Protocol C3601009

A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, COMPARATIVE STUDY TO ASSESS THE EFFICACY, SAFETY AND TOLERABILITY OF AZTREONAM-AVIBACTAM (ATM-AVI) AND BEST AVAILABLE THERAPY FOR THE TREATMENT OF SERIOUS INFECTIONS DUE TO MULTI-DRUG RESISTANT GRAM- NEGATIVE BACTERIA PRODUCING METALLO-BETA-LACTAMASE (MBL)

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 21-April-2020

[redacted]

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

[redacted]

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3601009 is based on the protocol dated 05JUL2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
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 C3601009. 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 (ATM-AVI) and best available therapy (BAT) at the Test of Cure (TOC) visit in the microbiological Intent-To-Treat (micro-ITT) population for the treatment of selected serious infections that are due to MBL-producing Gram-negative bacteria.	Proportion of subjects with clinical cure at the TOC visit in the micro-ITT analysis set.
Secondary Objectives:	**Secondary Endpoint(s):**
To evaluate the efficacy of ATM-AVI and BAT at the TOC in the Microbiologically Evaluable (ME) population, and at the End of Treatment (EOT) visit in the micro-ITT and ME populations.	• Proportion of subjects with clinical cure at the TOC visit in the ME analysis set; • Proportion of subjects with clinical cure at the EOT visit in the micro-ITT and ME analysis sets.

To assess the microbiological response to ATM-AVI at the EOT and TOC visits in the micro-ITT and ME populations.	• Proportion of subjects with a favorable (defined as eradication or presumed eradication) per-subject microbiological response at the EOT and TOC visits 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.
To assess 28-day all cause mortality.	Proportion of subjects who died on or before 28 days from randomization in the Intent-To-Treat (ITT) and micro-ITT analysis sets.
To evaluate the safety and tolerability profile of ATM-AVI and BAT.	Safety and tolerability as assessed by adverse events, physical examination, vital signs, electrocardiograms, and laboratory assessments in the safety analysis set.

Exploratory Objectives:	**Exploratory Endpoint(s):**
To evaluate the phannacokinetics (PK) of ATM and AVI in subjects with serious infections and to attempt to characterize the relationship between exposure and clinical and microbiological response for ATM-AVI.	• PK of aztreonam and avibactam in subjects in the population PK analysis set; • PK/phaimacodynamic (PD) relationship between exposure and clinical and microbiological response for ATM-AVI in the population PK analysis set.
To assess 14-day all-cause mo1iality.	Proportion of subjects who died on or before 14 days from randomization in the ITT and micro-ITT anal sis sets.
To collect data to allow an explorato1y evaluation of health utilization*.	• Length of hospital stay, including any readmissions up to TOC (days); • Length of study treatment (days); • Length of intensive care unit stays (days); • Transfened to the intensive cai·e unit (Yes/No); • Mechanical ventilation (Yes/No) for hospital-acquired pneumonia/ventilator-associated pnemnonia subjects; • Length of mechanical ventilation (days) for hospital-acquired pneumonia/ventilator-associated pnemnonia subjects; • Subsequent unplanned surgical intervention after treatment success versus failure (up to the TOC visit) for complicated intra-abdominal infection subjects.
CCI [redacted]	[redacted]

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

[redacted]

2.2. Study Design

This is a prospective, randomized, multicenter, open-label, parallel group, comparative study to determine the efficacy, safety, and tolerability of ATM-AVI versus best available therapy (BAT) in the treatment of hospitalized adults with complicated intra-abdominal infection (cIAI), nosocomial pneumonia (NP) including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), complicated urinary tract infection (cUTI), or bloodstream infections (BSI) due to MBL-producing Gram-negative bacteria.

Adult hospitalized subjects with a confirmed diagnosis of cIAI, HAP/VAP, cUTI or BSI due to MBL-producing Gram-negative pathogens requiring administration of intravenous antibacterial treatment will be enrolled in this study.

Approximately 60 subjects with infections due to MBL-producing Gram-negative bacteria will be enrolled. MBL status of the isolates will be determined at the local level before enrollment of subjects, and will be confirmed at the central microbiology laboratory.

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 of study treatment, a TOC visit (Visit 17) on Day 28 (±3 days) and a LFU visit (Visit 18) on Day 45 (±3 days). Each subject is expected to complete the study, including the Late Follow-Up (LFU) visit.

After obtaining written informed consent and confirming eligibility, subjects will be randomized in a 2:1 ratio to the ATM-AVI treatment group or the BAT treatment group according to a central randomization schedule (approximately 40 (ATM-AVI) subjects and approximately 20 (BAT) subjects per group). Subjects will be stratified at randomization based on infectious disease type (cIAI, HAP/VAP, cUTI and BSI). The number of subjects with cUTI will be no more than approximately 75% of the study population.

Please refer to Protocol Section 5.5 more details with regard to treatment arms, dosage and mode of administration and duration of treatment.

The recommended minimal duration of treatment is 5 days for cIAI, cUTI and BSI and 7 days for HAP/VAP. The maximal duration of treatment is 14 days. Subjects will receive their study therapy by study center personnel while in the hospital.

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

[redacted]

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 recorded at scheduled visits (EOT and TOC) 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 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 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 microbiological Intent-To-Treat (micro-ITT) analysis set. The proportion of subjects with clinical cure for the micro-ITT analysis set is defined as the number of subjects with clinical cure at TOC divided by the number of subjects in the micro-ITT 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 TOC in the ME analysis set;
- Proportion of subjects with clinical cure at the EOT in the micro-ITT and ME analysis sets;

- Proportion of subjects with a favorable (defined as eradication or presumed eradication) per-subject microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets;

- Proportion of subjects with favorable (defined as eradication or presumed eradication) per-pathogen microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets;

- Propo1tion of subjects who died on or before 28 days after randomization in the ITT and micro-ITT analysis sets;

- Safety and tolerability as assessed by adverse events, physical examination, vital signs, ECGs, and laborato1y assessments.

3.3. Exploratory Endpoints

The explorato1y outcome measures are:

- PK of aztreonam and avibactam in subjects in the population PK analysis set.

- PK/PD relationship between exposure and clinical and microbiological response for ATM-AVI in the population PK analysis set.

- Propo1tion 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 intensive care unit (ICU) stay (days);

  - TransfeITed to the ICU (Yes/No);

  - Length of study treatment (days);

  - Mechanical ventilation for *HAPN* AP subjects (Yes/No);

  - 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]

[redacted]

3.4. Baseline Variables

3.4.1. Baseline Clinical Laboratory and Vital Signs

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

3.4.2. Baseline Microbiology

Culture, identification, and determination of the MBL status of pathogens, isolated from adequate specimens, is performed at the local laboratory. All pathogens will then be sent to the central laboratory for confirmation of identification and, where appropriate, MBL status. If there is a discrepancy between the local and central lab identification/results, the central lab results will be used in the microbiological analyses. Local lab results will only be used in microbiological analyses if there are no central lab results available.

Baseline Pathogens are defined as those obtained from adequate specimens closest (and prior) to the start of study treatment. 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. However, this does not apply when the specimen that yields no pathogens closest to study treatment start is blood; any pathogens resulting from blood obtained in the 5 days prior to study treatment start will be considered baseline pathogens.

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

Collection of intra-abdominal specimen (for cIAI subjects only)

Subject must have an adequate specimen for culture obtained from an abdominal source (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) during a surgical intervention within 5 days prior to screening from which a study-qualifying pathogen was isolated. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery.

Additional specimens will be collected, as clinically appropriate, in the event of repeat surgical procedures prior to the start of study treatment.

Collection of respiratory specimen (for HAP/VAP subjects only)

Subjects must have an adequate respiratory specimen obtained within 5 days prior to screening for Gram stain and culture from which a study-qualifying pathogen was isolated. Acceptable respiratory specimens from ventilated patients include endotracheal aspirate, Bronchoalveolar lavage (BAL), Mini BAL, or Protected-Specimen Brush (PSB) sample. Acceptable respiratory specimens from non-ventilated patients include expectorated or induced sputum, Bronchoalveolar lavage (BAL), Mini BAL, or Protected-Specimen Brush (PSB) sample. Expectorated or induced sputum specimen Gram stain must show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Low Power Field (LPF) to be suitable.

For subjects with HAP, repeat respiratory specimens are not required at Visit 2 (Baseline), unless a study-qualifying respiratory sample was obtained from a non-ventilated subject and the subject is subsequently ventilated (or the subject had a bronchoscopy). In this case, a repeat adequate respiratory specimen should be obtained prior to the first dose of study treatment.

Collection of Blood (for all subjects)

Subjects with BSI must have an adequate blood specimen obtained within 5 days prior to screening that contained a study-qualifying pathogen upon culture.

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 taken at Visit 2 (Baseline) prior to first dose of study treatment if blood cultures are not available within 48 hours prior to randomization.

Collection of Urine Specimen (for cUTI subjects only)

Subjects must have an adequate specimen of urine for culture collected within 5 days prior to screening, that contained $\geq 10^5$ CFU/mL of a study-qualifying pathogen upon culture. Another adequate specimen of urine must be obtained for culture at Visit 2 (Baseline) prior to the first dose of study treatment.

3.5. Stratification Variables

Randomization will be stratified based on infectious disease type (cIAI, HAP/VAP, cUTI, and BSI).

3.6. 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.

3.6.1. 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.

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 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 selected secondary and exploratory objectives. The ITT analysis set will also be used to evaluate the primary objective, if the ITT and micro-ITT analysis sets differ.

4.1.2. 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 MBL-positive Gram-negative baseline pathogen from an adequate specimen at the start of study treatment. The following scenarios would result in subjects being excluded from the micro-ITT population and included in the ITT population only:

1. Subjects with inherently resistant pathogens (for example, monomicrobial infections due to any *Acinetobacter* spp.);

2. Subjects with an MBL-producing pathogen obtained from an adequate study-qualifying specimen prior to screening which was not present in the repeat (if applicable) adequately obtained specimens closest (and prior) to the start of study therapy.

The determination of subjects' baseline pathogens and inclusion/exclusion status for the micro-ITT analysis set will be decided by the study team. In their review, the study team will also take into account the adequacy of any specimens prior to the start of study treatment.

Subjects in the micro-ITT analysis set will be analyzed according the treatment to which they are randomized. The micro-ITT analysis set is the primary analysis set used to evaluate the primary objective. It will also be used to evaluate secondary and exploratory objectives.

4.1.3. Microbiologically Evaluable (ME) Analysis Set

The Microbiologically Evaluable (ME) analysis set is defined as all subjects who:

- Met the definition of the micro-ITT analysis set;

- Received at least 48 hours of study therapy (ATM-AVI or BAT) or received <48 hours of study therapy before discontinuing study drug due to an AE;

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

- Had the baseline entry organism(s) genetically confirmed by central microbiological testing. (If the subject had an MBL-producing isolate based on local laboratory results, which could not be confirmed by the central lab, the subject is excluded from the ME analysis set. However, for the situation where the central lab is unable to confirm (eg, isolate is lost or damaged), the subject would be included in the ME analysis set, based on the local lab results);

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

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 objectives.

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. Subjects in the safety analysis sets will be analyzed according to the treatment they receive.

[redacted]

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. All analyses will be descriptive.

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.

[redacted]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Primary Analysis

The primary descriptive efficacy analysis will be the estimate of the clinical cure rate and 95% confidence interval (CI) in each treatment arm (ATM-AVI and BAT) in the micro-ITT analysis set. Single arm CIs will be computed using Jeffrey's method (Brown et al. 2001; Cai 2005).[1,2] 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 micro-ITT set at the TOC visit.

The primary descriptive analysis will be conducted using the clinical response assessment determined by the blinded independent adjudication committee. The investigator's assessment of clinical response will also be summarized in the micro-ITT analysis set 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 primary analysis.

6.1.2. Sensitivity/Robustness Analyses

An analysis of the Investigator's assessment of clinical response in the micro-ITT analysis set at the TOC visit will be performed as a sensitivity analysis.

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

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 EOT and TOC visits by differing analysis sets [eg, ME], proportion of subjects with favorable microbiological response, and those who died on or before 28 days after randomization [overall and by infection type], etc) will be assessed and presented similar to the primary endpoint.

For the Safety analyses, please see Section 6.6.

[redacted]

6.3. Exploratory Endpoints

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

Health resource utilization data will be summarized by treatment aim, 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 (days) of ICU stay, transfer to ICU, length of study treatment (calendai·and 24-hour days; see Section 6.6.7), mechanical ventilation (and length if needed) for *HAPN*AP subjects, and unplanned surgical intervention for cIAI subjects. Health resource utilization variables will also be summarized by clinical response at TOC (success/cure and failure). Descriptive statistics (number, mean, standai·d 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 propo1iion of hospital re-admissions) assessment will be included in these analyses. In addition, except for hospitalization (all patients 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 calendai·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/dischai·ge 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 similai·ly. These length of stay/duration vai·iables will be summarized with and without patients who died to evaluate the impact of the duration vai·iables for patients who died on the overall assessment of these vai·iables.

CCI [redacted]

6.3.1. Pharmacokinetic Analyses

Aztreonam and avibactam plasma concentrations versus time will be depicted graphically in the Clinical Study Repo1i (CSR). The final phaimacokinetic data will be pooled with data from other studies to conduct a population phaimacokinetic analysis (using Nonlineai·Mixed Effects (NLME) Modelling. Using these pai·ameter estimates (mean phannacokinetic pai·ameters including inter individual vai·iance estimates), Monte-Cai-losimulation will be unde1iaken and potential phaimacokinetic/phaimacodynamic relationships will be explored. Full details of the phaimacokinetic and phaimacokinetic/phannacodynamic analysis will be given in the Population Phaimacokinetic Modeling Analysis Plan (PMAP). These results

[redacted]

will be reported separately in a Population Pharmacokinetic Modeling Analysis Report (PMAR).

6.4. Subset Analyses

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

- Infection type (cIAI, HAP [overall and for VAP and non-VAP], cUTI, BSI);
- Resistance group. Resistance groups will include: aztreonam-non-susceptible, meropenem-non-susceptible isolates and isolates producing ESBLs (eg., CTX-M), serine carbapenemases (eg, KPC), and MBL subclassification (eg, VIM, NDM, IMP);
- 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);
- Baseline APACHE II score category (≤10 or >10) based on the data collected from the eCRF;
- For cUTI patients: acute pyelonephritis or complicated lower UTI;
- Monomicrobial vs polymicrobial infections at baseline;
- Geographic region (Western Europe; Eastern Europe; China; RoW);

Further analyses for regions (eg, Asian, or other regions) and countries (eg, 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 (eg, concomitant aminoglycoside use).

6.5. Baseline and Other Summaries and Analyses

Baseline variables are defined as outlined in Section 3.4.

Demographic and baseline characteristics, including age, gender, height, weight, primary diagnosis, complicating factors for cUTI, mechanical ventilation status (for HAP/VAP patients) 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 and by pathogen type (*Enterobacteriaceae*, other Gram-negative pathogens, Gram-positive aerobes etc.), MBL-status (positive/negative), and MBL subclassification (eg, VIM, NDM, IMP). 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, urine or blood) may be performed. The susceptibility profile of baseline pathogens and MIC frequency distributions of 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.

6.6. 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.

6.6.1. 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, and SAEs will be summarized for the full study period using the safety analysis set.

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

6.6.2. 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.

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.

6.6.3. 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. The vital signs data will also be listed.

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

6.6.4. 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.

6.6.5. 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. All the physical examination data will be listed.

6.6.6. Detailed Infection-related Focused Physical Examination

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

[redacted]

6.6.7. 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.

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, BAT) 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 defined in Section 6.4).

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.

[redacted]

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.

[redacted]

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
AVI	Avibactam
BAL	Bronchoalveolar lavage
BAT	Best Available Therapy
BP	Blood Pressure
BPM	Beats Per Minute
BSI	Bloodstream Infection
CAC	Clinical Adjudication Charter
CDARS	Clinical Data Analysis and Reporting System
cIAI	Complicated intra-abdominal infection
CI	Confidence interval
CORD	Clinical Oversight Review Dashboard
CrCl	Creatinine clearance
CSR	Clinical Study Report
cUTI	Complicated Urinary Tract Infection
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	Multidrug resistant
ME	Microbiologically Evaluable

[redacted]

MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
Micro-ITT	Microbiological Intent-To-Treat
N/A	Not applicable
NLME	Nonlinear Mixed Effects Modelling
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
VAP	Ventilator-associated pneumonia
VCAS	Virtual Clinical Adjudication System

Appendix 2. Table 2: Summary of Efficacy Analyses

EndpointN ariable	Analysis Set	Statistical Method	Timepoint	Objective
Clinical Cure (as assessed by the Adjudication Committee)	micro-ITT	Summa1y of Proportion 95% CI for Treatment Group	TOC	Primaiy Endpoint
Clinical Cure as assessed by the Investigator	micro-ITT	Summa1y of Propo1tion 95% CI for Treatment Group	TOC	Sensitivity/Suppo1tive Analysis
Clinical Cure where all deaths ai·e considered failures	micro-ITT	Summa1y of Propo1tion 95% CI for Treatment Group	TOC	Sensitivity/Suppo1tive Analysis
Clinical Cure	ITT,ME	Summa1y of Propo1tion 95% CI for Treatment Group	TOC	Secondaiy Endpoint
Clinical Cure	micro-ITT, ITT, and ME	Summa1y of Propo1tion 95% CI for Treatment Group	EOT	Secondaiy Endpoint
Clinical Cure by Infection Type	micro-ITT and ME	Summa1y of Propo1tion 95% CI for Treatment Group	EOT, TOC	Secondaiy/Key Subset Analysis
Clinical Cure by Resistance group. Resistance groups will include: aztreonam-non-susceptible, meropenem-non-susceptible isolates, and isolates producing ESBLs (eg, CTX-M), serine carbapenemases (eg, KPC), and MBL subclassification (eg, VIM, NDM, IMP)	micro-ITT	Summa1y of Propo1tion	EOT, TOC	Secondaiy/Key Subset Analysis

Subjects with favorable per-subject microbiological response	micro-ITT and ME	Summa1y of Proportion	TOC andEOT	Secondaiy Endpoint
Subjects with favorable per-pathogen microbiological response	micro-ITT and ME	Summa1y of Propo1tion	TOC andEOT	Secondaiy Endpoint
Death (overall and by infection type)	ITT and micro-ITT	Summa1y of Propo1tion 95% CI for Treatment Group	On or before 28 days after randomization	Secondaiy Endpoint
Death	ITT and micro-ITT	Summa1y of Propo1tion	On or before 14 days after randomization	Explorato1y Endpoint
Health Utilization	ITT	Summaiy	UptoTOC (LFU for hospital readmissions)	Explorato1y Endpoint
Health Utilization by Clinical Response (Cure/Failure)	ITT	Summaiy	UptoTOC (LFU for hospital readmissions)	Explorato1y Endpoint

[redacted]

Appendix 3. Criteria for Potentially Clinically Significant Lab Results

Table 3: 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 4: 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 5: 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.