Protocol C3601002

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

Statistical Analysis Plan
(SAP)

Version: 2

Date: 25-JUN-2020

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3601002 is based on protocol amendment I dated 05JUL2018.

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
Version 2/ Amendment 1	CCI [redacted]	[redacted]
	Included details regarding the Clinical Adjudication Committee in Section 3.1	Detail included for clarity as the clinical response detennined by the Clinical Adjudication Committee will be used in the analyses of the clinical response efficacy endpoints.
	Details added in Section 3.5.2 regarding baseline microbiology	Details added to described how baseline pathogens will be defined.
	Modified descriptions of some safety endpoints/analysis	Modified for clarity and to be consistent with Pfizer standard safety data repo1ting.
	Definition of treatment-emergent adverse event modified to: An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event sta1ted after the study medication start date and time.	The TEAE definition was modified per Pfizer guidance.
	Removed 3-tier approach to adverse event safety analysis.	It was decided to not include the 3-tier AE approach since statistical comparisons are not conducted for efficacy analysis in this descriptive study; thus, they should not be conducted for safety analysis either. However, pre-specified events of clinical impo1tance (previously planned as Tier 1 AEs) will be evaluated.
	Inclusion of details in Section 4.1 regarding	Details provided for clarity and transparency on the efficac anal sis set

[redacted]

	determination of efficacy analysis sets.	determination process.
	Details added regarding the evaluation of the 95% CI for the difference in the clinical cure rates between the treatment groups in Section 6.1.	Details are provided to outline that the evaluation of the 95% CI for the difference in cure rates is pre-specified and to provide the power associated with evaluating the 95% CI versus various lower bound values.
	Details added for the health resource utilization analysis in Section 6.4.	More details added for the health resource utilization analyses for clarity and it is also noted that the results of these analyses will be included in the clinical study report (noted in Section 2.1).
	Addition of Criteria for Vital Signs Abnormalities (Appendix 4).	Criteria outlined for evaluation of vital signs abnormalities, which is planned as part of the safety analysis.
1.0	Not Applicable	Not Applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3601002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

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).

[redacted]

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.

[redacted]

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 (e.g., 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 (e.g., 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 (e.g., 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 (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*	• 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.

*: Results of health utilization analyses will be included in the Clinical Study Report.

2.2. Study Design

This is 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 ± metronidazole and meropenem ± colistin in the treatment of hospitalized adults with complicated intra-abdominal infection or nosocomial pneumonia including hospital-acquired pneumonia and ventilator-associated pneumonia, in regions with endemic or emerging carbapenem resistance, and where metallo-β-lactamase-producing multi-drug resistant pathogens are suspected.

[redacted]

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 End of Treatment 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 aztreonam-avibactam ± metronidazole treatment arm or the meropenem ± colistin treatment arm. Randomization will be stratified based on infectious disease type (complicated intra-abdominal infection and hospital-acquired pneumonia/ventilator-associated pneumonia). For complicated intra-abdominal infection, subjects will also be stratified by Acute Physiology and Chronic Health Evaluation score (≤10 and >10) (Protocol Appendix 5). For hospital-acquired pneumonia/ventilator-associated pneumonia, subjects will also be stratified by mechanical ventilation status (Y/N).

The study will randomize approximately 375 subjects (approximately 300 subjects with complicated intra-abdominal infection and approximately 75 subjects with hospital acquired pneumonia/ventilator associated pneumonia). It is estimated that approximately 25 subjects will be identified with metallo-β-lactamase-producing Gram-negative pathogens in the aztreonam-avibactam ± metronidazole treatment arm, and approximately 12 subjects in the meropenem ± colistin treatment arm.

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.

For subjects randomized to aztreonam-avibactam ± metronidazole, sparse blood samples will be collected for population pharmacokinetic assessments and pharmacokinetic/pharmacodynamic relationships will be evaluated in subjects where plasma samples and clinical and microbiological response data have been collected.

Each subject is expected to complete the study, including the Late Follow-Up visit.

Participants in the study must be inpatients at the study site institution to receive study medication.

2.3. 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 will be assessed at EOT and TOC by an independent clinical adjudication committee (central assessor) in a blinded fashion with the aim of unbiased adjudication of the primary objective measure. Data will be provided to the adjudication committee relating to the subject's clinical response 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 analyses conducted for interim External Data Monitoring Committee (E-DMC) safety reviews (See Protocol Section 9.5 and E-DMC Charter).

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

The primary efficacy outcome measure is the proportion of subjects with clinical cure (as determined by the Independent Clinical Adjudication Committee) at the Test of Cure (TOC) visit in the Intent-To-Treat (ITT) and Clinically Evaluable (CE) co-primary 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 set. For the non-United States countries, the ITT and CE analysis sets are co-primary analysis sets. 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. The proportion of subjects with clinical cure for the CE analysis set is defined as the number of subjects with clinical cure at TOC divided by the number of subjects in the CE analysis set.

The Clinical Adjudication Committee (CAC) will use pre-specified criteria, as per the protocol, to determine clinical responses. All data will be reviewed by the CAC members within a Virtual Clinical Adjudication System (VCAS). The CAC will be blinded to study treatment allocations and investigator assessments of clinical response. All adjudication outcomes will be documented on electronic Adjudication Forms and stored within VCAS and will be transferred for merging with the clinical dataset for analysis. More details on the CAC can be found in the CAC Charter.

3.2. Secondary Endpoints

The secondary outcome measures are:

- Proportion of subjects with clinical cure at the TOC visit in the micro-ITT and ME analysis sets;
- 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;
- 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;
- Safety and tolerability as assessed by adverse events, physical examination, vital signs, electrocardiograms, and laboratory assessments in the safety analysis set.

Per-subject and per-pathogen (Section 3.3 Tertiary Endpoint) microbiological responses that are presumed based on clinical response will be based on the adjudicated clinical response.

3.3. Tertiary Endpoints

- 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 (e.g., 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 (e.g., 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 pathogen-resistance type (e.g., ATM- non-susceptible, ESBL- positive, carbapenamase- positive, MBL-positive) at the EOT and TOC visits in the micro-ITT and ME analysis sets.

3.4. Exploratory Endpoints

The exploratory outcome measures 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);

[redacted]

- 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.

3.5. Baseline Variables

3.5.1. Baseline Clinical Laboratory and Vital Signs

Baseline clinical laboratory (Hematology, Clinical Chemistry, etc.) and vital signs values will be defined as the last non-missing value observed before treatment begins.

3.5.2. Baseline Microbiology

The central lab results will be used in the microbiological analyses. Local lab results will only be used in microbiological analyses when central lab results are not available.

Baseline pathogens are defined as those obtained from adequate specimens closest (and prior) to the start of study treatment. Any pathogens resulting from blood obtained in the 48 hours prior to study treatment start will be considered baseline pathogens.

For all specimens other than blood, if an adequate specimen closest (and prior) to the start of study treatment yields no pathogens and was obtained on a date subsequent to an adequate specimen from the same source that yielded a pathogen, the subject will be considered to have no baseline pathogens. Analysis of the pathogens from the previous adequate specimen, as baseline pathogens, may be conducted if a sufficient number of subjects fall into this scenario.

Adequate specimens for culture at baseline for each infection type are outlined below:

Cultures of abdominal site infections (for cIAI subjects only)

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

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

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 HAP/VAP (ideally before receipt of any systemic antibiotics). An adequate and appropriate baseline respiratory specimen 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;

[redacted]

- 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 subject 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 samples from expectorated or induced sputum must show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Lower Power Field (LPF) upon a Gram-stain.

In some circumstances, subjects may have multiple respiratory specimens obtained after the onset of signs and symptoms of pneumonia within the 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.

Collection of Blood for Culture (for all subjects)

Blood cultures should be performed at the Baseline visit prior to the first dose of study treatment, if blood cultures are not available within 48 hours prior to randomization. Any blood cultures obtained within 48 hours prior to randomization will be valid.

[redacted]

3.6. Stratification Variables

Randomization will be stratified based on infectious disease type (complicated intra-abdominal infection and hospital-acquired pneumonia/ventilator-associated pneumonia). For complicated intra-abdominal infection, subjects will also be stratified by Acute Physiology and Chronic Health Evaluation score (≤10 and >10). For hospital-acquired pneumonia/ventilator-associated pneumonia, subjects will also be stratified by mechanical ventilation status (Y/N).

3.7. Safety Endpoints

The safety endpoints of this study are:

- Incidence of adverse events by study period: treatment period [from first dose to EOT], from EOT to LFU, and for the full study period [from first dose to LFU];
- Incidence of clinical laboratory abnormalities (defined as Potentially Clinically Significant [PCS] results) and summary of values and change from baseline in clinical laboratory measures by scheduled visit;
- Incidence of vital sign abnormalities and summary of measurements and change from baseline in vital sign measures by scheduled visit;
- Incidence of ECG abnormalities and summary of measurements and change from baseline in ECG measures by scheduled visit;
- Incidence of abnormalities in the complete physical examination by scheduled visit.

3.7.1. Adverse Events

An adverse event (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. An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started after the study medication start date and time.

In addition to standard AE summaries, pre-specified events of clinical importance, maintained in the product's Safety Review Plan, will be summarized. These will include the following categories of events: AEs potentially related to liver disorder, *Clostridium difficile* colitis and hypersensitivity/anaphylaxis. The list will be finalized prior to database lock.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to database lock and classifications will be documented per standard operating procedures. When determining if subjects meet the criteria for inclusion in each analysis set, the study team will not have access to treatment group information during the assessment [exception: PopPK analysis set (which only includes subjects from the

[redacted]

ATM-AVI treatment group), where the determination will be made by Clinical Pharmacology and Pharmacometrics].

4.1. Efficacy Analysis Sets

The evaluation of subject data for subject exclusion from efficacy analysis sets will be completed and documented by the study team prior to database lock. The review of subject data for analysis set exclusion will be performed on an ongoing basis during the study. The review of subject data will include:

- Programmed output produced by programming and statistical personnel separate from the sponsor study team;
- Data Listings produced from the database and reviewed by Data Management and Clinical;
- Reports of potentially important protocol deviations including those which may impact efficacy (utilizing the CORD system).

4.1.1. 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 to which they are randomized. The ITT analysis set will be used to evaluate the primary, secondary and tertiary objectives.

4.1.2. Clinically Evaluable (CE) Analysis Set

The CE analysis set is defined as all subjects who:

- Met the definition of the ITT analysis set;
- Met 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 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;
- Did not receive prior antibiotics other than as outlined as acceptable in Exclusion Criteria #3 in the protocol;

[redacted]

- Had no important protocol deviations that may affect the assessment of efficacy. The criteria for identifying important protocol deviations will be finalized as part of the final evaluability review before database lock. Protocol Deviations will be tracked and documented throughout the study in the Clinical Oversight Review Dashboard (CORD) system;

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

- Did 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 to which they are randomized. The CE analysis set will be used to evaluate selected primary, secondary and tertiary objectives.

4.1.3. 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 baseline pathogen from an adequate specimen obtained prior to the start of study treatment. Subjects with inherently resistant pathogens (for example, monomicrobial infections due to any *Acinetobacter* spp.), and those subjects with only Gram-positive pathogens will be excluded from the micro-ITT analysis set. Subjects in the micro-ITT analysis set will be analyzed according to the treatment to which they are randomized. The micro-ITT analysis set will be used to evaluate selected secondary and tertiary objectives.

4.1.4. Microbiologically Evaluable (ME) Analysis Set

The ME analysis set includes all subjects commonly included in both micro-ITT and CE analysis sets and includes subjects who have at least 1 etiologic pathogen from an adequate baseline culture regardless of susceptibility to study agents. Subjects in the ME analysis set will be analyzed according to the treatment to which they are randomized. The ME analysis set will be used to evaluate selected secondary and tertiary objectives.

4.1.5. 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.

4.1.6. 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. Subjects in the micro-MITT analysis set will be analyzed according to the treatment they received. The micro-MITT analysis set will be used in sensitivity analysis of microbiological response endpoints.

4.2. Safety Analysis Set

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

4.3. 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 or AVI and will be used to report all PK data.

4.4. Other Analysis Sets

4.4.1. All Subjects Analysis Set

This analysis set will include all subjects enrolled into the study (ie., subjects who have signed an informed consent form for the study) and will be used for reporting of disposition and demographics. (listing only).

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

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

5.2. General Methods

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. Listings of individual subject data will also be produced.

Categorical and qualitative variable summaries for safety will include the frequency and percentage of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for each treatment group, unless otherwise specified.

For the reporting of descriptive statistics for continuous and quantitative data, the mean and median values will be presented to 1 more decimal-place precision than were recorded in the source data. The SD will be presented to 2 more decimal-places of precision and the minimum and maximum values will be presented to the same decimal-places of precision as the source data. Percentages will be presented to 1 decimal-place of precision.

Unless specified otherwise, all analysis will be performed using SAS®, release 9.1 or higher.

5.3. Methods to Manage Missing Data

For efficacy data, missing data will not be imputed.

For safety data, missing dates will be programmatically handled according to Pfizer standards.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Primary Analysis

The prima1y descriptive efficacy analysis (for non-US countries) will be the estimate of the clinical cure rate and 95% confidence interval (CI) in each treatment aim (ATM-AVI± MTZ and MER± COL) in the ITT and CE co-prima1y analysis sets. The estimate of the clinical cure rate and 95% CI in each treatment aim in the ITT analysis set will be the primary analysis for the US. Single aim 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 indetenninate in each treatment aim will be tabulated for the ITT and CE analysis sets at the TOC visit (Day 28 ± 3 days).

The prima1y descriptive analysis will be conducted using the clinical response assessment dete1mined by a blinded independent clinical adjudication committee. The Investigator's assessment of clinical response will also be summarized in the ITT and CE analysis sets at the TOC visit as a sensitivity analysis (See Section 6.1.2). 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 prima1y analysis.

Difference in clinical cure rate between treatment anns at TOC visit (ATM-AVI± MTZ minus MER± COL) and coITesponding 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 Nunninen and an additional suppo1iing descriptive analysis will be conducted using the stratified Miettinen and Nunninen method (Miettinen and Nmminen 1985), if each stratum has at least 3 subjects per each treatment group.

6.1.2. Sensitivity/Robustness Analyses

An analysis of the Investigator's assessment of clinical response in the ITT and CE analysis sets at the TOC visit will be performed as a sensitivity analysis.

A sensitivity analysis will be performed for clinical response at TOC (adjudicated response) using the MITT population which includes subjects who were randomized and received any amount of study drug.

Sensitivity analysis of the primary endpoint (clinical response at TOC, adjudicated response) will also be conducted in the ITT population that considers all deaths prior to the TOC as clinical failures.

A sensitivity analysis of the use of concomitant antibiotics (other than those allowed per the protocol – Gram positive coverage and aminoglycosides) on the primary endpoint (clinical response at TOC) in the ITT population will be conducted. Subjects who receive at least 1 dose of a restricted/prohibited concomitant medication will be included in this analysis of the primary endpoint.

6.2. Secondary Endpoints

Secondary endpoints and corresponding analysis methods are also summarized in Appendix 2 Table 1.

Secondary efficacy outcome measures (evaluating the proportion of subjects with clinical cure [based on adjudicated clinical response] at the TOC visit by differing analysis sets {e.g., ME], by MBL status and infection type; proportion of subjects with favorable per-subject microbiological response, and those who died on or before 28 days after randomization [overall and by infection type]) will be assessed and presented similar to the primary endpoint.

In addition to an analysis of clinical response at TOC by infection type, additional efficacy (clinical and microbiological), safety, and baseline analyses by infection type will be conducted to evaluate the cIAI and HAP/VAP populations separately. These analyses will be outlined in the Analysis and Reporting Plan.

Additional descriptive analyses will also be performed for the secondary and tertiary (refer to Section 6.3) outcomes of clinical cure rate and microbiological favorable response rate at EOT and TOC using the microbiological modified Intent-To-Treat population. which is a subset of the micro-ITT population comprising those subjects who received any amount of intravenous study drug.

For the Safety analyses, please see Section 6.7.

6.2.1. Pharmacokinetic Analyses

Aztreonam and avibactam plasma concentrations versus time will be depicted graphically in the Clinical Study Report (CSR). The final pharmacokinetic data will be pooled with data from other studies to conduct a population pharmacokinetic analysis (using Nonlinear Mixed Effects [NLME] 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. Full details of the pharmacokinetic and pharmacokinetic / pharmacodynamic analysis will be given in the Pharmacokinetic Modeling Analysis Plan (PMAP). These results will be reported separately in a Population Pharmacokinetic Modeling Analysis Report (PMAR).

6.3. Tertiary Endpoints

Tertiary endpoints and corresponding analysis methods are also summarized in Appendix 2 Table 1.

Tertiary efficacy outcome measures (evaluating the proportion of subjects with clinical cure [based on adjudicated clinical response] at the EOT visit by differing analysis sets, MBL status and infection type; proportion of subjects with favorable microbiological response at EOT) will be assessed and presented using similar methods as used for the primary endpoint.

For descriptive tertiary outcome measures, number and percentage in each treatment arm will be tabulated. Response summaries will be presented for the proportion of subjects with a favorable clinical, per-subject microbiological, and per-pathogen microbiological response at the EOT and TOC visits overall and by resistance type. Resistance type will include: aztreonam-non-susceptible, meropenem-non-susceptible isolates and isolates producing ESBLs, serine carbapenemases, and MBLs (selected analyses for MBL status is secondary).

6.4. Exploratory Endpoints

Subjects will be summarized by the value of their composite score of symptom-based objective clinical measures. This analysis is dependent on development of a composite score of symptom-based objective clinical measures and validation. If available prior to completion of this study (prior to database lock), this analysis will be conducted.

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

Health resource utilization data will be summarized by treatment arm, total, and, where applicable and numbers permit, by infection type. This will include length (days) of hospital stay, hospital readmissions during the study (through TOC and, additionally, through LFU), length of ICU stay, transfer to ICU, length of study treatment (calendar and 24-hour days; see Section 6.7.7), mechanical ventilation (and length if needed) for HAP/VAP subjects, and unplanned surgical intervention for cIAI subjects. Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) will be provided for

duration/length of stay variables; counts and percentages will be presented for categorical variables.

For health resource utilization endpoints, only events that are in progress at the time of randomization or that begin after randomization and on or before the date of the TOC (and additionally through LFU for proportion of hospital re-admissions) assessment will be included in these analyses. In addition, except for hospitalization (all subjects will be hospitalized), duration summaries will focus on subjects who have the event.

The length of hospital stay will be calculated as the difference between the date of discharge and the date of randomization plus 1. As multiple hospital stays are possible, the total number of calendar days on which the subject was in hospital for the period from date of randomization until the TOC visit will be derived. The length of stay in ICU up to the TOC visit will be derived from the ICU admittance/discharge dates. For subjects with multiple stays in ICU, the total number of calendar days on which the subject was in ICU for the period from date of randomization until the TOC visit will be derived. Duration of mechanical ventilation will be calculated similarly. These length of stay/duration variables will be summarized with and without subjects who died to evaluate the impact of the duration variables for subjects who died on the overall assessment of these variables.

6.5. Subset Analyses

Subgroup analyses of the primary endpoint (clinical cure rate at TOC) will include:

- Baseline renal function category: Severe (CrCl 16-30 mL/min) renal impairment, Moderate (CrCl 31-50 mL/min) renal impairment, Normal renal function or Mild renal impairment (CrCl 51-150 mL/min), Augmented renal function (CrCl 151+ mL/min).

- For cIAI subjects: APACHE II score category (≤10 or > 10) based on the data collected from the eCRF.

- For cIAI subjects: Diagnosis of Appendicitis (Appendiceal perforation or peri-appendiceal abscess) vs non appendicitis diagnosis.

- For HAP/VAP subjects: Mechanical Ventilation status at baseline (Yes/No), based on the data collected from the eCRF.

- Prior systemic antibiotic use (yes/ [≤24 hr / >24 hr] / no) within 48 hr window prior to first dose of study treatment.

- Monomicrobial vs polymicrobial infections at baseline (vs no pathogen).

- Concomitant Aminoglycoside Use – Subjects who receive at least 1 dose of protocol allowed aminoglycoside therapy during the study treatment period vs subjects who receive none.

- Geographic region (Western Europe; Eastern Europe; China; RoW).
- Further analyses for regions (e.g., Asian, or other regions) and countries (e.g., China) may be performed to satisfy local regulatory submission requirements if needed.

Some categories listed above may be combined when they contain a small number of subjects with evaluable data. Other subgroups may be evaluated as numbers permit.

As noted in secondary and tertiary endpoints, response summaries will be presented by infection type (complicated intra-abdominal infection or hospital-acquired pneumonia/ventilator-associated pneumonia), and by MBL status and pathogen resistance type.

6.6. Baseline and Other Summaries and Analyses

Baseline variables are defined as outlined in Section 3.5.

Demographic and baseline characteristics, including age, gender, height, weight, primary diagnosis, mechanical ventilation status (for HAP/VAP subjects) and APACHE II score will be summarized by treatment arm.

Baseline microbiology will be summarized by treatment arm. Pathogens at baseline will be summarized overall and by infection type. Pathogens will be summarized by individual baseline pathogen, by pathogen type (*Enterobacteriaceae*, other Gram-negative pathogens, Gram-positive aerobes, etc.), by MBL status (positive/negative), and by resistance type (including aztreonam non-susceptible, meropenem non-susceptible isolates and isolates producing ESBLs, serine carbapenemases). The number of subjects with monomicrobial vs polymicrobial (2, 3, 4, ≥5 pathogens) at baseline will be summarized. If numbers permit, analyses by specimen type (intra-abdominal specimen, respiratory specimen or blood) may be performed. The susceptibility profile of baseline pathogens and MIC frequency distributions to study treatment will also be summarized. Microbiological culture results will be listed.

Medical history and Physical Exam (General and Focused) will be summarized. The clinical signs and symptoms of infection will be summarized by visit and treatment arm. Prior and Concomitant medications will be summarized. Antibiotic medications will be summarized and listed separately.

The number of subjects in each of the analysis sets will be summarized. In addition, the number of subjects who were excluded from the analysis sets will be summarized by reasons for the exclusion.

A summary of the number of subjects in each country and each center will be produced for all randomized subjects.

6.7. Safety Summaries and Analyses

Standard summary tables and listings will be generated using Pfizer's Clinical Data Analysis and Reporting System (CDARS) for the following parameters: adverse events, lab parameters (hematology, blood chemistry, and urinalysis), vital signs, ECGs, physical examinations, discontinuations from study, discontinuations from treatment, and treatment duration.

Unless otherwise noted, AEs will be sorted alphabetically for system organ class and then preferred term.

6.7.1. Adverse Events

TEAEs will be summarized by number and percent by system organ class (SOC) and preferred term (PT). All TEAEs will be summarized 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]). Deaths, TEAEs leading to discontinuation, TEAEs by SOC, preferred term, and relationship to study therapy, TEAEs by SOC, preferred term, and severity, TEAEs by SOC, preferred term and baseline CrCl status, pre-specified AEs of clinical importance, and SAEs will be summarized for the full study period using the safety analysis set.

In addition, AEs will be summarized by subjects who received non-study concomitant antibiotics (i.e. excluding protocol-allowed study antibiotic treatments) at any time during the treatment period versus those who did not receive antibiotics during the treatment period. In this summary all adverse events will be included regardless of whether they occurred prior to starting the antibiotic or not.

All AEs, including prior to first dose and treatment emergent adverse events (TEAEs), will be listed.

6.7.2. Laboratory Data

Laboratory data (central and local) for hematology, clinical chemistry, and urinalysis will be summarized by study visit. Frequencies of potentially clinically significant values and changes from baseline occurring during the clinical study will also be presented (hematology and clinical chemistry). Potentially clinically significant criteria are outlined in Appendix 3.

Shifts from low, normal, and high relative to the normal range between baseline and each post-baseline time point will be evaluated for hematology and clinical chemistry laboratory parameters. For urinalysis, shifts from negative (or normal), trace and positive will be tabulated. Arterial Blood Gas (ABG) results, where available, will be summarized and listed.

In addition, a summary table will be presented which will indicate the number of subjects who separately meet the criteria for potential Hy's Law or Hy's Law after the start of study treatment at any time up to the LFU visit: The AST, ALT, total bilirubin and ALP elevations can occur at any time in the specific review period and do not need to occur simultaneously.

[redacted]

A listing of subjects with a value of ≥3xULN for ALT or AST or a value of ≥2xULN for total bilirubin in any one of the AST, ALT, total bilirubin parameters at any time during the study (baseline or post-baseline) will be also presented. This listing will contain all the ALT, AST, total bilirubin and ALP study data for such subjects.

6.7.3. Vital Signs

Vitals signs data, including blood pressure, heart rate, and body temperature will be summarized by visit. The number of subjects with vital sign abnormalities in blood pressure and heart rate will also be summarized. Criteria for vital signs abnormalities can be found in Appendix 4.

For those subjects with HAP/VAP, respiratory rate (breaths per minute) and peripheral oxygen saturation will be summarized.

6.7.4. Electrocardiogram

A single independent third-party using uniform techniques will carry out formal reading and interpretation of ECG data for purposes of the study. Data will be transferred to Pfizer for inclusion in summary analyses.

The incidence of abnormal values (for example: elevated QT, QTcB, and QTcF values) and changes from baseline in the electrocardiogram parameters will be summarized by treatment arm.

6.7.5. Physical Examination

The numbers and percentage of subjects with an abnormal complete physical exam assessment for each body system will be displayed by scheduled visit.

6.7.6. Detailed Infection-related Focused Physical Examination

Results of the detailed focused (infection-related abdominal or respiratory signs and symptoms per indication) assessment will be summarized by visit.

6.7.7. Extent of Exposure and Compliance

Exposure to study therapy in calendar days will be summarized by treatment group and overall and listed. The duration of therapy in calendar days will be calculated as follows:

Date of last dose of study drug - date of first dose of study drug +1.

In addition, exposure to study therapy in 24-hour days will be calculated and summarized by treatment group and overall and listed. The duration of therapy in 24-hour days will be calculated as follows.

Date and Time of last dose of study drug - date and time of first dose of study drug.

[redacted]

Compliance over the whole treatment period will be calculated as follows:

$$\text{Compliance} = \frac{\text{Actual Number of Doses Received}}{\text{Planned Number of Doses}} * 100$$

The planned number of doses will be calculated as follows:

The planned number of doses = 1+ the nearest integer of [(Time of the last dose of study drug– time of the first dose of study drug)/number of hours between doses].

A subject is considered compliant if between 80% and 120% of the planned number of doses is received. Interruption in therapy is considered non-compliance only if the compliance criteria described above is not met. Medication compliance will be summarized (n, mean, standard deviation, median, minimum and maximum) by treatment group. The compliance will also be summarized in the following categories: <80%, ≥ 80% to 120%, and >120% by the number and percentage of subjects in each treatment group.

Additionally, the number of infusions and the number of each individual component of study therapy (ATM-AVI, metronidazole, meropenem) will be summarized by baseline renal function (Severe renal impairment, Moderate renal impairment, Normal renal function or Mild renal impairment, and Augmented renal function, as outlined in Section 6.5).

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. An external data monitoring committee (E-DMC) will be responsible for ongoing monitoring of the safety of subjects in the study according to the E-DMC Charter.

8. REFERENCES

1. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical Science 2001, 16 (2):101-117.

2. Cai TT. One-sided confidence intervals in discrete distributions. J Stat Plan Inference 2005;131(1):63-68.

3. Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Statistics in Medicine 1985: 213-226.

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9. APPENDICES

Appendix 1. Abbreviations

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

Abbreviation or special term	Explanation
ABG	Arterial blood gas
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
ATM	Aztreonam
ATM-AVI	Aztreonam-avibactam
ATM-AVI ± MTZ	Aztreonam-avibactam ± metronidazole
AVI	Avibactam
BAL	Bronchoalveolar lavage
BP	Blood Pressure
BPM	Beats Per Minute
CAC	Clinical Adjudication Committee
CDARS	Clinical Data Analysis and Reporting System
CE	Clinically evaluable
cIAI	Complicated intra-abdominal infection
CI	Confidence interval
COL	Colistin (colistimethate sodium)
CORD	Clinical Oversight Review Dashboard
CrCl	Creatinine clearance
CSR	Clinical Study Report
ECG	Electrocardiogram
ECRF	Electronic Case Report From
E-DMC	External data monitoring committee
EOT	End of treatment
ESBL	Extended-spectrum β-lactamase
HAP	Hospital-Acquired Pneumonia
ICU	Intensive care unit
ITT	Intent-To-Treat
LFU	Late Follow-up
LLN	Lower Limit of Normal
LPF	Low Power Field
MBL	Metallo-β-lactamase
MDR	Multi-drug resistant
ME	Microbiologically Evaluable

[redacted]

Abbreviation or special term	Explanation
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
NLME	Nonlinear Mixed Effects
NP	Nosocomial pneumonia
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PMAP	Population Modeling Analysis Plan
PMAR	Population Modeling Analysis Report
popPK	Population pharmacokinetic
PSB	Protected-specimen brush
PT	Preferred Term
RoW	Rest of World
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
ULN	Upper limit of normal
US	United States
VAP	Ventilator-associated pneumonia
VCAS	Virtual Clinical Adjudication System

Appendix 2. Table 1: Summary of Efficacy Analyses

EndpointN ariable	Analysis Set	Statistical Method	Timepoint	Objective
Clinical Cure (as assessed by the CAC)	ITT and CE	Summa1y of Proportion 95% CI for Treatment Group and Difference	TOC	Primaiy Endpoint (US = ITT, Non-US = CE & ITT)
Clinical Cure (as assessed by the CAC)	CE	Summa1y of Propo1tion 95% CI for Treatment Group and Difference	TOC	Seconda1y Endpoint (for US)
Clinical Cure as assessed by the Investigator	ITT and CE	Summa1y of Propo1tion 95% CI for Treatment Group and Difference	TOC	Sensitivity/Suppo1tive Analysis
Clinical Cure	MITT	Summa1y of Propo1tion 95% CI for Treatment Group and Difference	TOC	Sensitivity/Suppo1tive Analysis
Clinical Cure where all deaths are considered failures	ITT	Summa1y of Propo1tion 95% CI for Treatment Group and Difference	TOC	Sensitivity/Suppo1tive Analysis
Clinical Cure by restricted/prohibited concomitant antibiotics use	ITT and CE	Summa1y of Proportion 95% CI for Treatment Group and Difference	TOC	Sensitivity/Suppo1tive Analysis
Clinical Cure	micro-ITT and ME	Summa1y of Propo1tion 95% CI for Treatment Group and Difference	TOC	Secondaiy Endpoint
Clinical Cure by Infection Type	ITT and CE	Summa1y of Propo1tion 95% CI for Treatment Group and Difference	TOC	Secondaiy Endpoint
Clinical Cure by MBL status (positive/negative)	micro-ITT and ME	Summa1y of Proportion	TOC	Secondaiy Endpoint

[redacted]

EndpointN ariable	Analysis Set	Statistical Method	Timepoint	Objective
Subjects with favorable per-subject microbiological response	micro-ITT and ME	Summa1y of Proportion 95% CI for Treatment Group	TOC	Secondaiy Endpoint
Death (overall and by infection type)	ITT and micro-ITT	Summa1y of Proportion 95% CI for Treatment Group and Difference	On or before 28 days after randomization	Secondaiy Endpoint
Subjects with favorable per-subject microbiological response	micro-MITT	Summa1y of Propo1tion	TOC andEOT	Secondaiy Sensitivity/Suppo1tive Analysis
Clinical Cme	ITT, micro-ITT, CE, andME	Summa1y of Proportion 95% CI for Treatment Group and Difference	EOT	Te1tiaiy Endpoint
Clinical Cure by Infection Type	ITT and CE	Summa1y of Proportion 95% CI for Treatment Group and Difference	EOT	Te1tiaiy Endpoint
Clinical Cme by MBL status	micro-ITT and ME	Summary of Propo1tion	EOT	Te1tiary Endpoint
Clinical Cure by Pathogen Resistance Type (aztreonam-non-susceptible, meropenem-non-susceptible isolates, and isolates producing ESBLs, serine cai·bapenemases)	micro-ITT and ME	Summa1y of Proportion	TOC andEOT	Te1tiaiy Endpoint
Subjects with favorable per-subject microbiological response	micro-ITT and ME	Summa1y of Propo1tion 95% CI for Treatment Group	EOT	Te1tiaiy Endpoint
Subjects with favorable per-pathogen microbiological response	micro-ITT and ME	Summa1y of Proportion	TOC andEOT	Te1tiaiy Endpoint

[redacted]

EndpointN ariable	Analysis Set	Statistical Method	Timepoint	Objective
Subjects with favorable per-subject microbiological response by Pathogen Resistance Type (aztreonam-non-susceptible, meropenem-non-susceptible isolates, and isolates producing ESBLs, serine cai·baoenemases. and MBLs)	micro-ITT and ME	Summa1y of Proportion	TOC andEOT	Te1iiaiy Endpoint
Subjects with favorable per-pathogen microbiological response	micro-MITT	Summa1y of Proportion	TOC andEOT	Te1iiaiy Sensitivity/Suppo1iive Analysis
Total Score for the Composite Endpoint of Symptom-Based Objective Clinical Measures	ITT and CE	Summaiy		Explorato1y Endpoint
Death	ITT and micro-ITT	Summa1y of Propo1iion	On or before 14 days after randomization	Explorato1y Endpoint
Health Utilization	ITT and CE	Summaiy	UptoTOC (LFU for hospital readmissions)	Explorato1y Endpoint

[redacted]

Appendix 3. Criteria for Potentially Clinically Significant Lab Results

Table 1: Clinical Chemistry

	PCS Low Decrease; if both Below LLN and % Decrease from Baseline		PCS High Increase: if both Above ULN and % Increase from Baseline	
Parameter	**Lower Limit**	**% decrease from baseline**	**Upper Limit**	**% increase from baseline**
Albumin	< 0.5 × LLN	> 50%	> 1.5 × ULN	> 50%
Alkaline phosphatase	< 0.5 × LLN	> 80%	> 3.0 × ULN	> 100%
Alanine aminotransferase	N/A	N/A	> 3.0 × ULN	> 100%
Aspartate aminotransferase	N/A	N/A	> 3.0 × ULN	> 100%
Bicarbonate	< 0.7 × LLN	> 40%	> 1.3 × ULN	> 40%
Blood urea nitrogen	< 0.2 × LLN	> 100%	> 3.0 × ULN	> 200%
Calcium, total	< 0.7 × LLN	> 30%	> 1.3 × ULN	> 30%
Chloride	< 0.8 × LLN	> 20%	> 1.2 × ULN	> 20%
Creatinine	N/A	N/A	> 2.0 × ULN	> 100%
Gamma-glutamyl transferase	N/A	N/A	> 3.0 × ULN	N/A*
Glucose (nonfasting)	< 0.6 × LLN	> 40%	> 3.0 × ULN	> 200%
Inorganic phosphorus	< 0.5 × LLN	> 50%	> 3.0 × ULN	> 200%
Potassium	< 0.8 × LLN	> 20%	> 1.2 × ULN	> 20%
Sodium	< 0.85 × LLN	> 10%	> 1.1 × ULN	> 10%
Total bilirubin	N/A	N/A	> 1.5 × ULN	> 100%
Indirect Bilirubin	N/A	N/A	> 1.5 × ULN	> 100%
Direct bilirubin	N/A	N/A	> 2.0 × ULN	> 150%
Total protein	< 0.5 × LLN	> 50%	> 1.5 × ULN	> 50%

LLN = lower limit of normal value provided by the central laboratory
ULN = upper limit of normal value provided by the central laboratory
N/A = not applicable

[redacted]

Table 2: Hematology

	PCS Low Decrease: if both Below LLN and % Decrease from Baseline		PCS High Increase: if both Above ULN and % Increase from Baseline	
Parameter	**Lower Limit**	**% decrease from baseline**	**Upper Limit**	**% increase from baseline**
Hemoglobin	< 0.7 × LLN	> 30%	> 1.3 × ULN	> 30%
Hematocrit	< 0.7 × LLN	> 30%	> 1.3 × ULN	> 30%
Platelet count	< 0.65 × LLN	> 50%	> 1.5 × ULN	> 100%
Red blood cell count	< 0.7 × LLN	> 30%	> 1.3 × ULN	> 30%
White blood cell count (total)	< 0.65 × LLN	> 60%	> 1.6 × ULN	> 100%
Neutrophils	< 0.65 × LLN	> 75%	> 1.6 × ULN	> 100%
Lymphocytes	< 0.25 × LLN	> 75%	> 1.5 × ULN	> 100%
Eosinophils	N/A	N/A	> 4.0 × ULN	> 300%
Monocytes	N/A	N/A	> 4.0 × ULN	> 300%
Basophils	N/A	N/A	> 4.0 × ULN	> 300%

LLN = lower limit of normal value provided by the central laboratory
ULN = upper limit of normal value provided by the central laboratory
N/A = not applicable

[redacted]

Appendix 4. Criteria for Vital Signs Abnormalities

Table 1: Criteria for Vital Signs Abnormalities

Parameter	Criteria
Systolic BP (mm Hg)	• Value >150 and increase from baseline ≥30 • Value <90 and decrease from baseline ≥30
Diastolic BP (mm Hg)	• Value >100 and increase from baseline ≥ 20 • Value <50 and decrease from baseline ≥20
Heart Rate (BPM)	• Value <40 or >120