ITT and CE analysis sets, and had at least 1 Gram-negative pathogen. The ME analysis set will be used to evaluate selected secondary and tertiary objectives.

9.2.1.5. Modified Intent-To-Treat Analysis Set

The modified ITT (MITT) analysis set will include all randomized subjects who receive any amount of study drug. Subjects in the MITT analysis set will be analyzed according to the treatment they received. The MITT analysis set will be used in the sensitivity analysis of the primary endpoint.

9.2.1.6. Microbiological Modified Intent-To-Treat (micro-MITT) Analysis Set

The microbiological modified ITT (micro-MITT) analysis set is a subset of the micro-ITT analysis set and includes all subjects who receive any amount of study drug. The

micro-MITT analysis set will be used in sensitivity analysis of microbiological response endpoints.

9.2.2. Safety Analysis Set

The safety analysis set will be used for reporting safety data and will include all subjects who received any amount of IV study treatment. Subjects in the safety analysis sets will be analyzed according to the treatment they receive.

9.2.3. Population Pharmacokinetic (popPK) Analysis Set

The population pharmacokinetic (popPK) analysis set will include all subjects who have at least 1 plasma concentration data assessment available for ATM-AVI±MTZ and will be used to report all PK data.

9.2.4. Other Analysis Sets

9.2.4.1. All Subjects Analysis Set

This analysis set will compromise all subjects enrolled into the study and will be used for reporting of disposition.

9.3. Outcome Measures for Analyses

9.3.1. Primary Outcome Variable

The primary efficacy outcome measure is the proportion of subjects with clinical cure at TOC in the ITT and CE analysis sets. For the US regulatory submission, the ITT analysis set will be used for the primary analysis while CE analysis set will be the secondary analysis. The proportion of subjects with clinical cure for the ITT analysis set is defined as the number of subjects with clinical cure at TOC divided by the number of subjects in the ITT analysis set. Details are included in the SAP.

9.3.2. Secondary Outcome Variables

The secondary outcome measures are:

- Proportion of subjects with clinical cure at TOC visit in the micro-ITT and ME analysis sets.
- Proportion of subjects with clinical cure at the TOC visits by infection type in the ITT and CE analysis sets.
- Proportion of subjects with clinical cure at the TOC visit for subjects with MBL-positive pathogens in the micro-ITT and ME analysis sets.
- Proportion of subjects with a favorable per-subject microbiological response at the TOC visit in the micro-ITT and ME analysis sets.
- Proportion of subjects who died on or before 28 days after randomization in the ITT and micro-ITT analysis sets.

- PK of ATM and AVI in subjects with cIAI or HAP/VAP infections.

- PK/PD relationship between exposure and clinical and microbiological response for ATM-AVI.

9.3.3. Tertiary Outcome Variables

- Proportion of subjects with clinical cure at the EOT visit in the ITT, micro-ITT, CE and ME analysis sets.

- Proportion of subjects with clinical cure at the EOT visit by infection type in the ITT and CE analysis sets.

- Proportion of subjects with clinical cure at the EOT visit for subjects with MBL-positive pathogens in the micro-ITT and ME analysis sets.

- Proportion of subjects with clinical cure at the EOT and TOC visits by pathogen resistance type (eg, ATM-non-susceptible, ESBL- positive, carbapenamase- positive, etc) in the micro-ITT and ME analysis sets.

- Proportion of subjects with a favorable per-subject microbiological response at the EOT visit in the micro-ITT and ME analysis sets.

- Proportion of subjects with a favorable per-pathogen microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets.

- Proportion of subjects with a favorable per-subject microbiological response by pathogen resistance type (eg, ATM-non-susceptible, ESBL-positive, carbapenamase-positive, MBL- positive) at the EOT and TOC visits in the micro-ITT and ME analysis sets.

- Proportion of subjects with a favorable a per-pathogen microbiological response by per-resistance type (eg, ATM-non-susceptible, ESBL-positive, carbapenamase-positive, MBL-positive) at the EOT and TOC visits in the micro-ITT and ME analysis sets.

9.3.4. Exploratory Outcome Variables

The exploratory outcome measures assessing the outcomes are:

- Summary of total score for the composite endpoint of symptom-based objective clinical measures (ITT and CE analysis sets).

- Proportion of subjects who died on or before 14 days after randomization.

- For the health utilization objective:

    - Length of hospital stay, including any readmissions up to TOC (days);

- Length of ICU stay (days);
- Transferred to the ICU (Yes/No);
- Length of study treatment (days);
- Mechanical ventilation (Yes/No) for HAP/VAP subjects;
- Length of mechanical ventilation (days) for HAP/VAP subjects;
- Subsequent unplanned surgical intervention after treatment success vs failure (up to the TOC visit) for cIAI subjects.

9.3.5. Safety Variables

The following safety data will be collected: AEs, physical examination, vital signs, ECGs and laboratory values.

9.4. Methods for Statistical Analyses

All data will be presented by treatment arm. Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

No formal hypothesis testing will be performed for this study. Any comparisons between treatment arms will only be assessed as evidence of an effect, no formal statistical comparisons will be made.

Methodology for dealing with missing data will be specified in the SAP.

Important protocol deviations are defined as any important variations from the protocol that could affect the assessment of efficacy and will be defined in the SAP. An important protocol deviation may include:

1. Those who entered the study even though they did not satisfy the entry criteria.
2. Those who developed withdrawal criteria from IP or from study or for both during the study but were not withdrawn.
3. Those who received the wrong treatment or dose.
4. Those who received an excluded concomitant treatment.
5. Those identified through review of all protocol deviations reported during the study.

9.4.1. Analysis of the Primary Variable

The primary descriptive efficacy analysis (for non-US countries) will be the estimate of the clinical cure rate and 95% confidence interval (CI) in each treatment arm (ATM-AVI ±MTZ

and MER ±COL) in the ITT and CE co-primary analysis sets. The estimate of the clinical cure rate and 95% CI in each treatment arm in the ITT analysis set will be the primary analysis for the US. Single arm CIs will be computed using Jeffrey's method (Brown et al. 2001; Cai 2005). The number and percentage of subjects who had a clinical response of clinical cure, clinical failure, and indeterminate in each treatment arm will be tabulated for the ITT and CE analysis sets at the TOC visit.

The primary descriptive analysis will be conducted using the clinical response assessment determined by a blinded independent adjudication committee (Section 9.7). The Investigator's assessment of clinical response will also be summarized in the ITT and CE analysis sets at the TOC visit. In case of any discrepancy between the Investigator's and adjudication committee's clinical response assessment, the adjudication committee's assessment will prevail.

Difference in clinical cure rate between treatment arms at TOC visit (ATM-AVI ±MTZ minus MER ±COL) and corresponding two-sided 95% CI will be calculated for the ITT and CE analysis sets. The two-sided 95% CI for the observed difference in the cure rates (ATM-AVI ±MTZ group minus MER ±COL group) will be computed using the method proposed for unstratified designs by Miettinen and Nurminen and an additional supporting descriptive analysis will be conducted using the stratified Miettinen and Nurminen method (Miettinen and Nurminen 1985), if each stratum has at least 3 subjects per each treatment group.

9.4.2. Analysis of the Secondary/Tertiary Variable(s)

Secondary and tertiary efficacy outcome measures will be assessed and presented using the same methods as described in Section 9.4.1. For descriptive secondary/tertiary outcome measures, number and percentage in each treatment arm will be tabulated. Summaries will be presented for the overall population, and also split by infection type (cIAI or HAP/VAP), and by resistance group (eg, ESBL status, carbapenemase status, and MBL status).

The final PK data will be pooled with data from other studies to conduct a popPK analysis (using Nonlinear Mixed Effects Modelling [NONMEM]). Using these parameter estimates (mean PK parameters including inter individual variance estimates), Monte-Carlo simulation will be undertaken and potential PK/PD relationships will be explored. ATM and AVI plasma concentrations versus time will be depicted graphically in the CSR. Full details of the PK and PK/PD analysis will be given in the popPK Analysis Plan. These results will be reported separately.

The proportion of subjects who died on or before 28 days after randomization will be presented for the overall population, and also split by infection type.

9.4.3. Subgroup Analysis

Subgroup analysis may include subject characteristics, disease severity, prior antibiotic use, infection type and pathogen resistance type. More details on the subgroup analyses will be provided in the SAP.

9.4.4. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct reviews of the data which will include no summaries of data by treatment arm during the course of the study for the purpose of safety assessment, and/or to support clinical development.

9.4.5. Supportive Analyses

Additional descriptive analyses of the primary endpoint (clinical cure rate) will be performed for the effect of protocol-allowed additional antibiotics (eg, Gram-positive antibiotics, aminoglycosides).

An additional descriptive analysis will be performed for clinical cure at TOC using the MITT population which comprises subjects who were randomized and received any amount of IV study drug.

Additional descriptive analyses will be performed for the secondary and tertiary outcomes of clinical cure rate and microbiological favourable response rate at EOT and TOC using the micro-MITT which is a subset of the micro-ITT comprising those subjects who have received any amount of IV study drug.

Sensitivity analyses will be performed using the modified Intent-To-Treat and microbiological modified Intent-To-Treat. The modified Intent-To-Treat and microbiological modified Intent-To-Treat are subsets of the Intent-To-Treat and microbiological Intent-To-Treat respectively and include all randomized subjects who receive any amount of intravenous study drug.

Details of sensitivity analyses will be fully documented in the SAP.

9.4.6. Exploratory Analysis

Subjects will be summarized by the value of their composite score of symptom-based objective clinical measures.

The proportion of subjects who died on or before 14 days after randomization will be presented by treatment arm.

Further details on the analysis methods for response endpoint utilizing objective measures of clinical response and evaluation of health resource utilization will be detailed in the SAP.

9.4.7. Analysis Methods for Safety Variables

AEs will be summarized by means of counts summaries by preferred term separately for the study periods (treatment period [from first dose to EOT], from EOT to LFU, and for the full study period [from first dose to LFU].) All AEs and treatment emergent adverse events (TEAEs) will be listed (including prior to first dose). Deaths, AEs leading to discontinuation, and SAEs will be summarized.

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for all laboratory parameters.

The incidence of markedly abnormal values and changes from baseline in the ECG parameters will be summarized by treatment arm.

Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

9.5. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the E-DMC Charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

Programming and statistical personnel separate from the Sponsor study team will be responsible for producing the E-DMC analyses. The Sponsor study team will not receive any unblinded summary analyses intended for the E-DMC review.

9.6. Independent Clinical Hepatologist Review of Potential Hy's Law Cases

With regards to any cases of potential Hy's Law (PHL), the Pfizer Medical Monitor will initially review the case (as described in Appendix 4) and then the case will be referred for independent clinical hepatologist review. The independent clinical hepatology review will be unblinded to study treatment allocation. The independent clinical hepatologist also will be available for consultation for cases of liver enzyme test abnormalities not specifically meeting the criteria for PHL or qualifying as liver-related SAEs.

9.7. Independent Adjudication Committee

An independent adjudication committee consisting of at least three experts will be convened at regular intervals during the study. This independent adjudication committee is the central blinded assessor (see Section 5.2).

A charter will be in place for the adjudication committee. The adjudication committee will be blinded to study treatment and will review the clinical response assessments at EOT and TOC visits. In case of a discrepancy with the Investigator's assignment of clinical response, the adjudication committee's assessment will prevail for the analysis.

In addition, for cIAI subjects classified as a clinical failure, and all cIAI subjects classified as a cure who undergo another procedure (eg, another surgical procedure) subsequent to randomization, the adjudication committee will review the adequacy of the surgical source control. All cIAI subjects assessed by the adjudication committee as having inadequate initial infection source control (ie, the cIAI procedure performed was not considered to be adequate to control the source of infection) will be reclassified as having an indeterminate clinical response and will be excluded from the clinically evaluable (CE) and Microbiologically Evaluable (ME) analysis sets.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

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

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

11.3. Data Protection

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

Participants' personal data will be stored at the study site in either an encrypted electronic and/or paper form and will be password protected or secured in a locked room, as applicable

to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

12. ETHICS

12.1. Regulatory and Ethical Considerations

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

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

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

12.2. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study subject or his or her legally acceptable representative is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State**.**

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

Publication of the results of the study will be in accordance with Pfizer and COMBACTE-CARE publication policies.

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

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

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

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

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

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

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58. Metronidazole 500 mg/ 100 mL; Hospira, Inc, Lake Forest, IL 60045, USA

59. Colistimethate sodium (equivalent to 150 mg colistin base activity per vial) (USP); Fresenius Kabi USA, LLC; Lake Zurich IL 60047, USA

Appendix 1. Abbreviations

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

Abbreviation or special term	Explanation
A-aDO_2	Alveolo-arterial oxygen difference
ABG	Arterial blood gas
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AmpC	A Class C β-lactamase (Amp=ampicillinase)
APACHE	Acute Physiology and Chronic Health Evaluation
APS	Acute Physiology Score
AST	Aspartate aminotransferase
ATM	Aztreonam
ATM-AVI	Aztreonam-avibactam
ATM-AVI±MTZ	Aztreonam-avibactam±metronidazole
AUC	Area under the plasma concentration versus time curve
$AUC_{(0\text{-}24,ss)}$	Steady state area under the curve between time zero and 24 hours after dose
AVI	Avibactam
BAL	Bronchoalveolar lavage
BP	Blood pressure
BPM	Beats per minute
β-hCG	β-human chorionic gonadotropin
CAZ	Ceftazidime
CAZ-AVI	Ceftazidime-avibactam
CBA	Colistin base activity
CE	Clinically evaluable
CHE	Chronic Health Evaluation
cIAI	Complicated intra-abdominal infection
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CLSI	Clinical Laboratory Standards Institute
C_{max}	Maximum plasma concentration
COL	Colistin (colistimethate sodium)
COMBACTE-CARE	Combatting Bacterial Resistance in Europe – Carbapenem-resistance A consortium which consists of 19 academic and 3 pharmaceutical partners focusing on carbapenem resistance in Europe
CrCL	Creatinine clearance
CRE	Carbapenem-resistant *Enterobacteriaceae*
CRF	Case Report Form

Abbreviation or special term	Explanation
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CLSI	Clinical and Laboratory Standards Institute
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C_T	Threshold concentration
CT	Clinical Trial
CTA	Clinical trial application
CT scan	Computerized tomography scan
CTX	Cefotaximase
CTX-M	A type of Class A β-lactamase (CTX=cefotaximase)
CV	Cardiovascular
CYP	Cytochrome P 450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DGR	Dangerous Goods Regulations
DILI	Drug Induced Liver Injury
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic data capture
E-DMC	External data monitoring committee
EDP	Exposure during pregnancy
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ELD	Extended loading dose
EOT	End of treatment
ESBL	Extended-spectrum β-lactamase
ESRD	End-stage renal disease
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GGT	Gamma-glutamyl Transferase
GMP	Good Manufacturing Practice
HAP	Hospital-Acquired Pneumonia
HCO_3	Hydrogencarbonate or bicarbonate
HIV	Human immunodeficiency virus
HL	Hy's Law

Abbreviation or special term	Explanation
IATA	International Airline Transportation Association
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive care unit
ID	Identifier
IMI	Innovative Medicines Initiative
IND	Investigational new drug
INR	International normalized ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
IU	International units
IUD	Intrauterine device
IV	Intravenous(ly)
IRT	Interactive response technology
KPC	Klebsiella pneumoniae carbapenemase
LD	Loading dose
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LFU	Late Follow-up
LH	Luteinizing hormone
LPF	Low Power Field
LSLV	Last Subject Last Visit
MAP	Mean arterial pressure
MBL	Metallo-β-lactamase
MDR	Multidrug resistant
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MER	Meropenem
MER ±COL	Meropenem ±colistin
MIC	Minimum inhibitory concentration
MITT	Modified Intent-To-Treat
Micro-ITT	Microbiological Intent-To-Treat
Micro-MITT	Microbiological modified Intent-To-Treat
MTZ	Metronidazole
N/A	Not applicable
NDM	New Delhi Metallo-β-lactamase
NONMEM	Nonlinear Mixed Effects Modelling

Abbreviation or special term	Explanation
NP	Nosocomial pneumonia
O_2	Oxygen
OAT	Organic anion transporter
OXA	A type of Class D β-lactamase (OXA=oxacillinase)
PACL	Protocol Administrative Change Letter
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PCD	Primary completion date
PD	Pharmacodynamic
PHL	Potential Hy's Law
PHT	Pulmonary hypertension
PI	Principal investigator
PK	Pharmacokinetic
pO_2	Partial pressure of oxygen
popPK	Population pharmacokinetic
PSB	Protected-specimen brush
PT	Prothrombin Time
PTA	Probability of target attainment
q6h	Every 6 hours
q8h	Every 8 hours
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOA	Schedule of Activities
SOAP	Sepsis Occurrence in Acutely Ill Patients
SRSD	Single Reference Safety Document
TBili	Total bilirubin
TCS	Tata Consultancy Services
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
UK	United Kingdom
ULN	Upper limit of normal
UN	United Nations
US	United States
VAP	Ventilator-associated pneumonia
VIM	Verona Integron encoded metallo-β-lactamase
WBC	White blood cells
WHO	World Health Organization
WHOdrug	World Health Organization drug dictionary
WP2b	Work package 2b

Appendix 2. International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

The IATA classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following United Nation (UN) number and proper shipping name:

- UN 3373 – Biological Substance, Category B;
- are to be packed in accordance with UN3373 and IATA 650.

Exempt - all other materials with minimal risk of containing pathogens:

- Clinical study samples will fall into Category B or exempt under IATA regulations;
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging;
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content;
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable;
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix 3. Calculation of Estimated Creatinine Clearance

Calculation of the estimated creatinine clearance

Estimated CrCL will be calculated using the following Cockcroft-Gault formula (Cockcroft and Gault 1976). The weight obtained at Screening[1] should be used to qualify for entry into the study. In order to determine the need to adjust the dose and/or dosing interval of IV study treatment to be administered, the subject's estimated CrCL must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the subject's most recent actual (not ideal) body weight, and the Cockcroft-Gault formula.

Cockcroft-Gault formula:

Estimated CrCL is calculated by Cockcroft-Gault as follows:

For serum creatinine in mg/dL:

estimated CrCL = [(140 – age) × weight in kilograms]/[72 × serum creatinine in mg/dL]

[× 0.85 if female]

For serum creatinine in μmol/L:

estimated CrCL = [(140 – age) × weight in kilograms × constant]/[serum creatinine in μmol/L]

where constant = 1.23 for males and 1.04 for females

[1] For the purpose of assessing eligibility, a patient's weight obtained during the current hospitalization may be used if the patient's clinical condition at the time of screening does not allow this assesment to be performed.

Appendix 4. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of HL. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 8.5.2 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets PHL criteria at any point during the study.

The Investigator participates, together with the Pfizer Medical Monitor, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

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

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

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

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

Hy's Law (HL)

The case with laboratory abnormalities defined in Potential Hy's Law (PHL) as above, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBili, but there is no specified timeframe within which the elevations in transaminases and TBili must occur.

A PHL case becomes a confirmed HL case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT >3 x ULN;
- AST >3 x ULN;
- TBili > 2 x ULN.

A central laboratory will be used. When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to the Pfizer Medical Monitor).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met where this is the case the Investigator will:

- Notify the Pfizer Medical Monitor;
- Request a repeat of the test (new blood draw) by the central laboratory;
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see 2. Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Sites will also use local laboratories. The Investigator will promptly review each new laboratory report and if the identification criteria are met the investigator will:

- Notify the Pfizer Medical Monitor;
- Determine whether the subject meets PHL criteria (see 2. Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits;
- Promptly enter the laboratory data into the laboratory CRF.

4. Follow-up

4.1 Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the Pfizer Medical Monitor that the subject has not met PHL criteria;
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See **6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment**);
- Notify the Pfizer Medical Monitor who will then inform the central Study Team.

The Pfizer Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated;
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Pfizer Medical Monitor;
- Complete the relevant CRF modules as information becomes available;
- If at any time (in consultation with the Pfizer Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Pfizer Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The Pfizer Safety Risk Lead will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBili elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF;

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Pfizer standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBili elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to Pfizer standard processes:

    - The 'Medically Important' serious criterion should be used if no other serious criteria apply;

    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above;

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to subjects who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the subjects' condition[#] compared with the last visit where PHL criteria were met[#]:
  - If there is no significant change no action is required;
  - If there is a significant change notify the Pfizer Medical Monitor, who will inform the central Study Team, then follow the subsequent process described **4.2 Potential Hy's Law Criteria met** of this Appendix.

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBili) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Pfizer Medical Monitor if there is any uncertainty.

7. Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease, or did the subject meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in **6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment**?

If No: follow the process described in **4.2 Potential Hy's Law Criteria met of this Appendix**

If Yes:

Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met:

- If there is no significant change no action is required;
- If there is a significant change follow the process described in **4.2 Potential Hy's Law Criteria met of this Appendix.**

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBili) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Pfizer Medical Monitor if there is any uncertainty.

References

FDA 2009

Appendix 5. Acute Physiology and Chronic Health Evaluation - APACHE II Score

APACHE II Classification System

APACHE II Score Form

(Knaus et al 1985)[31]

Subject ID # _____ **Date of Assessment** _____

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE (Check one range per variable and write the severity score in the column to the right)					LOW ABNORMAL RANGE				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Severity Score
1. Temperature – Rectal (°C) (add 0.5°C to oral temp, 1.0°C to axillary temp)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9	
2. Mean arterial pressure (mm Hg)	≥160	130–159	110–129		70–109		50–69		≤49	
3. Heart rate (ventricular response) (bpm)	≥180	140–179	110–139		70–109		55–69	40–54	≤39	
4. Respiratory rate (non-ventilated or ventilated) (breaths per minute)	≥50	35–49		25–34	12–24	10–11	6–9		≤5	
5. Oxygenation A-aDO_2 or PaO_2 (mm Hg) a) FiO_2 ≥0.5:record A-aDO_2	≥500	350–499	200–349		<200					
b) FiO_2 <0.5:record only PaO_2					>70	61–70		55–60	<55	
6. Arterial pH* – If no ABGs record Serum HCO_3 below	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15	
7. Serum Sodium (mmol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110	
8. Serum Potassium (mmol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5	
9. Serum Creatinine (mg/dL) (Double points for acute renal failure)	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6			
10. Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20	

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE (Check one range per variable and write the severity score in the column to the right)					LOW ABNORMAL RANGE				
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**	**Severity Score**
11. White Blood Count (total/mm^3) (in 1000s)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1	
12. Glasgow Coma Scale (Score = 15 minus actual GCS)	(Best GCS in the 24 hours prior to screening)									(15 – GCS total)
	Eye	Verbal	Motor	GCS total = (Eye + Verbal + Motor)						
A. Total Acute Physiology Score (APS)	Total severity points indicated for in the column to the right									
*Serum HCO_3 (venous-mmol/L) Not preferred, use if no ABGs	≥52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15	

APACHE II Score Form continued

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

Abbreviations: A-aDO_2 = alveolo-arterial oxygen difference; ABG = arterial blood gas; APS = Acute Physiology Score; CHE = Chronic Health Evaluation; CV = cardiovascular; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; HCO_3 = hydrogencarbonate or bicarbonate; PaO_2 = partial pressure of oxygen in arterial blood; PHT = pulmonary hypertension.

APACHE II Score Worksheet provided to be used to calculate the APACHE II score.

- Abstract data from the 24 hour interval prior to screening or during screening.
- Enter the value for each line item. Calculate APACHE II score using most recent local laboratory results.

APACHE II Worksheet instruction

A - Physiological components

- Document one score for each of the physiological variables. Then calculate and document the total Acute Physiological Score (APS).

- The following will be accepted as core temperatures: rectal, esophageal, bladder, tympanic, or central. If the only temperature data available is from the oral or axillary routes, convert the temperature to an APACHE II core value using the following conversion factors:
  - Actual oral temperature (°C) + 0.5°C= Rectal (core) temperature;
  - Actual axillary temperature (°C) + 1.0°C = Rectal (core) temperature.
- For the MAP value, use arterial line data if available, otherwise calculate the MAP from the cuff pressure using the following formula:

  MAP = 1/3 (SBP – diastolic blood pressure [DBP]) + DBP

  (Example: BP 90/60, MAP = 1/3 (90 - 60) + 60 = 10 + 60 = 70)

  Note: If a DBP was not obtained, do not calculate a MAP, record "not done".
- Oxygenation
  - in case the FiO_2 is >50%, calculate the alveolo-arterial oxygen difference ($A\text{-}aDO_2$) using the following formula, use ABGs results:

    $A\text{-}aDO_2$=[(FiO_2 (713)-(partial pressure of carbondioxide ($PaCO_2$)/0.8)] - PaO_2

    (Example: FiO_2=0.6; PaO_2=56; and $PaCO_2$=26

    (0.6 x 713) minus (26 : 0.8) minus 56

    427 - 32.5 = 395.3 - 56 = 339.3 = $A\text{-}aDO_2$ (mm Hg)

    To calculate use FiO_2 (in decimal), $PaCO_2$ (mm Hg) and PaO_2 (mm Hg).
  - If the FiO_2 is <50%, record the lowest PaO_2.

- In case there is no ABG available assume normal oxygenation (Variable score = 0).

- Serum creatinine (μmol/L): double point score for acute renal failure. Creatinine conversion from μmol/L to mg/dL to be: 88.4 μmol/L= 1 mg/dL.
- WBC Count. Record WBCs in 1000s (eg, a WBC count of 30000 cells/mm3 would be recorded as 30).
- Arterial PH should be substituted by serum bicarbonate (HCO3) if there are no ABGs available in the previous 24 hours.

B – Age Points

- Circle the appropriate point for the subjects age range.

C - Chronic Health Points

If the subject has a history of severe organ system insufficiency or is immunocompromised assign chronic health points as follows:

- For nonoperative or emergency postoperative subjects: 5;
- For elective postoperative patients: 2;
- Subject does NOT have a history of severe organ system insufficiency and is NOT immunocompromised: 0.

They will receive the points only once (which means even if they have 2 criteria, the maximum is either 2 or 5).

GLASGOW COMA SCALE

For the Glasgow Coma Scale (GCS) score, determine the lowest (worst) number for each of the three factors in the scale (eye opening, verbal response, and motor response). Add together these 3 numbers, and then subtract this number from 15 to get the final GCS score. The subject's neurological status during a single neurological assessment should be evaluated.

Since it is not possible to assess the GCS in subjects who are sedated and paralyzed, by convention the GCS is regarded as normal, unless it is known that there was a brain injury prior to sedation. In that case the last measured GCS is to be used; if there is no brain injury prior to sedation the GCS is 15, thus the neurologic score will be 0.

Appendix 6. 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 microbiology laboratory manual. All microbiological isolates (except anaerobic bacterial pathogens isolated from subjects with respiratory infections) must be shipped to the central reference laboratory for confirmation of microbiological assessments. An unstained Gram-stain slide of each respiratory specimen from induced sputum and expectorated sputums must also be sent to the central reference laboratory.

All 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. All cultured 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.

1. Specimen collection

    a. Intra-abdominal specimens: Intra-abdominal specimens should be obtained for culture at initial qualifying surgical procedure (performed within 24 hours before or after randomization). If additional surgical procedures are performed, additional abdominal site specimens should be obtained for microbiological culture. An adequate abdominal specimen (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) should be obtained from all subjects and sent to the local laboratory for culture, identification, and in vitro susceptibility testing. If treatment is discontinued early because the subject is failing therapy and the subject 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 CRF should indicate whether or not a sample was obtained.

    b. Respiratory specimens: Baseline respiratory specimens (see below) must be obtained for culture within 48 hours prior to randomization and after development of signs and symptoms of NP (ideally before receipt of any systemic antibiotics). An adequate and appropriate baseline respiratory pecimen should be sent to the local laboratory for Gram-stain (expectorated and induced sputum only) and culture. Isolated organisms need to be identified, and tested for in vitro susceptibility.

        Appropriate specimens from ventilated subjects include:

        - endotracheal aspirate;
        - BAL;
        - mini-BAL;
        - PSB sample.

Appropriate specimens from non-ventilated subjects include:

- expectorated or induced sputum;
- BAL;
- mini-BAL;
- PSB sample.

Note that there may be non-ventilated subjects who develop HAP and subsequently require intubation and mechanical ventilation. If such subjects require ventilation prior to the first dose of study treatment, a specimen appropriate for the subject should be obtained even if the patient has already provided a sputum sample. In addition, subjects undergoing bronchoscopy prior to the first dose of study treatment should provide a respiratory specimen during the procedure even if a sputum sample or endotracheal aspirate has already been obtained.

To be adequate, respiratory specimen from expectorated or induced sputum must show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Lower Power Field (LPF) upon a Gram-stain.

When clinically indicated, pleural fluid should be sampled for Gram- stain, culture identification, in vitro susceptibility testing; isolates should be sent to the central laboratory for confirmation. Additionally, (when indicated) cell counts, pH and lactate dehydrogenase (LDH) of pleural fluid as well as serum LDH should also be obtained. It is not necessary to submit a Gram-stain slide of pleural fluid to the central laboratory.

If treatment is discontinued early because the subject is failing therapy or other reasons, an appropriate respiratory specimen for culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered. The CRF should indicate whether or not a sample was obtained.

In some circumstances, subjects may have multiple respiratory specimens obtained after the onset of signs and symptoms of pneumonia within 48 hours prior to randomization. The baseline respiratory culture is defined as the last respiratory culture obtained via BAL, mini-BAL or PSB prior to randomization. If BAL, mini-BAL or PSB specimens are not available, the baseline respiratory culture will be defined as the last respiratory culture obtained via endotracheal aspirate prior to randomization. If none of these are available, the baseline culture is defined as the last sputum culture obtained prior to randomization. In case a repeat respiratory specimen is obtained after randomization, but prior to the first dose of study treatment, this will be defined as baseline.

The status and/or results of the baseline respiratory culture (ie, whether the results are pending or known; pathogen(s) identification and/or the susceptibility profile of the identified pathogens) should be used to determine whether the protocol requirements for open-label Gram-positive or Gram-negative agents have been met as described in Section 5.10. Only baseline cultures should be used for determining the need for open-label agents.

c. Blood specimen: Blood cultures should be performed prior to the first dose of study treatment (if blood cultures are not available within 48 hours prior to randomization) and thereafter as clinically indicated. Two sets of blood should be collected (ie, 4 bottles) from 2 different sites for aerobic and anaerobic incubation. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. One set of blood cultures must be obtained through a venipuncture. Collect samples, ideally over a period of 2 hours at least 10 to 20 minutes apart from separate sites. If a subject is on antibiotics, blood cultures should ideally be taken immediately before the next dose. Organisms isolated from blood cultures obtained within 48 hours prior to randomization or at Screening/Baseline will be assigned a microbiologic response similar to those given for pathogens isolated from cultures of abdominal or respiratory specimens (see Table 10 for list of response categories). Details concerning the collection of blood cultures are provided in the laboratory manual.

2. Shipment of isolates

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 reference laboratory will monitor and verify resistant isolates reported by the local laboratory. All shipment documentation for samples sent from the local laboratory to the central reference laboratory should be maintained and available for review by the Contract Research Organization (CRO) representative.

3. 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, respiratory and abdominal specimens. The disk diffusion method as established by the Clinical and Laboratory Standards Institute (CLSI) should be used to determine susceptibility for ATM-AVI and meropenem for all isolates. Discs with ATM-AVI and meropenem will be supplied by the central reference laboratory. Reporting of susceptibility results on ATM-AVI to the Principal Investigator will be detailed in the study site manual. The laboratory may perform any additional testing on meropenem (eg, MIC) and any additional agents as they normally do to provide susceptibility results of isolated aerobic microorganisms. Disk zone size determinations for interpretation of susceptibility for all isolated aerobic microorganisms will be according to CLSI methodology for comparator agents. All aerobic isolates should be sent to the central reference laboratory for confirmation of identification and susceptibility testing. Characterization of β-lactamases

associated with the bacterial pathogens and molecular profiling (eg, pulse-field gel electrophoresis, whole genome sequencing) will be performed or coordinated by the central laboratory.

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 MIC testing for MTZ, meropenem and possible additional comparator agents. Anaerobic isolates originating from subjects with intra-abdominal infections need to be sent to the central reference laboratory for confirmation of identification and susceptibility testing. Anaerobic bacterial pathogens isolated from subjects with respiratory infections do not need to be sent, but must be entered into the CRF as having an anaerobe present.

The Investigator should record information on all specimens according to the Investigator's manual supplied by the central reference laboratory. The central reference laboratory will confirm pathogen identifications and susceptibility test results on all clinical isolates reported and shipped by the local laboratory. If discrepancies occur between the results obtained at the central reference laboratory and those obtained at the study site local laboratory, a CRO representative will request that a second sample of the isolate in question be shipped. In the instance of differences in pathogen identification or susceptibilities, the central reference laboratory results will take precedence over the local laboratory result. If microorganisms that are isolated at the local laboratory do not survive shipping to the central reference laboratory, a CRO representative will request that a second sample of the isolate in question be shipped. Local laboratory results may be used if a microorganism does not survive shipping or is not recoverable from the local laboratory.

Appendix 7. Colistin Conversion Table

Olistimethate Sodium	Colistimethate Sodium	Colistin-base Activity
(IU)	(mg)	(mg)*
12 500	1	0.4
150 000	12	5
1 000 000	80	34
4 500 000	360	150
9 000 000	720	300

Abbreviations: CBA = colistin base activity; IU = international unit.

* Based on a nominal potency of the drug substance of 12,500 IU/mg or 0.424 mg CBA/mg: both IU and mg CBA are expressions of potency and have only approximate relation to the mass. The calculation for the conversion of CBA (mg) to colistimethate sodium (IU) for the purpose of following the dosing regimen in IU, should be modified if the potency stated by the manufacturer is different to the nominal potency used in this conversion table.

Reference

European Medicines Agency completes review of polymyxin-based medicines. Recommendations issued for safe use in subjects with serious infections resistant to standard antibiotics. European Medicines Agency 2014, London, UK (EMA/643444/2014, 24 October 2014).

Appendix 8. Summary of Changes from Original Protocol through Amendment

Document	Version Date	Summary of Changes and Rationale
Amendment 1	05 July 2018	• Increased sample size per FDA feedback in Protocol Summary/Study sites and number of subjects planned, Target Subject Population and Statistical Methods, Section 3 Study Design, Section 9.1. Sample Size Determination. Per FDA guideline "Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases Guidance for Industry (August 2017)": In general, a safety database for a drug that is the subject of a streamlined development program should include approximately 300 patients at the dose and duration of therapy proposed for marketing. The number of subjects was increased to meet FDA guideline. • Increased number of countries and sites corresponding to the increase of sample size in Protocol Summery and Section 1.4.1 Study Design and Control Group. • Modified wordings on the Primary Objective and the 1st two Secondary Objectives (ie, from "compared to" to "and") to reflect no formal comparisons between treatment groups and included study analysis sets in the 1st Secondary Objective to differentiate from the Primary Objective in Protocol Summary/Table Objectives and Section 2 Study Objectives. • Changed "aztreonam-resistant" or "ATM-resistant" to "aztreonam-non-susceptible" or "ATM-non-susceptible" in Protocol Summary/ Table Objectives, Section 2 Study Objectives, Section 7.1.2.1 Microbiological Response Assessment and Section 9.3.3 Tertiary Outcome Variables for clarity. • Modified wordings on treatment day (eg, from "full day" to "day"; from "The duration of treatment is 5 to 14 days for cIAI and 7 to 14 days

		for HAP/VAP" to "The recommended minimal duration of treatment is 5 days for cIAI and 7 days for HAP/VAP. The maximal duration of treatment is 14 days") to reflect calendar day per Pfizer standard in Protocol Summary/Duration of treatment, Section 1.4.1 Study Design and Control Group, Section 1.4.3 Dose Selection for Metronidazole, Section 3 Study Design, Section 5.6 Administration (Dose and Treatment Regimen) and Section 6.2.2 Visit 3 to 15: Ongoing Treatment (Days 2 to 14). • Replaced reference to Aztreonam and Avibactam with combined test product Aztreonam-Avibactam in Protocol Summary/Table Investigational product, dosage form and strength and Table 2 Identity of Investigational Product. • Deleted the reference to 1g aztreonam and 1 mIU colisitn in Protocol Summary/Table Investigational product, dosage form and strength and Table 2 Identity of Investigational Product to be consistent with study drug supply in IP Manual. • Added "Note: Comparators and co-administered drug are supplied centrally via the sponsor. In some instances, locally obtained commercial supplies will be utilized in accordance with local regulations" and "Note: Aztreonam, Meropenem, Colistin and Metronidazole are commercial products over-labeled with the study clinical label" in Protocol Summary Table Investigational product, dosage form and strength and Table 2-Identity of Investigational Product for clarity. • Removed "first dose", "second dose" and "third and subsequent doses" and added "first" before Maintenance Dose on Day 1 to increase clarity on dose description in Protocol Summary/Table Aztreonam-avibactam ±metronidazole treatment arm, Table 3 ATM-AVI Doses in Relationship to CrCL, Section 5.6.1 ATM-AVI ±MTZ and Table 13 Pharmacokinetic ATM-AVI Sample Collection Time Points.

		• Modified wordings on creatinine clearance monitoring for consistency across the protocol in Project Summary/Aztreonam-avibactam ±metronidazole treatment arm. • Changed "randomization" to "first dose of study treatment" in Clinically Evaluable Analysis Set and in the use of other systemic antimicrobials in Protocol Summary/Definition of analysis sets, Section 5.10 Concomitant Treatment(s) and Section 9.2.1.2 Clinically Evaluable (CE) Analysis Set to be consistent with Concomitant Treatment definition per Pfizer standard. • Deleted "(and wound examination for cIAI subjects)" in study procedure "Performing focused physical examination (and wound examination for cIAI subjects) (see Section 7.2.2)" to avoid redundancy with Section 7.2.2 Physical Examination in Table 1 Schedule of Activities, Section 6.1.1 Visit 1: Eligibility/Screening Procedures, Section 6.2.1 Visit 2: Baseline Procedures and Day 1 of Treatment, Section 6.2.2 Visit 3 to 15: Ongoing Treatment, Section 6.2.3.1 Visit 16: End of Treatment, Section 6.2.3.2 Visit 17: Test of Cure andVisit 18: Late Follow up (Day 45 ±3 days). • Added "Collection of imaging and surgical report in subjects with cIAI" at every visit except Late Follow-up visit in Table 1 Schedule of Activities, Section 6.1.1 Visit 1: Eligibility/Screening Procedures, Section 6.2.1 Visit 2: Baseline Procedures and Day 1 of Treatment, Section 6.2.2 Visit 3 to 15: Ongoing Treatment, Section 6.2.3.1 Visit 16: End of Treatment and Section 6.2.3.2 Visit 17: Test of Cure for collecting source data on case adjudication of clinical responses for cIAI subjects. • Added wordings of "local lab for eligibility criteria confirmation" in footnote b of Table 1 Schedule of Activities, Section 6.2.1 Visit 2: Baseline Procedures and Day 1 of Treatment (Day 1) for clarity.

		• Corrected wordings related to the serum HCO_3 use in place of arterial pH if no ABGs available in footnote c of Table 1 Schedule of Activities and Appendix 5 Acute Physiology and Chronic Health Evaluation. • Specified acceptable time frame of chest X-ray/CT scan (within 48 hours prior to randomization) for HAP/VAP subjects in Section 6.1.1. Visit 1: Eligibility/Screening Procedures, Footnote f of Table 1 Schedule of Activities and Section 7.2.6.1 Chest X-ray/ CT Scan to be consistent with Section 4.1.3 Additional Inclusion Criteria (Criterion 2) for HAP/VAP subjects. • Specified respiratory specimen collection to increase clarity on respiratory specimen reference time point and Baseline definition across the protocol in footnotes h and i of Table 1 Schedule of Activities, Section 6.1.1. Visit 1: Eligibility/Screening Procedures, Section 6.2.1. Visit 2: Baseline Procedures and Day 1 of Treatment, Section 7.3 Microbiology and Appendix 6 Microbiological Assessments. • Clarified blood sample collection for culture to avoid unnecessary repeat sampling and increase clarity and consistency of blood specimens for culture across protocol in footnote k of Table 1 Schedule of Activities, Section 6.1.1 Visit 1: Eligibility/Screening Procedures, Section 6.2.2. Visit 3 to 15: Ongoing Treatment, Section 7.3 Microbiology and Appendix 6 Microbiological Assessments. • Updated wordings on Phase 2a study descriptions per Phase 2a study status in Section 1.3 Rationale for Conducting This Study. • Included local lab blood sample at Screening, corrected PK sample volume/pregnancy test frequency and updated number of samples and total blood volume accordingly in Table 14 Volume of Blood to Be Drawn from Each Subject and Section 1.6 Benefits/Risk and Ethical

		Assessment for clarity. • Changed colistin infusion duration from "30 min" to "30-60 min" in Figure 1 Study Outline for consistency across protocol. • Changed comparator group name from MER-COL to MER ±COL in Figure 2 Study Treatment for consistency across protocol. • Changed "duration of the study" to "duration of study treatment" relevant to the statement of effective method of contraception in Exclusion Criterion 20 in Section 4.2 Exclusion Criteria (4.2.1 All Subjects) to increase the clarity and consistency on the time frame of contraception requirement across protocol. • Changed "prior to study entry" to "prior to screening" in Exclusion Criterion 21 to increase the clarity on the reference time point about participating in other investigational interventional studies in Section 4.2 Exclusion Criteria (4.2.1 All Subjects). • Deleted "or female condom" in the 3rd contraception method in Section 4.6.1 Contraception to accommodate globally acceptable contraception methods. • Added "or as necessitated by the clinical status of the subject during the period of hospitalization, eg, unconscious/ventilated" as acceptable obviation of the need for contraception in Section 4.6.1 Contraception to accommodate the specific study population, eg, ventilated/unconscious subjects. • Changed "study drug" to "test product" for ATM-AVI to differentiate from comparator for MER ±COL/The change is clarification in Section 4.4 Randomization Criteria and Section 5.1 Allocation to Treatment. • Changed "MER-positive" to "MER-resistant" in Section 5.6.2 MER ±COL Treatment Arm for

		clarity. • Added wordings on optional aminoglycosides in Section 5.6.3 Optional Aminoglycosides to align with the texts in Protocol Summary/Meropenem ±colistin treatment arm. • Added wordings of "and administered per local label" on Polymyxin B (the alternative to Colistin) to provide the guidance on Polymyxin B administration in Section 5.6.2 MER±COL Treatment Arm. • Changed "enrollment" to either "informed consent" or "the start IV study treatment" in Table 8 Prohibited Concomitant Medications to increase the clarity on time frame for Prohibited Concomitant Medications. • Modified definition of "Cure" and "Indeterminate" of clinical responses in Table 9 Definition of Clinical Response Categories at the EOT and TOC visits and "Indeterminate" of microbiological response in Table 10 Definition of Microbiological Response Categories at the EOT and TOC Visits per FDA feedback for clarity. • Changed "100X field" to "Lower Power Field (LPF)" in footnote a of Table 10 Definition of Microbiological Response Categories at the EOT and TOC Visits and Appendix 6 Microbiological Assessments for clarity. • Removed the wordings of "(from an intra-abdominal culture for cIAI subjects or an adequate respiratory specimen for HAP/VAP subjects)" from Table 11 Definition of Emergent Infection Categories to accommodate the situation of emergent infection arising from other sites instead of the original site of infection. • Deleted "and exact time" in the statement on ECG recording in CRF in Section 7.2.3 ECG as the time of each of the triplicate ECGs will be provided in the non-CRF data transfer from the vendor and it is not necessary to collect the time of ECGs in the

		CRF. • Clarified PK sampling time point in reference to IV ATM-AVI Loading Dose, Extended Loading Dose and Maintenance Dose in Table 13 Pharmacokinetic ATM-AVI Sample Collection Time Points to be consistent with Figure 3 and ATM-AVI Pharmacokinetic Sample Collection Time Points for Subjects with CrCL >30 mL/min (Q6h Maintenance Dose) and Figure 4 ATM-AVI Pharmacokinetic Sample Collection Time Points for Subjects with CrCL >15 to ≤30 mL/min (Q8h Maintenance Dose). • Modified wordings on PK sample collections and drug concentration measurements to increase clarity in Section 7.4.1 Collection of Plasma Samples for Analysis of Aztreonam-Avibactam and Section 7.4.2 Determination of Drug Concentration per Pfizer Clinical Pharmacology protocol template. • Specified storage time frame for microbiology isolates for clarity in Section 7.6.1 Storage, Re-use and Destruction of Biological Samples. • Added wordings on SAE report for fatal case due to disease progression to align with Pfizer standard on fatal case report in Section 8.4.4.2 Disease Progression. • Changed "study entry" to "randomization" for the starting point on renal function monitoring for clarity in Section 8.5.1 Renal Function. • Deleted ">1.5" in 2nd bullet point with the statement of "INR>1.5" in Section 8.5.2 Monitoring of Liver related Laboratory Parameters for error correction. • Changed "each visit" to "EOT and TOC visits" in reference to the clinical response assessments by the adjudication committee for error correction in Section 9.7 Independent Adjudication Committee. • Adding wordings on COMBACTE-CARE

		publication policies for clarity in 15.2 Publications by Investigators. • Added "(except anaerobic bacterial pathogens isolated from subjects with respiratory infections)" in the statement for required shipment of microbiological isolates to the central reference laboratory in Appendix 6 Microbiological Assessments for clarity. • Clarified Intra-abdominal specimen collection for culture to increase clarity and consistency of Intra-abdominal specimens for culture across protocol in Appendix 6 Microbiological Assessments. • Other typographical or administrative edits to improve readability, clarity and consistency.
Original protocol	20 October 2017	Not applicable (N/A)

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