Revised Clinical Study Protocol

Drug Substance Ceftazidime-Avibactam (CAZ-AVI)

Study Code D4280C00001

Edition Number 1

Date

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults

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Date

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of Local Amendment
1			
2			

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

is responsible for all aspects of study management, monitoring, medical monitoring, data management, statistical analysis, and report writing under supervision of AstraZeneca as documented in the relevant agreements between and AstraZeneca.

PROTOCOL SYNOPSIS

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ-AVI) Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults

International Coordinating Investigator

Study centers and number of patients planned

This will be a multicenter study enrolling approximately 1106 hospitalized patients (18 to 90 years of age, inclusive) with a presumed (pre-operative) or definitive (intra-operative or postoperative) diagnosis of complicated intra-abdominal infection (cIAI).

Study period	Phase of development
Estimated date of first patient enrolled	Phase III
Estimated date of last patient completed	Phase III

Objectives

Primary objective

- To assess the noninferiority of ceftazidime-avibactam (CAZ-AVI) plus metronidazole compared to meropenem with respect to clinical cure at Test-of-Cure (TOC) visit in patients who have at least 1 identified pathogen.

Secondary objectives

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at TOC in patients who are microbiologically evaluable (ME)

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at End of Treatment (EOT) with intravenous (IV) therapy, and at Late Follow-Up (LFU) both in patients who have at least 1 identified pathogen and in patients who are ME

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at EOT, TOC, and LFU in patients who are clinically evaluable (CE)

- To determine the per-patient and per-pathogen microbiologic response of CAZ-AVI plus metronidazole compared to meropenem at EOT, TOC, and LFU both in patients who have at least 1 identified pathogen and in patients who are ME

- To evaluate the efficacy of CAZ-AVI plus metronidazole versus meropenem in pathogens resistant to ceftazidime

- To compare the time to first defervescence of CAZ-AVI plus metronidazole versus meropenem in patients who are on IV study therapy and who have fever at study entry both in patients who are CE and in patients who are ME

- To evaluate the safety and tolerability profile of CAZ-AVI plus metronidazole compared to meropenem in the treatment of patients with cIAIs in the safety analysis set

- To evaluate the pharmacokinetics of the individual components of CAZ-AVI (avibactam and ceftazidime) in patients with cIAIs

- To evaluate CAZ-AVI exposure and the antimicrobial response relationship in patients with cIAIs.

Exploratory objectives

- To explore the timing of the resolution of signs and symptoms associated with cIAIs for patients receiving CAZ-AVI plus metronidazole versus meropenem

- To assess the consequence of first-line treatment failure in the treatment of patients with cIAIs as defined by the health utilization variables. The results of this analysis will not be included in the clinical study report (CSR) for this study.

Study design

This is a prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of CAZ-AVI plus metronidazole versus meropenem in the treatment of adults with cIAIs, defined as infections that require surgical intervention and extend beyond the hollow viscus into the peritoneal space. The minimum duration of treatment with IV study therapy is 5 full days (15 doses) (including any doses taken before or during surgery if applicable) for patients with normal

renal function or mild renal impairment and the maximum duration of treatment with IV study therapy is 14 full days, where a full day is defined as a 24-hour period. Each patient is expected to complete the study, including LFU, within approximately 7 weeks. The entire study duration is expected to be approximately 23 months. Those patients who remain on IV study therapy after 5 days (15 doses) will receive their IV study therapy by study center personnel while in the hospital or qualified health care provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT, TOC, and LFU visits following discharge from the hospital.

Approximately 1106 hospitalized patients (18 to 90 years of age, inclusive) with a presumed (preoperative) or definitive (intra-operative or postoperative) diagnosis of cIAI will be enrolled. The diagnosis of infection will be based on the patient's clinical syndrome and intra-operative findings, including intra-operative cultures. Operative intervention includes open laparotomy, laparoscopic procedures, and percutaneous drainage procedures. All patients will undergo a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study therapy.

After obtaining written informed consent and confirming eligibility, patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule. Patients will be stratified by baseline severity of disease (Acute Physiology and Chronic Health Evaluation II [APACHE II] score [Knaus et al 1985]; levels: ≤10 or >10 to ≤30 [see Appendix F]) and by region (North America and Western Europe, Eastern Europe, and the rest of the world). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to 25% of the study population.

Study periods are defined in the following table.

Study periods

Eligibility/Screening period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0
Treatment period	
Visit 2 (Baseline/Randomization)	Day 1
Visits 3 to 15 (Days 2 to 14)	On therapy
Visit 16 (End of Treatment [EOT] with IV therapy)	Within 24 hours after the completion of the last infusion of IV study therapy
Follow-up period	
Visit 17 (Test of Cure [TOC])	Day 28 visit[a]
Visit 18 (Late Follow-Up [LFU])	Day 42 visit[b]

[a] If it is not possible to perform the TOC visit on Day 28 (eg, the patient is on holiday), the allowed visit window is Day 28 to 35.

[b] If it is not possible to perform the LFU visit on Day 42 (eg, the patient is on holiday), the allowed visit window is Day 42 to 49.

Abbreviation: IV, intravenous.

Target patient population

Approximately 1106 (553 per treatment group) hospitalized patients (18 years of age to 90 years of age, inclusive) with a presumed (preoperative) or definitive (intra-operative or postoperative) diagnosis of cIAI will be enrolled in the study.

Investigational product (CAZ-AVI plus metronidazole), dosage, and mode of administration

Patients randomized to receive CAZ-AVI will receive meropenem placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 30 minutes, immediately followed by CAZ-AVI (500 mg of avibactam and 2000 mg of ceftazidime) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes, immediately followed by metronidazole (500 mg) administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes. In patients with normal renal function and patients with mild renal impairment, treatments will be repeated every 8 hours (±30 minutes); dose regimen adjustments for patients with moderately impaired renal function are described in Section 5.5.2.2. Details for administration of CAZ-AVI, metronidazole, and meropenem placebo can be found in the handling instructions document.

Comparator (meropenem), dosage, and mode of administration

Patients randomized to receive the comparator will receive meropenem (1000 mg) administered by IV infusion in a volume of 100 mL at a constant rate over 30 minutes, immediately followed by CAZ-AVI placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes, immediately followed by metronidazole placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes. In patients with normal renal function and patients with mild renal impairment, treatments will be repeated every 8 hours (±30 minutes); dose regimen adjustments for patients with moderately impaired renal function are described in Section 5.5.2.2. Details for administration of meropenem, CAZ-AVI placebo, and metronidazole placebo can be found in the handling instructions document.

Duration of treatment

Intravenous study therapy will be continued for a period of time (minimum 5 full days; maximum 14 full days) deemed appropriate by the investigator based upon fever and other signs and symptoms that demonstrate clear evidence of local and systemic improvement. After 5 full days of IV study therapy and at the discretion of the investigator, all study therapies may then be discontinued if the patient has shown clinical improvement such that no further antimicrobials are required (see Section 3.1).

Outcome variables:

- Primary efficacy variable

The primary efficacy outcome variable is the proportion of patients with clinical cure at the TOC visit in the microbiological modified intent-to-treat (mMITT) analysis set.

- Secondary efficacy variables

  The secondary efficacy outcome variables include the following:

  – Proportion of patients with clinical cure at the TOC visit in the ME and extended ME analysis sets

  – Proportion of patients with clinical cure at the EOT and LFU visits in the mMITT, ME, and extended ME analysis sets

  – Proportion of patients with clinical cure at EOT, TOC, and LFU in the CE analysis set

  – Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

  – Proportion of favorable per-pathogen microbiological response at the EOT, TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

  – Favorable per-pathogen microbiologic response at the EOT, TOC, and LFU visits by minimum inhibitory concentration (MIC) categories in the mMITT, ME, and extended ME analysis sets

  – Favorable per-patient clinical response and favorable per-patient microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME, and extended ME analysis sets

  – Proportion of patients with a favorable per-pathogen microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME, and extended ME analysis sets

  – Time to first defervescence while on IV study therapy in the CE, ME, and extended ME analysis sets for patients who have fever at study entry.

- Safety and tolerability

  Safety and tolerability will be assessed by the incidence and severity of adverse events (AEs) and serious AEs (SAEs), exposure, mortality, reasons for discontinuations of IV study therapy and study, vital sign measurements (blood pressure and heart rate), physical examination findings, 12-lead ECG parameters

(QRS, RR interval, heart rate, QT interval [QT], corrected QT (QTc) interval using Bazett formula [QTcB] and Fridericia formula [QTcF]), and clinically important changes in clinical chemistry, hematology, and urinalysis laboratory values.

- Pharmacokinetics

  Avibactam and ceftazidime compartmental pharmacokinetic (PK) parameters derived from population PK analysis, and potential PK/pharmacodynamic (PD) relationships will be reported separately. Summary statistics of ceftazidime and avibactam plasma concentrations at specified sampling windows will be reported in the CSR.

- Exploratory variables

  – Signs and symptoms associated with cIAIs at recorded time points

  Exploratory health utilization variables (to be reported outside of the CSR) include the following:

  – Length of hospital stay

  – Length of intensive care unit stay and/or transfer to the intensive care unit

  – Length of IV therapy

  – Mortality caused by cIAIs (up to the LFU visit).

Statistical methods

The primary efficacy objective will be to assess the noninferiority of CAZ-AVI plus metronidazole compared to meropenem with respect to the proportion of patients with clinical cure at the TOC visit. The primary efficacy outcome variable will be assessed in the mMITT analysis set. Additional analysis sets are defined for the secondary efficacy outcome variables and for the safety analysis.

- **Microbiological modified intent-to-treat analysis set**

  The mMITT analysis set includes all patients who:

  – Met the disease definition of cIAI and have at least 1 Gram negative pathogen identified at study entry (regardless of isolate susceptibilities). Patients with a bacterial species typically not expected to respond to both study drugs (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.) will be excluded.

- **Clinically evaluable analysis set at the EOT, TOC, and LFU visits (see clinical response assessment table, Section 6.3.1)**

The CE analysis set at the EOT, TOC, and LFU visits, respectively, includes all patients meeting the following criteria:

- Had an appropriate diagnosis of cIAI. As an exception, patients with a bacterial species typically not expected to respond to both study drugs (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.) will be excluded.
- **EITHER**
  - Received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered

  OR
  - Received therapy <48 hours before discontinuing treatment due to an AE.
- Was evaluated at the EOT, TOC, or LFU visit with a clinical response of cure or failure.
- Had no important protocol deviations that would affect the assessment of efficacy.
- Did not receive any prior antibiotic therapy other than the protocol allowed antibiotics with specified duration in Section 4.2 exclusion criterion 17.
- Did not receive concomitant antibiotic therapy with potential activity against any of the baseline pathogens between the time of randomization and the time of the EOT, TOC, or LFU culture, respectively, except for protocol allowed antibiotics for the coverage of *Enterococcus* spp. and methicillin-resistant *Staphylococcus aureus*. This does not include patients who have failed and require additional antibiotic therapy. Topical antibacterials and antifungals are permitted except that they may not be applied to the surgical site.
- Considered to have had adequate initial infection source control.

- **Microbiologically evaluable analysis set at the EOT, TOC, and LFU visits**

The ME analysis set at the EOT, TOC, and LFU visits includes all patients meeting the following criteria:

- Included in a subset of CE patients at EOT, TOC, and LFU, respectively
- Had at least 1 Gram negative pathogen in the initial/prestudy culture that is susceptible to both study agents

- **Extended microbiologically evaluable analysis set at the EOT, TOC, and LFU visits**

  The extended ME analysis set at the EOT, TOC, and LFU visits includes all patients meeting the following criteria:

  – Included in a subset of CE patients in EOT, TOC, or LFU, respectively.

  – Had at least 1 Gram negative pathogen in the initial/prestudy culture regardless of susceptibility.

- **Safety analysis set**

  The safety analysis set will include all patients who received any amount of IV study therapy.

- **PK analysis set**

  The PK analysis set will include all patients who had at least 1 plasma concentration data value available for either ceftazidime or avibactam.

Synthesis of historical trials has indicated that a 12.5% margin is appropriate for assessment of noninferiority in cIAI trials; however, there are regional variations in the regulatory requirements for noninferiority trials. In order to meet these requirements globally this trial has been sized to provide 90% power for a 10% noninferiority margin, required in some regions (therefore providing >95% power to assess noninferiority using a 12.5% margin). Assuming that both treatments have an underlying clinical cure rate of 70% in the mMITT analysis set, in order to provide 90% power for a 10% noninferiority margin using the lower limit of a 2-sided 95% confidence interval (CI), 442 randomized patients per treatment group will be needed for the mMITT analysis set. Assuming that 80% of the randomly assigned patients will be included in the mMITT analysis set, 553 randomized patients per treatment group based on the mMITT rate will be needed. Consequently, a total of approximately 1106 eligible patients will be randomized in the study. The sample size was calculated using nQuery® version 7 (Statistical Solutions Ltd Cork, Ireland) using the Newcombe-Wilson (Newcombe 1998) score method (uncorrected).

For the primary efficacy outcome variable, a 2-sided 95% CI for the observed difference in the proportion of patients with the clinical cure between CAZ-AVI plus metronidazole and meropenem will be calculated. The unstratified method of Miettinen and Nurminen (Miettinen and Nurminen 1985) will be applied to calculate the 2-sided 95% CI for the observed difference in the proportions. The sponsor will conclude noninferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) is greater than –12.5%, however, noninferiority may be assessed using a 10% margin in regions where this is a regulatory requirement. A sensitivity analysis stratified by the prespecified stratification factors will also be performed for the primary outcome variable in the mMITT analysis set. The stratification factors are baseline severity of disease (APACHE II score; levels: ≤10 or

>10 to ≤30) and region (North America and Western Europe, Eastern Europe, and the rest of the world). The analysis for clinical cure at TOC will also be performed and presented by subgroups according to baseline characteristics in the mMITT analysis set. The subgroups to be analyzed will include, but not be limited to, baseline severity of disease, primary site of infection, the diagnosis of perforated appendix/appendiceal abscess, infectious process, initial operative procedure, baseline postoperative and nonpostoperative infections, prior antibiotic use, monomicrobial or polymicrobial infection, baseline pathogens, age, sex, race, and region.

Secondary efficacy outcome variables considering proportions will be analyzed by determining 2-sided 95% CIs for the observed difference in the outcome proportion between CAZ-AVI plus metronidazole and meropenem (using the unstratified Miettinen and Nurminen method as described for the primary outcome variable). For time to event secondary variables, treatment groups will be compared using a log-rank test. Also, the median time to event will be calculated using the Kaplan-Meier approach. Analyses of baseline characteristics, health utilization variables, and safety outcomes will be summarized using descriptive statistics or frequency counts in tables, listings, and figures as appropriate. With the exception of microbiological cultures, baseline will be defined as the last nonmissing assessment before the start of IV study therapy. For microbiologic cultures the initial culture (required at time of surgical intervention) will be defined as baseline.

Clinical cure, per-patient microbiological response, and per-pathogen microbiological response will be presented by treatment group for patients infected by ceftazidime-resistant pathogens. Per-pathogen microbiological response will be presented by MIC in the CAZ-AVI treatment group. This will also be undertaken for the meropenem treatment group as a reference.

Pharmacokinetic analysis

Descriptive statistics of individual plasma concentrations for ceftazidime and avibactam will be summarized and listed according to the nominal sampling windows after dosing for the PK analysis set and will be reported in the CSR. Ceftazidime and avibactam compartmental PK parameters derived from population PK analysis and potential PK/PD relationships will be reported separately. Individual compartmental PK parameters of avibactam and ceftazidime for cIAI patients will be derived via a population modeling approach.

The avibactam and ceftazidime concentration, patient demographic, and disease status data, will be combined with the data from appropriate clinical studies for the population PK analysis. Individual compartmental PK parameters for patients with avibactam and ceftazidime plasma concentration data available will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, such as maximum concentration (C_{max}), minimum concentration, area under the plasma concentration-time curve at steady state, and terminal half-life will be derived from the predicted avibactam and ceftazidime concentration time courses. The appropriate avibactam and ceftazidime exposure outcome variables predicted by the population PK modeling will be used for a PK/PD modeling for appropriate microbiological or clinical cure outcome variables.

Safety and tolerability analysis

The safety analysis will be performed using the safety analysis set. Safety parameters include AEs, clinical laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses. No inference will be made for safety analysis. Throughout the safety results sections, erroneously treated patients (eg, those randomized to treatment CAZ-AVI plus metronidazole but actually received meropenem) will be accounted for in the actual treatment received group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this clinical study protocol.

Abbreviation /special term	Explanation
β-hCG	β-human chorionic gonadotrophin
%T	Percentage of time above a threshold concentration
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
BP	Blood pressure
CAZ-AVI	Ceftazidime-avibactam
CE	Clinically evaluable
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CLSI	Clinical Laboratory Standards Institute
C_{max}	Maximum concentration
CrCl	Creatinine clearance
CSA	Clinical study agreement
CSR	Clinical study report
C_T	Threshold concentration
cUTI	Complicated urinary tract infection
DNA	Deoxyribonucleic acid
EC	Ethics committee, synonymous to institutional review board and independent ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of Treatment
eRT	eResearch Technology, Inc
ESBL	Extended-spectrum β-lactamase
FU	Follow-up
GCP	Good Clinical Practice

Abbreviation /special term	Explanation
HHC	Home health care
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KPC	*Klebsiella pneumoniae* carbapenemase
LFU	Late Follow-Up (Day 42 visit [allowed visit window: Day 42 to 49])
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MIC50	Minimum inhibitory concentration to inhibit the growth of 50% of organisms
MIC90	Minimum inhibitory concentration to inhibit the growth of 90% of organisms
mMITT	Microbiological modified intent to treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
OAE	Other significant adverse event (see definition in Section 11.2.1)
PD	Pharmacodynamic
PK	Pharmacokinetic
PTA	Probability of target attainment
QT	QT interval
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett formula
QTcF	Corrected QT interval using Fridericia formula
RR	Respiratory rate
SAE	Serious adverse event (see definition in Section 6.4.2)
spp.	Species
SRP	Surgical review panel
TOC	Test of Cure (Day 28 visit [allowed visit window=Day 28 to 35])
ULN	Upper limit of normal

1. INTRODUCTION

1.1 Background

1.1.1 Complicated intra-abdominal infections

Complicated intra-abdominal infections (cIAIs) are local or systemic infections that occur as a result of a perforation in the gastrointestinal tract or by a necrotic gut wall spilling bacteria into the peritoneal space, leading to abscess formation and/or generalized peritonitis. These infections require operative intervention or percutaneous drainage in conjunction with broad-spectrum antibacterial therapy. Adequate surgical source control is critical to successful treatment of intra-abdominal infections. Other important determinants of outcome include age, nutritional status, underlying comorbidities (eg, cardiovascular disease, diabetes, and malignancy), severity and extent of infection, and in particular Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Knaus et al 1985) (Mazuski et al 2002, Solomkin et al 2010). Almost all intra-abdominal infections are polymicrobial and are caused by organisms from the gastrointestinal tract, including aerobes and facultative and obligate anaerobes. Enterobacteriaceae are isolated most commonly.

The 2002 Guidelines from the Therapeutic Agents committee of the Surgical Infection Society (Mazuski et al 2002) and the 2010 Guidelines of the Infectious Diseases Society of America (Solomkin et al 2010) recommend broad-spectrum single agent (β-lactam/β-lactamase inhibitor, carbapenem) or combination therapy regimens (metronidazole plus cephalosporin or aztreonam or fluoroquinolone). Specific regimens are recommended for higher risk patients with severe or postoperative nosocomial intra-abdominal infections where resistant pathogens such as *Enterococcus* species (spp.) or *Pseudomonas* spp. may occur. Initial empiric therapy is critical because inappropriate treatment may be associated with delays in clinical response, increases in hospital stay, and an increased risk of mortality (Barie et al 2005, Krobot et al 2004).

1.1.2 Multidrug resistance

The prevalence of multidrug-resistance (resistance to at least 3 different antibiotic groups) strains among Gram-negative bacilli is increasing (D'Agata 2004, Gales et al 2001, Karlowsky et al 2003a, Karlowsky et al 2003b). Compared with infections due to antimicrobial-susceptible Gram-negative bacilli, infections due to multidrug-resistant Gram-negative bacilli lead to longer hospital stays, increased mortality, and greater costs of hospitalization (Cosgrove et al 2002, Giske et al 2008).

Resistance to β-lactam drugs in Gram-negative bacteria is most commonly attributed to β-lactamase production, either chromosomally or plasmid borne. Chromosomally mediated β-lactamase (Ambler Class C) production is mainly through expression of the *ampC* gene, which is either constitutive or inducible and is found among the Enterobacteriaceae and *Pseudomonas aeruginosa* (Jacoby 2009). Class C β-lactamases are resistant to marketed β-lactamase inhibitors (clavulanic acid, tazobactam, and sulbactam). In *Enterobacter* spp., the

expression of the *ampC* gene is repressed, but genetically stable derepressed variants can be selected by β-lactams, particularly third-generation cephalosporins. These mutants are resistant to most β-lactam antibiotics except carbapenems (Fraser et al 2010).

Serratia spp., *Morganella* spp., *Providencia* spp., *Enterobacter* spp., *Citrobacter freundii*, and *P. aeruginosa* have similar although not identical, chromosomal *ampC* β-lactamase genes that are inducible (Fraser et al 2010, Jacoby 2009). Plasmid-encoded *ampC* enzymes have been reported from *Klebsiella* spp. and *Escherichia coli* isolates. Ampicillin, amoxicillin, first- and second-generation cephalosporins, and cephamycins are strong *ampC* β-lactamase inducers. They are also rapidly inactivated by these β-lactamases; thus, resistance is readily documented in vitro (Fraser et al 2010).

1.1.3 Extended-spectrum β-lactamases

The most common of the β-lactamase-mediated mechanisms of resistance to β-lactam antibiotics among Gram-negative pathogens is that of extended-spectrum β-lactamases (ESBLs). These enzymes are plasmid-mediated β-lactamases of predominantly Ambler Class A. Extended-spectrum β–lactamases represent a major group of β-lactamases that are now found in a significant percentage of *E. coli*, *Klebsiella pneumoniae*, and other species of Enterobacteriaceae including *Enterobacter* spp., *Citrobacter* spp., *Proteus* spp., *Morganella morganii*, *Serratia marcescens*, and *Shigella dysenteriae*. They are also found in *P. aeruginosa* and *Burkholderia cepacia* (Bush 2001, Ambler et al 1991). Extended-spectrum β-lactamase-producing bacteria often show cross-resistance to other groups of antibiotics such as fluoroquinolones, aminoglycosides, tetracyclines, and trimethoprim/sulfamethoxazole.

Extended-spectrum β-lactamases are capable of efficiently hydrolyzing penicillins, narrow-spectrum cephalosporins, many extended-spectrum cephalosporins, cephalosporins containing an oxyimino group (cefotaxime, ceftazidime), and monobactams (aztreonam). The majority of ESBL-producing organisms produce more than 1 β-lactamase and strains producing multiple ESBLs are being reported. Different strains vary in the actual amount of each β-lactamase produced (Go and Cunha 2004).

Infections due to ESBL-producing organisms present a major therapeutic dilemma, as the choice of antibiotics is extremely limited. Clinical outcome is poor when third–generation cephalosporins are used to treat ESBL-producing organisms. Bacteria producing ESBLs should be considered resistant to all generations of cephalosporins, all penicillins, and to the monobactams (aztreonam). Even though cefepime (a fourth-generation cephalosporin) exhibits more stability to hydrolysis by ESBLs than the third–generation cephalosporins, a positive clinical outcome from treatment with this antibiotic has not been established. (Rodrigues et al 2004, Jacoby 1999, Rice et al 1996, Thauvin-Eliopoulos et al 1997).

Carbapenems are the drugs of choice for the serious infections caused by ESBL-producing organisms. Carbapenems are the only reliable β-lactam drugs for the treatment of severe *Enterobacter* spp. infections. Resistance to carbapenems is rare but occurs in strains that produce serine-carbapenemases (*K. pneumoniae* carbapenemase [KPC] enzymes). Over the past decade a group of serine-carbapenemases has been increasingly reported from around the

world (Hirsch and Tam 2010). As one example of this observation, resistance has been reported for imipenem in strains of *Enterobacter cloacae* (Fraser et al 2010). Hyper-production (stable derepression) of *ampC* β-lactamases, in association with some decrease in permeability to the carbapenems, may also cause resistance to these agents. Carbapenems are strong *ampC* β-lactamase inducers but, so far, are not degraded by the action of these β-lactamases. Widespread use of carbapenems may lead to the emergence of carbapenem-resistant *Acinetobacter baumannii*, *P. aeruginosa*, *Stenotrophomonas maltophilia,* and vancomycin-resistant enterococci (Rodrigues et al 2004).

1.1.4 Ceftazidime-Avibactam

Avibactam is a novel, non-β-lactam, β-lactamase inhibitor with a spectrum of activity encompassing both Class A and Class C β-lactamases. Beta-lactamase inhibition is effected through the formation of a stable covalent carbamoyl linkage through the active site serine. Avibactam, when associated with ceftazidime, has also been shown to be active against strains that express a combination of β-lactamase types, as well as strains that are concomitantly resistant to other antibacterial classes such as fluoroquinolones.

Beta-lactamase inhibition by avibactam is effected through the formation of a stable covalent carbamoyl linkage to the enzyme complex that is practically irreversible. It inhibited Class A and Class C β-lactamases by 50% at lower concentrations than did other currently marketed β-lactamase inhibitors such as clavulanic acid, tazobactam, and sulbactam. In addition, avibactam is a potent inhibitor of Class C enzymes whereas clavulanic acid, tazobactam, and sulbactam lack any activity against this class of enzymes. Unlike currently available β-lactamase inhibitors, avibactam does not induce β–lactamase production.

Avibactam inhibited KPC-2 β-lactamase in vitro and restored ceftazidime susceptibility to Enterobacteriaceae harboring KPC-2 or KPC-3 β-lactamase (Stachyra et al 2009). The potent in vitro activity of the ceftazidime and avibactam combination against Enterobacteriaceae producing Class A, and more importantly Class C, β-lactamases has been confirmed in vivo in murine pneumonia, septicemia, and pyelonephritis models.

Currently the options for the treatment of Gram-negative infections, especially multidrug-resistant strains including ESBL producers, are extremely limited. Until recently, there have been no new investigational compounds under early or late development specifically targeted to combat these organisms. Hence availability and development of new agents to treat these infections will be a welcome addition to the existing treatments.

1.1.5 Human experience – Phase I

At the time of this protocol, 4 clinical pharmacology studies have been completed:

- A Phase I double-blind, placebo-controlled, escalating single-dose study with and without ceftazidime in healthy adult male subjects (Study NXL104/1001)

- A Phase I double-blind, placebo-controlled, multiple-dose study over 5 or 10 days with and without ceftazidime, intravenous and oral formulations, in healthy adult male subjects (Study NXL104/1002).

- A Phase I open-label, single-dose study to assess the effect of renal impairment on pharmacokinetic (PK) parameters in patients with varying degrees of renal insufficiency and in patients with end-stage renal failure on hemodialysis (Study NXL104/1003)

- A Phase I open-label, single-dose study to assess effect of age and gender in healthy young and elderly male and female subjects (Study NXL104/1004).

The Phase I studies completed to date have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly male and female subjects. The PK and tolerability of avibactam have also been determined in subjects with different degrees of renal impairment (Study NXL104/1003). The relationship between avibactam renal clearance and calculated creatinine clearance was found to be linear, consistent with the predominantly renal excretion of avibactam. Based on the data from Study NXL104/1003, dosage adjustments will be required in patients with moderate or severe renal impairment. Population PK and PK/pharmacodynamic (PD) modeling support adjustments in the dose amount and frequency of administration for ceftazidime-avibactam (CAZ-AVI) that are consistent with those already recommended for ceftazidime (see Section 5.5.2.2).

Additional details can be found in the CAZ-AVI Investigator's Brochure.

1.1.6 Human experience – Phase II

A prospective, multicenter, double-blind, randomized, 2 arms, parallel group (1:1) study in 203 patients between the ages of 18 and 88 years with a complicated intra-abdominal infection (cIAI) has been completed (Study NXL104/2002; Lucasti et al 2011). This study was designed to assess safety, tolerability, and efficacy of CAZ-AVI (2000 mg ceftazidime plus 500 mg avibactam intravenous (IV) every 8 hours over 30 minutes) plus metronidazole (500 mg IV every 8 hours over 60 minutes) versus meropenem (1000 mg IV every 8 hours over 30 minutes) in the treatment of cIAI. The primary objective of the study was to estimate the efficacy of CAZ-AVI plus metronidazole with respect to the clinical response in baseline microbiologically evaluable (ME) patients (ie, patients with at least 1 pathogen isolated that was susceptible to both study drugs) with cIAI at the Test of Cure (TOC) visit, 2 weeks posttreatment compared with meropenem. Similar clinical response rates were seen in both treatment groups for the primary endpoint; 91.2% in the CAZ-AVI plus metronidazole group and 93.4% in the meropenem group. The most common adverse events (AEs) reported (>7.5% incidence overall) were nausea, vomiting, pyrexia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased alkaline phosphatase. Discontinuations due to AEs were infrequent (3.4% overall) in both groups. Five deaths were reported in the study (3 in the CAZ-AVI plus metronidazole group and 2 in the meropenem

group); none were considered related to study drug. Clinically significant laboratory abnormalities occurred uncommonly, including abnormalities in liver enzymes.

A second Phase II study (Study NXL104/2001; Vasquez et al 2011) has been completed in patients with a complicated urinary tract infection (cUTI). The study was a multicenter, investigator-blinded, randomized, 2-arm, parallel-group (1:1) study to estimate the efficacy, safety, and tolerability of CAZ-AVI (500 mg ceftazidime/125 mg avibactam IV every 8 hours over 30 minutes) versus imipenem (imipenem cilastatin 500 mg IV every 6 hours over 30 minutes) in 137 patients between the ages of 18 and 90 years with a cUTI. Twenty-seven patients (39.1%) in the CAZ-AVI group and 35 (51.5%) in the imipenem group were ME (ie, had at least 1 pathogen isolated that was susceptible to both study drugs). The primary objective of the study was to estimate the efficacy of CAZ-AVI with respect to microbiological response in ME patients with cUTIs at the TOC visit (5 to 9 days posttreatment) compared with imipenem. Similar microbiological response rates were seen in both treatment groups; at the TOC visit, 19/27 patients (70.4%) in the CAZ-AVI group and 25/35 patients (71.4%) in the imipenem group had a favorable microbiological response (eradication). The most common AEs reported (overall incidence >7.5%) were headache, diarrhea, anxiety, and infusion site reaction. Discontinuations due to AEs were uncommon (2 patients in the CAZ-AVI group, none in the imipenem group). One death was reported in the study (in the imipenem group). Clinically significant laboratory abnormalities occurred uncommonly, including abnormalities in liver enzymes.

Additional details can be found in the CAZ-AVI Investigator's Brochure.

1.2 Research hypothesis

The following hypotheses will be assessed during this study:

- Intravenous CAZ-AVI plus metronidazole administered every 8 hours will demonstrate clinical efficacy comparable to IV meropenem administered every 8 hours as treatment for patients with cIAI.
- The safety and tolerability profile of CAZ-AVI administered intravenously is acceptable.

1.3 Rationale for conducting this study

Avibactam is a novel non-β-lactam, β-lactamase inhibitor with a spectrum of activity against Ambler Class A and Class C β-lactamases, including class A carbapenemases such as KPC. Avibactam is being developed as an IV antibiotic formulation in combination with ceftazidime for the treatment of patients with serious Gram-negative bacterial infections. The strategy of using β-lactam, β-lactamase inhibitor combinations has been successful against Class A β-lactamases in a variety of bacterial infections. Gram-negative pathogens, including those producing ESBLs and AmpC β-lactamases, are important causes of cIAIs. These infections are typically polymicrobial and involve anaerobes such as the *Bacteroides fragilis* group. The spectrum of activity of CAZ-AVI when combined with metronidazole is well

suited for the treatment of pathogens commonly responsible for cIAIs. The data from the Phase II Study NXL104/2002 support further investigation of CAZ-AVI for the treatment of hospitalized adults with cIAI (see Section 1.1.6).

Meropenem has been selected as the comparator because it has established efficacy against the Gram-negative and anaerobic pathogens isolated in cIAIs. Meropenem is approved for and has been used widely for the treatment of cIAIs, and carbapenems are among the drugs of choice against ESBL-producing Gram-negative pathogens, especially in serious infections.

This is a Phase III study of CAZ-AVI with metronidazole designed to evaluate the efficacy, safety, and tolerability compared to meropenem in cIAI.

1.4 Benefit/risk and ethical assessment

Patients enrolled into this clinical study will have cIAIs that are of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to patients participating in this study is that they will receive effective antibiotic therapy for their infection. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for cIAIs, in the face of the changing pattern of antibiotic resistance. It is possible that CAZ-AVI will not prove to be a sufficiently effective treatment for cIAIs (ie, not as effective as the comparator treatment). This risk is mitigated in that the study patients are closely monitored and will be managed with appropriate therapies as determined by the investigator who is providing treatment.

The risk considerations for this study should encompass the known and potential risks for the development product CAZ-AVI and its component products avibactam and ceftazidime, as well as the risks associated with other treatments that might be administered as described in this protocol. Other possible treatments include the marketed products metronidazole and meropenem. As the risks for the marketed products are widely available in their respective prescribing information, such risks will not be discussed in this section.

The risks for CAZ-AVI have not been fully elucidated; however it is assumed that known or potential risks for CAZ-AVI should include those identified in the clinical study experience with CAZ-AVI, avibactam alone, and for ceftazidime alone. Additional risk information for avibactam and CAZ-AVI are located in the CAZ-AVI Investigator's Brochure.

The full risk profile for ceftazidime is described in the prescribing information for the product (refer to local ceftazidime product labeling). Important risks as laid out in the warnings and precautions in product labeling for ceftazidime include:

- Hypersensitivity reactions. Though patients with hypersensitivity and serious allergic reactions to cephalosporins carbapenem or other β-lactam antibiotics are excluded from the trial, first-time episodes of such reactions could occur.

- Antibiotic-associated diarrhea, *Clostridium difficile* diarrhea, colitis, and pseudomembranous colitis

- Bacterial overgrowth with nonsusceptible organisms
- Distal necrosis as a result of inadvertent intra-arterial administration of ceftazidime
- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae such as tremor, myoclonus, seizures, encephalopathy, and coma.

Potential risks for CAZ-AVI include the occurrence of events seen with ceftazidime alone, but that go beyond the frequency and/or severity of those seen with ceftazidime. Local intolerance has been seen in the preclinical studies, and has been monitored in the clinical program. In the Phase I studies, erythema and hematoma at the administration site were reported. In the Phase II study (NXL104/2002) examining CAZ-AVI plus metronidazole versus meropenem as a comparator in cIAIs, approximately 30% of participants in both the CAZ-AVI and meropenem comparator treatment group experienced at least 1 symptom of local intolerability, with pain, erythema, swelling, and tenderness reported most frequently across both groups. The majority of infusion site events were mild. There was a somewhat greater percentage of patients with moderate/severe intensity in the CAZ-AVI group, who also received IV metronidazole (17/101 16.8%) versus the meropenem group (11/102 10.8%). Of note, patients in the CAZ-AVI plus metronidazole group received an infusion of 3 different agents per dose, while patients in the meropenem group received an infusion with 1 study drug per dose.

In regard to hypersensitivity reactions, there was 1 report in the CAZ-AVI clinical trials, where the clinical investigator considered the events of skin rash and elevated liver function tests to be a possible hypersensitivity reaction because of the temporal relationship of the events to drug administration. In the CAZ-AVI development program, rashes have been reported. Elevations of liver enzymes independent of skin rashes or other potential signs of hypersensitivity have also been reported.

In summary, the known and potential risks of receiving the developmental antibiotic combination CAZ-AVI are expected to be similar to those seen with ceftazidime and cephalosporins in general. Thus far, no unique risks have been identified for the avibactam component or the combination of ceftazidime and avibactam. The risks of the marketed antibiotics are considered acceptable. While it is anticipated that CAZ-AVI will have similar efficacy for the treatment of cIAIs, it is possible that efficacy will not be demonstrated. For each patient in the trial, appropriate treatment of the cIAI is determined by the clinical investigator, based on the clinical response of the patient.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is

- To assess the noninferiority of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at TOC visit in patients who have at least 1 identified pathogen.

2.2 Secondary objectives

The secondary objectives of this study are

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at TOC in patients who are ME
- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to the clinical cure at End of Treatment (EOT) with IV therapy, and at Late Follow-Up (LFU) both in patients who have at least 1 identified pathogen and in patients who are ME
- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at EOT, TOC, and LFU in patients who are clinically evaluable (CE)
- To determine the per-patient and per-pathogen microbiologic response of CAZ-AVI plus metronidazole compared to meropenem at EOT, TOC, and LFU both in patients who have at least 1 identified pathogen and in patients who are ME
- To evaluate the efficacy of CAZ-AVI plus metronidazole versus meropenem in pathogens resistant to ceftazidime.
- To compare the time to first defervescence of CAZ-AVI plus metronidazole versus meropenem in patients who are on IV study therapy and who have fever at study entry both in patients who are CE and in patients who are ME
- To evaluate the safety and tolerability profile of CAZ-AVI plus metronidazole compared to meropenem in the treatment of patients with cIAIs in the safety analysis set
- To evaluate the pharmacokinetics of the individual components of CAZ-AVI (avibactam and ceftazidime) in patients with cIAIs
- To evaluate CAZ-AVI exposure and the antimicrobial response relationship in patients with cIAIs.

2.3 Exploratory objectives

The exploratory objectives of this study are

- To explore the timing of the resolution of signs and symptoms associated with cIAIs for patients receiving CAZ-AVI plus metronidazole versus meropenem
- To assess the consequence of first-line treatment failure in the treatment of patients with cIAIs as defined by the health utilization variables. The results of this analysis will not be included in the clinical study report (CSR) for this study

3. STUDY PLAN AND PROCEDURES

This clinical study protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a Phase III prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of CAZ-AVI plus metronidazole versus meropenem in the treatment of adults with cIAIs, defined as infections that require surgical intervention and extend beyond the hollow viscus into the peritoneal space. The minimum duration of treatment with IV study therapy is 5 full days (15 doses) for patients with normal renal function or mild renal impairment and the maximum duration of treatment with IV study therapy is 14 full days, where a full day is defined as a 24-hour period. Each patient is expected to complete the study, including LFU (Day 42 visit), within approximately 7 weeks. The entire study duration is expected to be approximately 23 months.

Approximately 1106 hospitalized patients (18 to 90 years of age, inclusive) with a presumed (preoperative) or definitive (intra-operative or postoperative) diagnosis of cIAI will be enrolled. The diagnosis of infection will be based on the patient's clinical syndrome and intra-operative findings, including intra-operative cultures. Operative intervention includes open laparotomy, laparoscopic procedures, and percutaneous drainage procedures. All patients will undergo a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study therapy.

After obtaining written informed consent and confirming eligibility, patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule. Patients will be stratified by baseline severity of disease (APACHE II score; levels: ≤10 or >10 to ≤30) (see Appendix F) and by region (North America and Western Europe, Eastern Europe, and the rest of the world). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to 25% of the study population.

Intravenous study therapy (CAZ-AVI plus metronidazole or meropenem) will be continued for a period of time (5 to 14 full days, where a full day is defined as a 24-hour period) deemed appropriate by the investigator based upon fever and other signs and symptoms that demonstrate clear evidence of local and systemic improvement. After 5 full days (15 doses for patients with normal renal function or mild renal impairment) of IV study therapy and at the discretion of the investigator, all study therapies may then be discontinued if the patient has shown clinical improvement. Those patients who remain on IV study therapy will receive their IV study therapy by study center personnel while in the hospital or qualified health care provider (eg, home health agency) as an outpatient. The patient is to return to the study center for their EOT, TOC, and LFU visits following discharge from the hospital.

After at least 5 full days of IV study therapy, if clinical improvement is clearly demonstrated (the patient has been afebrile [<37.8°C] for at least 24 hours, without the influence of aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs, white blood cells <12500/μL, and oral intake and bowel function has resumed), all study therapies may be discontinued at the discretion of the investigator. If any medication with antipyretic properties has been taken by the patient, if possible, temperature readings should be taken at the end of the dosing interval (eg, 6 hours after the most recent dose for medications that are taken every 6 hours and 8 hours after the most recent dose for medications that are taken every 8 hours) and prior to administering the next dose of antipyretic-containing medication. If analgesic medication is required for pain, the use of analgesics without antipyretic properties is preferred. If treatment with antibiotics is required beyond 14 days, the AstraZeneca physician or physician (as an AstraZeneca delegate) should be contacted.

An overall clinical assessment, vital sign measurement, and detailed abdominal assessment will be performed at Day 1 (Baseline), daily during treatment with IV therapy, and at the EOT, TOC, and LFU visits. The investigator is responsible for determining the appropriate duration of IV therapy and assessing the relationship of AEs to IV therapy.

If a patient experiences diarrhea during or after IV study therapy, *C. difficile*-associated diarrhea may be present. When clinically indicated, the investigator should send a stool sample for *C. difficile* toxin testing.

Patients must be withdrawn from IV study therapy under certain circumstances that are described in detail in Section 5.8 of the protocol. Patients withdrawn from the IV study therapy for any reason should receive therapy deemed appropriate by the investigator. In all cases, the reason for withdrawal from the study or discontinuation of IV therapy must be recorded in the electronic case report form (eCRF) and in the patient's medical records. If the patient is withdrawn from IV study therapy due to an AE, the AE must be reported in accordance with the procedures in Section 6.4.3. All patients should be followed, whenever possible, until the LFU visit for the final outcome assessment and safety. If withdrawal from treatment with IV therapy is a consequence of clinical failure, these patients will be considered as such for analysis. All nonserious AEs and serious AEs (SAEs) will be collected for each patient from the time when informed consent is obtained at Screening (Day –1 to 0) up to and including the LFU visit (Day 42 visit).

Study periods are defined in the table below:

Study periods

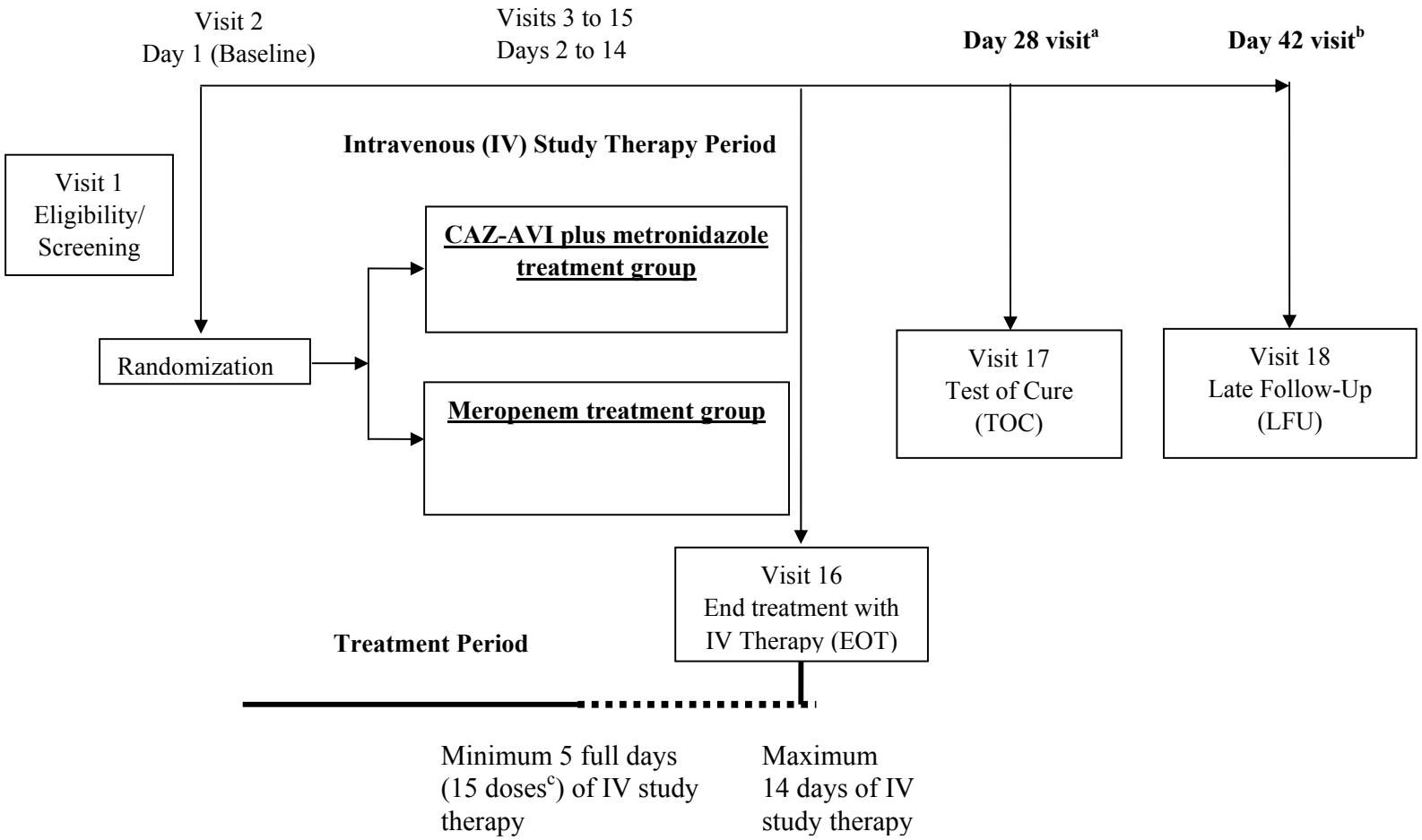
Eligibility/Screening period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0
Treatment period	
Visit 2 (Baseline/Randomization)	Day 1
Visits 3 to 15 (Days 2 to 14)	On therapy
Visit 16 (End of Treatment [EOT] with IV therapy)	Within 24 hours after the completion of the last infusion of IV study therapy
Follow-up period	
Visit 17 (Test of Cure [TOC])	Day 28 visit[a]
Visit 18 (Late Follow-Up [LFU])	Day 42 visit[b]

[a] If it is not possible to perform the TOC visit on Day 28 (eg, the patient is on holiday), the allowed visit window is Day 28 to 35.
[b] If it is not possible to perform the LFU visit on Day 42 (eg, the patient is on holiday), the allowed visit window is Day 42 to 49.
Abbreviation: IV, intravenous.

Plasma samples for PK sampling will be taken from all patients on Day 3 following a dose administration that is convenient for the plasma sample collections at the times presented in the study plan (for additional details see Section 6.5.1).

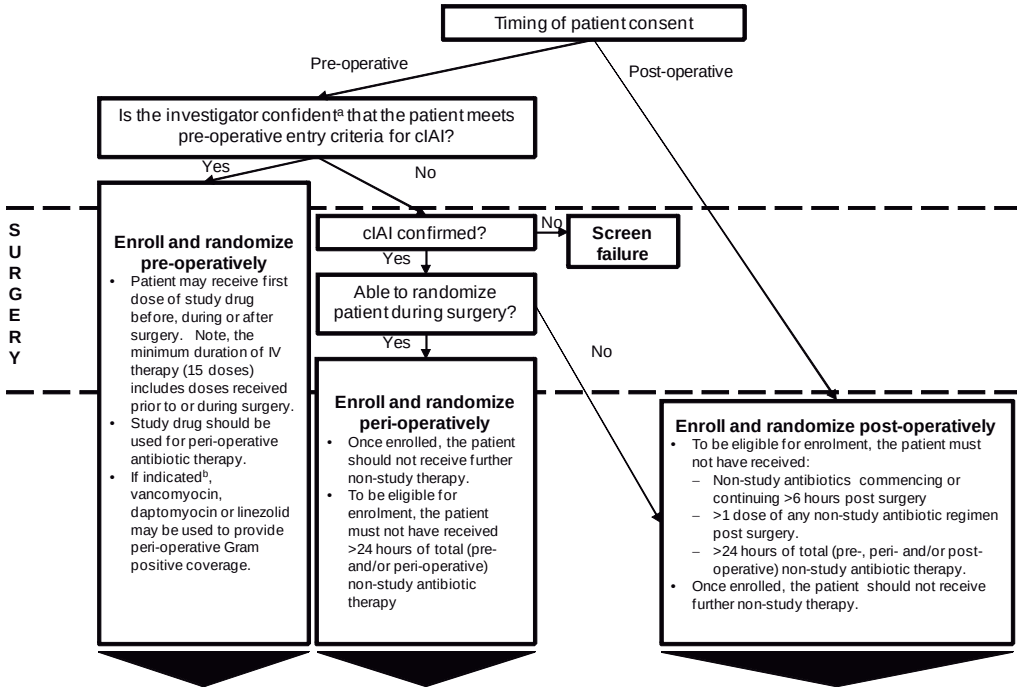
The study flow chart is presented in Figure 1, and a description of different pre-, peri- and postoperative enrollment scenarios are described in Figure 2. Details of the study plan are provided in Table 1.

Figure 1 Study flow chart



[a] If it is not possible to perform the TOC visit on Day 28 (eg, the patient is on holiday), the allowed visit window is Day 28 to 35.
[b] If it is not possible to perform the LFU visit on Day 42 (eg, the patient is on holiday), the allowed visit window is Day 42 to 49.
[c] For patients with normal renal function and patients with mild renal impairment.

Figure 2 Pre-, peri-, and post-operative enrollment scenarios



Note: Patients who undergo a surgical procedure with complete fascial closure are appropriate for the trial. The skin incision may be left open for purposes of wound management as long as complete fascial closure is accomplished. The use of negative pressure wound therapy in an open skin wound is permissible.

[a] Within a reasonable range of certainty based on the preoperative entry criteria described in Section 4.1, inclusion criterion 4. If a patient is enrolled preoperatively but does not have a cIAI confirmed during surgery, the investigator should inform the AstraZeneca physician or delegate immediately (see Section 5.3).

[b] If hospital policy or patient risk factors warrant use of an agent that covers *Enterococcus* spp. or MRSA for perioperative wound prophylaxis, these may be administered perioperatively in accordance with normal practice, but should not be continued unless *Enterococcus* spp. or MRSA is suspected as a pathogen in cIAI.

Abbreviations: cIAI, complicated intra-abdominal infection; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; spp., species.

Table 1 Study plan

	Eligibility/ Screening	**Treatment Period[a]**			**Follow-Up Period**	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16 EOT Visit**	**Visit 17 TOC Visit**	**Visit 18 LFU Visit**
Procedures and Assessments	**Days –1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical and surgical history	X					
Review prior and concomitant medications (including prior antibiotic therapy)	X	X	Daily	X	X	X
Complete physical examination[d]	X			X	X	X
Abdominal signs and symptoms plus abdominal and wound examinations postoperatively[e]	X	X[b]	Daily	X	X	X
Vital sign measurements[f]	X	X	Daily	X	X	X
12-Lead digital electrocardiogram		X[g]	X[h]	X		
Monitor adverse events[i]	X	X	Daily	X	X	X
APACHE II score (see Appendix F)	X					
Culture from site of abdominal infection[j]	Mandatory at surgical intervention	---------- As clinically indicated ----------				
Blood cultures[k]	X (mandatory)	---------If screening blood cultures results are positive, repeat at least every 3 days until negative. Blood cultures may also be obtained as clinically indicated.----------				
Blood and urine for safety analysis[l]	X	X[b]	Every 3 days	X	X	X

Table 1 Study plan

	Eligibility/ Screening	Treatment Period[a]			Follow-Up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16 EOT Visit	Visit 17 TOC Visit	Visit 18 LFU Visit
Procedures and Assessments	**Days –1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Estimate creatinine clearance[m]	X	X[b]	As clinically indicated			
Serum β-hCG for women of childbearing potential	X[n]				X	X
Randomization		X[o]				
Blood for PK analysis[p]			X			
Description of operative procedures[q]	X	X	X	X	X	X
Administer IV study therapy[r]		X	X			
Clinical response assessment[s]				X	X	X
Record radiologic examination[t]	X					
Investigator case summary/operative notes/hospital discharge summary[u]				---------- Ongoing as available ----------		

[a] A minimum of 5 full days (15 doses for patients with normal renal function and patients with mild renal impairment) to a maximum of 14 full days, where a full day is defined as a 24-hour period.

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

[c] Patients who discontinue IV study therapy should continue the study schedule as planned whenever possible; however, they should be scheduled for the EOT visit within 24 hours after the last IV dose.

[d] A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen, musculoskeletal, and neurological.

[e] The use of negative pressure wound therapy in an open skin wound is permissible. Surgical wound examination should occur daily even if inspection is limited by the presence of a negative pressure wound therapy device. A thorough wound evaluation should occur when a full dressing change is performed.

[f] Vital sign measurements including body temperature, heart rate, respiratory rate, and blood pressure should be assessed at Screening, Baseline, daily while the patient is receiving IV study therapy, at EOT, at TOC, and at the LFU visit. The patient should be resting in a supine position for at least 10 minutes before measuring blood pressure and heart rate. The patient's body temperature will also be evaluated at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature collection will be recorded. Height will be measured at Screening only; weight will be measured at Screening and as clinically indicated thereafter.

[g] A digital electrocardiogram (ECG) must be performed prior to dosing on Day 1 (Baseline). The ECG measurement should be performed in triplicate.

[h] Two mandatory digital ECG measurements must be performed on Day 3: one measurement at the end of a CAZ-AVI/CAZ-AVI placebo infusion and one measurement at the end of the corresponding meropenem/meropenem placebo infusion. Each ECG measurement should be performed in triplicate. If indicated, additional ECG assessments can be made at the discretion of the investigator; these assessments should be entered as an unscheduled assessment. If any significant increase of QTcF (ie, increase from baseline of ≥30 msec or QTcF >460 msec) is observed, then additional ECG assessments must be performed (see Section 6.4.9).

[i] Patients will be monitored for nonserious adverse events and serious adverse events from the time when informed consent is obtained at Screening up to and including the LFU visit. If a patient experiences diarrhea during or after IV study therapy, *C. difficile* associated diarrhea may be present. When clinically indicated, the investigator should send a stool sample for *C. difficile* toxin testing.

[j] These assessments will be used to determine microbiological outcome. Both aerobic and anaerobic cultures should be performed on specimens collected from the site of abdominal infection and on specimens collected from other clinically relevant intra-abdominal sites.

[k] If the screening blood culture results are positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. If repeat cultures have not been finalized negative by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit. When obtaining samples for blood cultures, 2 sets from 2 different sites must be collected (a total of 4 bottles; 2 aerobic and 2 anaerobic, each inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL of blood per collection). One set should be drawn through a venipuncture.

[l] Laboratory specimens (see Table 9) will be obtained prior to dosing and sent to the central reference laboratory at Screening, every 3 days during IV study therapy, EOT, TOC, and LFU. A direct Coombs test should be performed at the study center at Baseline, EOT (IV), and TOC if the local laboratory is equipped to do so; study centers unable to perform direct Coombs testing will not be required to perform this test. Abnormal safety laboratory results obtained throughout the study, including the LFU, should be followed up as clinically indicated (see also Appendix G). Local laboratory test results will be used to qualify patients for randomization.

[m] Study center personnel will calculate the estimated creatinine clearance at Screening and when clinically indicated (eg, clinically relevant increase or decrease in serum creatinine clearance) using serum creatinine results from the local laboratory. See Appendix E for the calculation of the estimated creatinine clearance.

[n] If the result of the serum β-hCG test cannot be obtained prior to dosing of investigational product, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG test result must still be obtained.

[o] On Day 1 (Baseline) before dosing.

[p] Blood samples for pharmacokinetics will be collected on Day 3 following a dose administration that is convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI/CAZ-AVI placebo infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI/CAZ-AVI placebo infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI/CAZ-AVI placebo infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient.

[q] With study entry and any subsequent procedures. If patient did not have surgery at Visit 1, details of the surgery need to be collected at Visit 2.

[r] If necessary, a 1-time dosing interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule 8 hours apart (±30 minutes). The dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose (ie, a –4 hour dosing window around the second dose). If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. Patients who remain on IV study therapy after 5 days (15 doses for patients with normal renal function or mild renal impairment) will receive their IV study therapy by study center personnel while in the hospital or qualified health care provider (eg, home health agency) as an outpatient. The patient is to return to the study center for their EOT, TOC and LFU visits following discharge from the hospital.

[s] If patients fail or relapse between scheduled visits, the assessment should be recorded as an unscheduled visit.

[t] Radiological examinations are not required for the study but the results should be recorded if done as part of the diagnosis. Radiological examinations include WBC scans, plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

[u] All documentation including surgical reports and imaging studies for any surgical intervention performed during the study must be submitted as it becomes available. For those patients whose surgical intervention was percutaneous drainage of an abscess, the interventional radiology report serves as the operative note. Any follow-up films used to assess outcome should also be submitted as they become available. See Section 3.1.1 for information regarding the Surgical Review Panel.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; β-hCG, β-human chorionic gonadotropin; EOT, End of Treatment; IV, intravenous; LFU, Late Follow-Up; PK, pharmacokinetic; QTcF, corrected QT interval using Fridericia formula; TOC, Test of Cure.

3.1.1 Surgical review panel

An independent expert surgical review panel (SRP) consisting of surgeons and 1 or more interventional radiologists will be convened at regular intervals throughout the study. There will be a charter for the SRP and the SRP will perform the response assessment classification while blinded to IV study therapy. For all patients classified as a clinical failure and all patients classified as cure at TOC or at LFU who undergo a second procedure, the SRP will review:

1. The adequacy of surgical source control, ie, whether adequate physical and mechanical measures have been undertaken (ie, debridement and/or abscess drainage during a surgical or interventional radiological procedure) in order to eliminate a source of infection, control ongoing contamination, and restore premorbid anatomy and function (Schein and Marshall 2004). Patients classified as a cure who have not undergone additional procedures will be assumed to have had adequate source control.

2. Investigators' clinical assessments.

After the SRP convenes, a decision may be made to review additional cases. If a discrepancy exists after the data are cleaned, the SRP's response assessment classification will prevail. In addition, patients assessed by the SRP as having inadequate initial infection source control will be re-classified as indeterminate and will be excluded from the CE and ME analysis sets.

3.1.2 Microbiological assessments

All microbiological assessments will be initiated at the local laboratory for specimen collection, shipment of isolates, and analysis of isolates according to the sections below and as outlined in more detail in the study site manual. All microbiological isolates must be shipped to the central reference laboratory for confirmation of microbiological assessments.

3.1.2.1 Specimen collection

An adequate abdominal culture specimen (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) should be obtained from all patients and sent to the local laboratory for culture, identification, and in vitro susceptibility testing. The specimens should be processed according to recognized methods that culture for both aerobic and anaerobic organisms (Murray et al 2007) following the standard operating procedures of the clinical microbiology laboratory at each study center. Blood culture specimens should be taken prior to enrollment (at Screening) and abdominal culture specimens should be obtained at the time of surgery. All cultured isolates should be kept by the local laboratory at –20°C or colder (preferably at -70°C) until the end of the study or when contacted by the central reference laboratory.

Blood cultures: Two sets of blood cultures should be collected (ie, 4 bottles) from 2 different sites for aerobic and anaerobic incubation. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. One set of blood cultures must be obtained

through a venipuncture. Organisms isolated in the blood at study entry will be assigned a microbiologic response similar to those given for pathogens isolated from abdominal cultures (see Table 7 for list of response categories). Details concerning the collection of blood cultures are provided in the laboratory manual.

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

3.1.2.2 Shipment of isolates

The central reference laboratory will supply the local laboratory with all media containing transport vials and instructions for shipment of isolates to the central reference laboratory and will also supply susceptibility testing discs for CAZ-AVI, meropenem and ceftazidime. The central reference laboratory will monitor and verify resistant isolates reported by the local laboratory. All shipment documentation for samples sent from the local laboratory to the central reference laboratory should be maintained and available for review by the representative.

3.1.2.3 Analysis of isolates

The local laboratory must identify all aerobic bacterial pathogens to the genus and species level using confirmatory, not presumptive, identification methods from blood and abdominal specimens. The disk diffusion method should be used for CAZ-AVI and the comparator meropenem as well as ceftazidime. Reporting of susceptibility results on CAZ-AVI to the principal investigator will be detailed in the study site manual. The laboratory can perform any additional testing on meropenem (eg, minimum inhibitory concentration [MIC]) and any additional agents as they normally do to provide susceptibility results of isolated aerobic microorganisms. Disk zone size determinations for interpretation of susceptibility for all isolated aerobic microorganisms will be according to Clinical Laboratory Standards Institute (CLSI) criteria for comparator agents. All aerobic isolates should be sent to the central reference laboratory for confirmation of identification and susceptibility testing. Characterization of β-lactamases associated with the bacterial pathogens and molecular profiling (eg, pulse-field gel electrophoresis) will be performed by

.

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

The investigator should record information on all specimens according to the investigator's manual supplied by the central reference laboratory. The central reference laboratory will

confirm pathogen identifications and susceptibility test results on all clinical isolates reported and shipped by the local laboratory. If discrepancies occur between the results obtained at the central reference laboratory and those obtained at the study site local laboratory, a representative will request that a second sample of the isolate in question be shipped. In the instance of differences in pathogen identification or susceptibilities, the central reference laboratory results will take precedence over the local laboratory result. If microorganisms that are isolated at the local laboratory do not survive shipping to the central reference laboratory, a representative will request that a second sample of the isolate in question be shipped. Local laboratory results may be used if a microorganism does not survive shipping or is not recoverable from the local laboratory.

3.2 Rationale for study design, doses, and control groups

This study is a randomized, double-blind, double-dummy, comparative design implemented to minimize potential bias in the investigator's assessment of clinical cure and safety events. Given the risk to patients and severity of disease, a placebo-controlled trial would not be ethically appropriate. This study will be conducted in hospitalized patients with cIAIs requiring surgical intervention and treatment with IV antibiotics.

The dose of ceftazidime approved for the treatment of serious Gram-negative infections for patients with a creatinine clearance >50 mL/min is 2000 mg for 30 minutes intravenously every 8 hours and for patients with a creatinine clearance ≥31 mL/min and ≤50 mL/min is 1000 mg for 30 minutes intravenously every 12 hours. The same dose regimen will be used in this study, except that the duration of the IV infusion will be increased from 30 minutes to 120 minutes. Additional information regarding dose rationale is presented in Section 3.2.1 below.

Complicated intra-abdominal infections are typically polymicrobial, potentially involving anaerobes such as the *B. fragilis* group. Metronidazole will be added to CAZ-AVI to provide coverage for anaerobic organisms. The spectrum of activity of CAZ-AVI when combined with metronidazole is well suited to treatment of pathogens commonly responsible for cIAIs.

Meropenem is approved for and widely used as treatment for cIAIs and carbapenems are considered the drugs of choice for treating infections due to ESBL-producing Gram-negative bacilli. The usual dose of meropenem for adults with cIAI is 1000 mg of meropenem intravenously every 8 hours.

3.2.1 Dose rationale

The intention for CAZ-AVI is that it will be active against clinically isolated Gram-negative bacteria that are resistant to other antibacterial agents. To ensure that CAZ-AVI can achieve this level of activity, the dose regimen for the Phase III clinical program was reassessed following completion of the Phase II clinical studies and emerging preclinical data.

3.2.1.1 Method of dose selection

Nonclinical data from in vitro susceptibility-testing and PD hollow fiber experiments, support the concept that a critical threshold concentration of avibactam is required to maintain continued suppression of β-lactamase activity for the same duration of the dosing interval that ceftazidime must be maintained above its MIC. As such, a target C_T of avibactam of 1 mg/L was used in calculating target attainments for the Phase III clinical program (see Section 4.1.2.3 of the CAZ-AVI Investigator's Brochure for further details).

Using all the available PK data for avibactam and ceftazidime and covariate information collected in healthy volunteers, patients with renal impairment, and patients with cIAIs (Study NXL104/2002), a population PK model for each compound was built. These models were used in Monte Carlo simulations to calculate the probability of target attainment (PTA). These PTA simulations were used to determine the dose regimen of both compounds that:

- maintains unbound avibactam plasma concentrations above the C_T (1 mg/L)
- maintains unbound ceftazidime plasma concentrations above an MIC of 8 mg/L for at least 50% of the dosing interval
- achieves the above PD targets with a joint PTA ≥0.9.

3.2.1.2 Rationale for selecting a new dose regimen in Phase III compared to Phase II

The CAZ-AVI dose and infusion time used in the Phase II study of cIAIs (Study NXL104/2002) was selected based on the labeled indication for ceftazidime combined with the 4:1 ratio of avibactam dosage determined from animal model work available at that time. Thus a dosage regimen of 2000 mg ceftazidime every 8 hours plus 500 mg avibactam every 8 hours was selected for study in the Phase II cIAI trial, matching the dose of ceftazidime for serious infections. The combined dose was administered as a 30-minute infusion, as indicated on the ceftazidime label. However, PTA simulations found that while a 2000 mg ceftazidime/500 mg avibactam dose is optimal, the 30-minute infusion might not give sufficient coverage to achieve the PD targets and joint PTA threshold of ≥0.9 described in Section 3.2.1.1 (for a 30-minute infusion, the joint PTA was <0.8). The simulations demonstrated that this would be better achieved by a 2-hour infusion (joint PTA ≥0.9).

Study NXL104/2002 employed a shorter duration of 30 minutes for CAZ-AVI and showed similar overall response rates for CAZ-AVI plus metronidazole and meropenem (see Section 1.1.6). The PK/PD approach that has been used to determine the most appropriate dose regimen in this study is based on the best preclinical data available combined with a well-established method of simulating the probability of PK/PD target attainment via a population PK model.

4. PATIENT SELECTION CRITERIA

Investigators should keep a record, the patient screening log, of patients who entered Screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive IV study therapy. There can be no exceptions to this rule. Patients discontinued from the study should be followed for safety.

Where patients who do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the physician immediately. The patient may continue to receive study therapy or be discontinued from study therapy at the investigator's discretion. The physician is to ensure that all such contacts are appropriately documented.

4.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Patient must provide a signed written informed consent prior to any study-specific procedures. However, if a patient is unable, the patient's legally acceptable representative may provide written consent, as approved by the institutional-specific guidelines. Those patients who are unconscious or considered by the investigator to be clinically unable to consent at Screening and who are entered into the study by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

2. Patient must be 18 to 90 years of age inclusive.

3. Female patient is authorized to participate in this clinical study if she meets the following criteria:

(a) Has been surgically sterilized or postmenopausal for at least 1 year or her sexual partner has had a vasectomy

OR

(b) Is of childbearing potential and all of the following conditions are met:

- Has had normal menstrual periods for the 3 months prior to study entry, and
- Has a negative serum pregnancy test (serum ß-human chorionic gonadotropin [ß-hCG]) within 1 day prior to study entry (if the results of the serum ß-hCG cannot be obtained prior to dosing of the investigational product (IP), a patient may be

enrolled on the basis of a negative urine pregnancy test, though serum ß-hCG must still be obtained), and

- Must be willing, during treatment and for at least 7 days after last dose of IV study therapy, to practice highly effective methods of birth control, such as intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), and medroxyprogesterone injections (Depo-Provera®), or remain sexually abstinent. Oral contraceptives should not be used as the sole method of birth control because the effect of CAZ-AVI on the efficacy of oral contraceptives has not yet been established. Barrier methods (such as male condom or diaphragm with spermicide) can be used if another method of acceptable contraception (not oral contraceptives) is also used.

4. **EITHER**:

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

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

(b) Diverticular disease with perforation or abscess

(c) Appendiceal perforation or peri-appendiceal abscess

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

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

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

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

OR

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

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

(b) Evidence of systemic inflammatory indicators, with at least 1 of the following:

- Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
- Elevated white blood cell count (>12000 cells/mm^3)
- Drop in blood pressure (BP) (however, systolic BP must be >90 mm Hg without pressor support)
- Increased heart rate(>90 bpm) and respiratory rate (RR) (>20 breaths/min)
- Hypoxia
- Altered mental status.

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

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

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

(e) Specimens from the surgical intervention will be sent for culture.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Patient has abdominal wall abscess or bowel obstruction without perforation or ischemic bowel without perforation.

3. Patient has simple cholecystitis, or gangrenous cholecystitis without rupture, or simple appendicitis, or acute suppurative cholangitis; or infected necrotizing pancreatitis or pancreatic abscess.

4. Patient whose surgery will include staged abdominal repair, or "open abdomen" technique, or marsupialization. This criterion is intended to exclude patients in whom the abdomen is left open, particularly those for whom reoperation is planned.

5. Patient is known at study entry to have a cIAI caused by pathogens resistant to the study antimicrobial agents.

6. Patient needs effective concomitant systemic antibacterials (oral, IV, or intramuscular) or antifungals in addition to those designated in the 2 study groups, except vancomycin, linezolid, or daptomycin if started for known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp. as per protocol Section 5.6.

7. No longer applicable as of Amendment 2.

8. Patient has perinephric infections.

9. Patient has indwelling peritoneal dialysis catheter.

10. Patient has suspected intra-abdominal infections due to fungus, parasites (eg, amebic liver abscess), virus, or tuberculosis.

11. Patient has a known history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to carbapenem or cephalosporin antibiotics or other β-lactam antibiotics or metronidazole.

12. Patient has any of the following laboratory values as defined below:

(a) Estimated creatinine clearance ≤30 mL/min calculated by Cockcroft-Gault method (Cockcroft and Gault 1976). Refer to Appendix E for calculation information.

(b) Hematocrit <25% or hemoglobin <8 g/dL

(c) Absolute neutrophil count <1000/mm^3

(d) Platelet count <75000/mm^3

(e) Bilirubin >3 × the upper limit of normal (ULN), unless isolated hyperbilirubinemia is directly related to the acute infection or known Gilbert's disease

(f) ALT or AST >3 × ULN values at Screening. Patients with elevations of AST and/or ALT up to 5 × ULN are eligible if these elevations are acute and directly related to the infectious process being treated. This must be documented.

(g) Alkaline phosphatase >3 × ULN. Patients with values >3.0 × ULN and <5.0 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

13. Patient has a body mass index >45 kg/m^2.

14. Patient has APACHE II score >30 (see Appendix F).

15. Patient is considered unlikely to survive the 6- to 8-week study period or has a rapidly progressive or terminal illness, including septic shock that is associated with a high risk of mortality.

16. Patient is unlikely to respond to 5 to 14 days of treatment with antibiotics.

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

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

- Patient received no more than 24 hours of total prior antibiotic therapy
- Patient received ≤1 dose of a treatment regimen postoperatively and antibiotics were not received more than 6 hours postprocedure (defined as 6 hours from the time of skin closure or, if skin closure is not performed, 6 hours from the time the wound dressing is applied)

(b) Patient is considered to have failed the previous treatment regimen. In this case, preoperative treatment of any duration with nonstudy systemic antimicrobial therapy for peritonitis or abscess is permitted provided that all of the following are met:

- The treatment regimen has been administered for at least 72 hours and is judged to have been inadequate.
- The patient has an operative intervention that is just completed or is intended no more than 24 hours after study entry.
- Findings of infection were documented at surgery.
- Specimens for bacterial cultures and susceptibility testing are taken at operative intervention
- No further nonstudy antibacterials are administered after randomization.

18. Patient has a concurrent infection that may interfere with the evaluation of response to the study antibiotic.

19. Patient is receiving hemodialysis or peritoneal dialysis.

20. Patient has a history of acute hepatitis, chronic hepatitis, cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure.

21. Patient has past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood.

22. Patient is immunocompromised as evidenced by any of the following:

(a) Human immunodeficiency virus infection, with either a current acquired immune deficiency syndrome-defining condition (eg, Kaposi's sarcoma, *Pneumocystis carinii* pneumonia) or a CD4 + T lymphocyte count <200/mm^3 at the time of study entry

(b) Metastatic or hematological malignancy requiring chemotherapeutic interventions within 6 weeks prior to randomization

(c) Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone).

23. Patient is participating in any other clinical study that involves the administration of an investigational medication at the time of presentation, during the course of the study, or who has received treatment with an investigational medication in the 30 days prior to study enrollment.

24. Patient is in a situation or has a condition that, in the investigator's opinion, may interfere with optimal participation in the study.

25. Patient is unlikely to comply with protocol, eg, uncooperative attitude, inability to return for follow-up visits, and unlikely to complete the study.

26. Patient has previously been treated with CAZ-AVI.

27. Patient has known inflammatory bowel disease (ulcerative colitis or Crohn's disease).

28. Patients has known *C. difficile*-associated diarrhea.

29. Patient had been previously enrolled in this study.

30. Patient is pregnant or breastfeeding. A serum β-hCG pregnancy test must be sent for women of childbearing potential at the screening visit. If the results of the serum β-hCG cannot be obtained prior to dosing of IP, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained. If either test is positive, the patient must be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant sexual

history, including methods of contraception, should be considered. Any patient whose sexual history suggests the possibility of early pregnancy must be excluded.

See Section 5.9 for procedures for withdrawal of incorrectly enrolled patients.

5. STUDY CONDUCT

5.1 Restrictions during the study

Hormonal contraceptives potentially subject to drug-to-drug interaction, such as pills, patches, and intravaginal devices are not acceptable methods of birth control during this study based on potential for antibiotics to alter gut flora, hormone absorption, and hormone effectiveness. If a female study participant was previously using hormonal contraceptives such as pills, patches, and intravaginal devices, she should follow her health care provider's specific recommendations for effective use of these methods after completing IV study therapy. Such recommendations may address the need for a second method of contraception until the hormonal method becomes fully effective.

5.2 Patient enrollment and randomization

Prior to enrollment and randomization, the investigator will:

1. Determine initial eligibility prior to performing any study-specific procedures

2. Obtain signed informed consent from the potential patient or his or her guardian/legal representative before any study-specific procedures are performed. Those patients who are unconscious or considered by the investigator clinically unable to consent at Screening and who are entered into the study by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

3. Complete patient eligibility.

4. Assign potential patient a unique enrollment number, beginning with "E0001001 (EXXXXYYY)" where XXXX reflects the center number and YYY will be allocated sequentially to enrolled patients at each center.

5. Confirm patient eligibility (see Sections 4.1 and 4.2).

6. After written informed consent has been obtained and eligibility established, the study center's unblinded pharmacist/designee will obtain the randomization code using the interactive voice response system (IVRS)/interactive web response system (IWRS). Refer to Section 5.2.1.

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

5.2.1 Procedures for randomization

Randomization codes will be computer-generated by AstraZeneca using the AstraZeneca Global Randomization System. Eligible patients will be randomized to treatment groups using an IVRS/IWRS. Details of the IVRS/IWRS procedures will be described in the user manual that will be provided to each center.

Eligible patients will be randomly assigned to treatment in a 1:1 ratio to meropenem placebo plus CAZ-AVI plus metronidazole or meropenem plus CAZ-AVI placebo plus metronidazole placebo.

Patients will be stratified by baseline severity of disease (APACHE II score; levels: ≤10 or >10 to ≤30) and by region (North America and Western Europe, Eastern Europe, and the rest of the world). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to 25% of the study population. Randomization codes will be assigned strictly sequentially to eligible patients (within each stratum).

Patients who are withdrawn after randomization will not be replaced. Any patient withdrawn from the study may not re-enter the study.

5.3 Procedures for handling patients incorrectly enrolled or randomized

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There will be no exceptions to this rule. Patients discontinued from the study should be followed for safety.

Where patients who do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the physician immediately. The patient may continue to receive study therapy or be discontinued from study therapy at the investigator's discretion. The physician is to ensure that all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study will be double-blinded with regard to IV treatment (CAZ-AVI plus metronidazole, or meropenem). After written informed consent has been obtained and eligibility established, using the IVRS/IWRS, the study center's unblinded pharmacist/designee will obtain the randomization code. The IVRS/IWRS will also confirm the IV study therapy assignment including the unique identification number(s) of the kits to be prepared for the patient's IV therapy. The unblinded pharmacist/designee will be responsible for maintaining accountability and preparing the blinded IV study therapy according to the handling

instructions. Study center personnel, with the exception of the unblinded pharmacist/designee, will remain blinded to the identity of the IV study therapy until the database has been locked and the study has been unblinded. In the case of a medical emergency requiring the investigator to know the identity of the IV study therapy, the investigator will follow the procedures outlined in Section 5.4.2.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment for each randomized patient, will be available to the investigators or pharmacists from the IVRS/IWRS. Interactive voice/web response system procedures will be described in the IVRS/IWRS user manual that will be provided to each center.

To maintain investigator blinding, the treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. In such a case, the patient should receive all appropriate medical care. Prior to any unblinding, the investigator should contact the AstraZeneca physician or physician (as an AstraZeneca delegate) or appropriate AstraZeneca study personnel to discuss options. The unblinding procedure will be done through the IVRS/IWRS system. As soon as possible and without revealing the patient's IV study therapy assignment (unless important to the safety of patients remaining in the study), the investigator must notify AstraZeneca/ if the blind is broken for any reason and the investigator was unable to contact AstraZeneca/ prior to unblinding. The investigator will record in the source documentation the date and reason for revealing the blinded treatment assignment for that patient; the treatment assignment itself should not be entered into source documentation.

AstraZeneca may break the code for SAEs that are unexpected and are believed to be causally related to the IV study therapy and that potentially require expedited reporting to regulatory authorities. In such cases, the minimum number of AstraZeneca/ personnel will be unblinded. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented and databases have been locked.

5.5 Treatments

5.5.1 Identity of investigational products

CAZ-AVI contains both avibactam and ceftazidime, which will be administered together in a single infusion bag. The following products may be used in the study:

CAZ-AVI:

- This will consist of a single vial filled with the sterile crystalline form of ceftazidime (2000 mg) and the sterile crystalline form of avibactam (500 mg). For IV administration, the crystalline powders are constituted using sterile water for injection, resulting in a concentrate solution.

- An amount of this solution, corresponding to the dose to be administered, is withdrawn from the vial and transferred into an infusion bag containing saline.

Information on the IP (CAZ-AVI plus metronidazole or meropenem) dosage, form, and strength is provided in Table 2. Investigational product and placebo metronidazole will be supplied by AstraZeneca. Normal saline solution (0.9%) for placebo CAZ-AVI and placebo meropenem will be supplied by the study centers.

Table 2 Investigational products: dosage form and strength

Investigational product	Dosage form and strength
CAZ-AVI	Ceftazidime-avibactam powder for concentrate for solution for infusion 2000 mg/500 mg
Metronidazole intravenous	Metronidazole 500 mg/100 mL solution for infusion
Meropenem	Meropenem powder for solution for infusion 1000 mg

5.5.2 Doses and treatment regimens

Patients randomized to receive CAZ-AVI will receive IV meropenem placebo (0.9% saline) immediately followed by IV CAZ-AVI (500 mg of avibactam and 2000 mg of ceftazidime), immediately followed by IV metronidazole (500 mg). Patients randomized to receive the comparator, meropenem, will receive IV meropenem (1000 mg) immediately followed by IV CAZ-AVI placebo (0.9% saline), immediately followed by IV metronidazole placebo (0.9% saline).

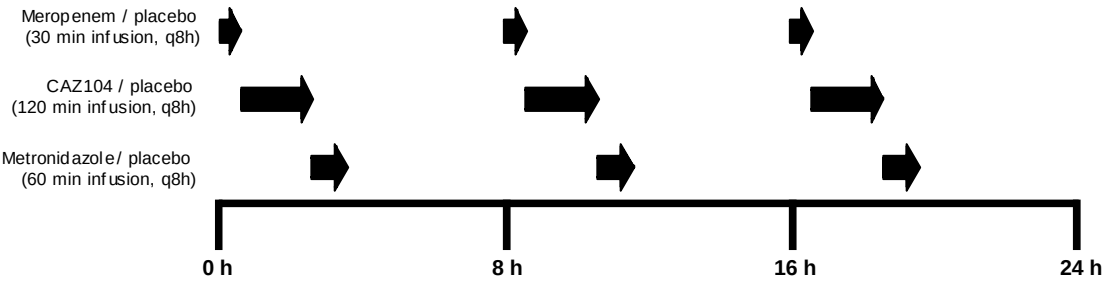
Meropenem (1000 mg)/meropenem placebo will be given in a 100-mL infusion bag at a constant IV rate over 30 minutes, CAZ-AVI/CAZ-AVI placebo will be given in a 100-mL infusion bag at a constant IV rate over 120 minutes, and metronidazole (500 mg)/metronidazole placebo will be give in a 100-mL infusion bag at a constant IV rate over 60 minutes. Dosing intervals for patients with normal renal function and mild renal impairment are described in Section 5.5.2.1; dose and dose interval adjustments for patients with moderate renal impairment are described in Section 5.5.2.2. Details for administration of meropenem/meropenem placebo, CAZ-AVI/CAZ-AVI placebo, and metronidazole/metronidazole placebo can be found in the handling instructions document.

Investigators should take into account the approximate 900 mL of normal saline (sodium chloride 0.9% USP) that patients will receive when assessing the patient's daily fluid intake.

5.5.2.1 Dosing intervals in patients with normal renal function and patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min)

Treatments will be repeated every 8 hours (±30 minutes) as described in Figure 3.

Figure 3 Schematic of dosing intervals for patients with normal renal function/mild renal impairment (for an arbitrary 24-hour period)



If necessary, a 1-time dosing interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule 8 hours apart (±30 minutes). The dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose (ie, a 1-time –4-hour window is allowed for the second dose). If a 1-time dose interval adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. If a dose adjustment is made, the end of the first dose day should be modified to be consistent with the dose adjustment.

For example, if the first dose was started at 10 AM, the second dose would be due at 6 PM. A 1-time adjustment of dosing times would allow the second dose to be delivered between 2 PM and 6 PM. All future doses would be given at 8 hours (±30 minutes) from the actual second dose. If a dose fluctuates from the scheduled time (eg, started 15 minutes early for a planned 4 PM dose), the next dose would still be scheduled for the 8-hour time from the planned dose, which would be 12 AM.

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

Serum creatinine levels must be measured at the local laboratory during Screening (Days -1 to 0) and as clinically indicated thereafter. In order to determine the need to adjust the dose and/or dosing interval of IV study therapy to be administered, the patient's estimated CrCl must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the patient's most recent actual (not ideal) body weight, and the Cockcroft-Gault formula provided in Appendix E. The results must be recorded in the eCRF.

Dose adjustments for CAZ-AVI or meropenem for patients with an estimated CrCl between 31 and 50 mL/minute (moderate renal impairment) are outlined in Table 3 and Table 4. A schematic of the dosing intervals for patients with moderate renal impairment is displayed in Figure 4. Since decreased renal function does not alter the pharmacokinetics of metronidazole, dosing adjustments for metronidazole are not needed.

Table 3 Ceftazidime/Avibactam adjustments for patients with renal impairment

Estimated creatinine clearance (mL/min)[a]	Meropenem placebo dose, interval, duration	Ceftazidime/Avibactam dose, interval, duration	Metronidazole dose, interval, duration
31 to 50 (moderate impairment)	meropenem placebo every 12 hours ±30 minutes over 30 minutes at a constant rate of infusion	1000 mg ceftazidime/250 mg avibactam every 12 hours ±30 minutes over 120 minutes at a constant rate of infusion	metronidazole 500 mg every 8 hours ±30 minutes over 60 minutes at a constant rate of infusion

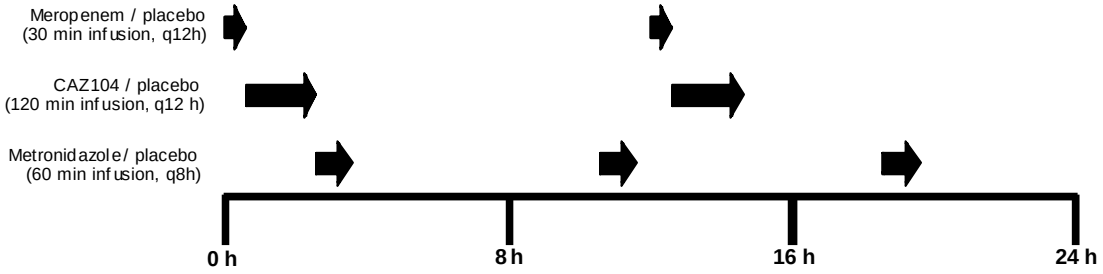
[a] Estimated creatinine clearance using Cockcroft-Gault formula (Appendix E).

Table 4 Meropenem adjustments for patients with renal impairment

Estimated creatinine clearance (mL/min)[a]	Meropenem dose, interval, duration	CAZ-AVI placebo dose, interval, duration	Metronidazole placebo dose, interval, duration
31 to 50 (moderate impairment)	1000 mg every 12 hours ±30 minutes over 30 minutes at a constant rate of infusion	CAZ-AVI placebo every 12 hours ±30 minutes over 120 minutes at a constant rate of infusion	0.9% saline every 8 hours ±30 minutes over 60 minutes at a constant rate of infusion

[a] Estimated creatinine clearance using Cockroft-Gault formula (Appendix E).

Figure 4 Schematic of dosing intervals for patients with moderate renal impairment – estimated creatinine clearance 31 to 50 mL/min (for an arbitrary 24-hour period)



In patients with moderate renal impairment, the CAZ-AVI dose is 1000 mg ceftazidime/250 mg avibactam.
Note: estimated creatinine clearance using Cockcroft-Gault formula (Appendix E).

If necessary, a 1‑time dosing interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule. The dosing interval adjustment must be such that the second dose is given a minimum of 8 hours and a maximum of 12 hours after the first dose (ie, a –4 hour window is allowed for the second dose). If a 1-time dose interval adjustment is made for the second dose, all further dosing times will be calculated based on the time of the

second dose. If a dose adjustment is made, the end of the first dose day should be modified to be consistent with the dose adjustment.

5.5.2.3 Dose regimen adjustments for patients whose CrCl drops below 31 mL/min while on IV study therapy

If subsequent to study entry and while still on IV study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (ie, estimated CrCl falls below 31 mL/min), retesting should be performed promptly. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl is below 31 mL/min, the investigator should use his or her discretion in determining whether an immediate dose change, a short period of continued observation, or discontinuation of therapy is warranted. Once a dose change is decided upon, the investigator should inform the dispensing pharmacist immediately. The pharmacist should then provide the appropriate dose adjustments as outlined in Table 5, to allow the patient to continue blinded study therapy.

Since a decline in renal function may be transient, CrCl should be closely followed in patients demonstrating renal dysfunction at any point before or during the study to ensure that therapeutic doses are being administered.

Table 5 Dose regimens and infusion times for patients whose estimated CrCl drops below 31 mL/min while on IV study therapy

Estimated CrCl (mL/min)	Infusion(s) to be administered within in an arbitrary 24-hour period			
	0 h	**8 h**	**12 h**	**16 h**
30 – 26	- Meropenem 1000 mg/placebo - CAZ-AVI (1000 mg CAZ, 250 mg avibactam)/placebo - Metronidazole 500 mg	Metronidazole 500 mg	Meropenem 1000 mg / placebo	Metronidazole 500 mg
25 – 16	- Meropenem 500 mg/placebo - CAZ-AVI (1000 mg CAZ, 250 mg avibactam)/placebo - Metronidazole 500 mg	Metronidazole 500 mg	Meropenem 500 mg / placebo	Metronidazole 500 mg
15 – 10	- Meropenem 500 mg/placebo - CAZ-AVI (500 mg CAZ, 125 mg avibactam)/placebo - Metronidazole 500 mg	Metronidazole 500 mg	Meropenem 500 mg / placebo	Metronidazole 500 mg
9 – 6	- Meropenem 500 mg/placebo - CAZ-AVI (500 mg CAZ, 125 mg avibactam)/placebo - Metronidazole 500 mg	Metronidazole 500 mg	None	Metronidazole 500 mg

Note: Meropenem infusion time = 30 min; CAZ-AVI infusion time = 120 min; Metronidazole infusion time = 60 min.
Abbreviation: CAZ, ceftazidime.

5.5.3 Additional study therapy

No additional study therapy will be provided during this study.

5.5.4 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local language.

The unblinded pharmacist at the site study center will prepare and label the individual IV infusions as assigned by the IVRS/IWRS, and according to the handling instructions.

5.5.5 Storage

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

5.6 Concomitant and poststudy treatment(s)

All prescription and over-the-counter medications being taken by the patient for the 2 weeks prior to study entry (considered prior treatment) and from randomization through the LFU visit (considered concomitant treatments) must be documented on the appropriate pages of the eCRF. Systemic antibiotics should be documented for the entire duration of the study (from 2 weeks prior to study entry through the LFU visit).

If *Enterococcus* species or MRSA is one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy is indicated, then open-label vancomycin, linezolid, or daptomycin may be added to either of the study regimens according to the usual practice of the investigator. If vancomycin, linezolid, or daptomycin are started empirically to cover MRSA or *Enterococcus* species, and if final culture results did not isolate MRSA or *Enterococcus* species, then the investigator should discontinue the additional Gram-positive coverage that was empirically added.

The use of other systemic antimicrobials not specified by this protocol is not permitted during the study. Antibiotic peritoneal lavage is not permitted (peritoneal lavage with saline or other nonantibacterial containing solution is allowed). Topical antibacterial and antifungals are permitted except that they may not be applied to the surgical site.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. If analgesic medications are needed for pain, the use of analgesic medication without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after being randomized to IV study therapy, the investigator should contact the AstraZeneca physician or physician (as an AstraZeneca delegate) before initiating therapy. Continued patient study participation will be determined based upon assessment of the safety risk to the patient if he or she were to continue in the study. Patients who have completed IV study therapy and are in the follow-up (FU) period should remain in the study as they are not actively on IV study therapy but being followed for outcomes.

Simultaneous administration of meropenem and/or metronidazole with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant agents, including warfarin, in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of the antibiotic to the increase in international normalized ratio is difficult to assess. In addition to the standard study safety laboratory assessments, frequent monitoring of the international normalized ratio should be performed during and shortly after coadministration of study therapy with an oral anticoagulant agent, as per local practice.

Probenecid interferes with the active tubular secretion of meropenem, resulting in increased plasma concentrations of meropenem. Therefore, coadministration of probenecid with meropenem is not recommended.

There is significant drug-drug interaction between meropenem and valproic acid or sodium valproate; therefore coadministration of meropenem and valproic acid or sodium valproate should be avoided.

5.7 Treatment compliance

The administration of all IV study therapy should be recorded in the appropriate sections of the eCRF.

The qualified study center personnel at the investigative study center will administer IV study therapy and treatment compliance will be assured. For those patients who are discharged from the hospital but continue on IV therapy, IV study therapy will be administered by a qualified health care provider. The dose, date, and exact start and stop time of administration of the IV study therapy will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

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

Intravenous study therapy will be dispensed in a blinded manner to the investigator or medically qualified personnel by the study center pharmacist. Intravenous study therapy will only be prepared and administered to patients by the study center pharmacists and medically qualified personnel who have been appropriately trained to prepare and administer IV study therapy. Written authorization of study personnel to administer IP must be documented for both hospital staff and, when applicable, home health care (HHC) staff, on the Delegation of Authority Log in one of 2 ways:

- All study staff trained and authorized by the investigator to administer IV study therapy are listed on the Delegation of Authority Log, OR
- The nurse manager(s)/supervisor(s) and study pharmacists authorized by the investigator are listed on the Delegation of Authority Log as the person(s)

responsible for ensuring that the nursing/pharmacy staff are appropriately trained on IV study therapy preparation/administration prior to preparing/administering it, and for maintaining current and complete training documentation at all times.

Written documentation of training of IV study therapy administration and pharmacy study center personnel will be kept current throughout the study, and ongoing training will be provided by study center personnel as assigned by the investigator on the Delegation of Authority Log. It is the investigator's responsibility to ensure that all documentation remains current and complete throughout the study. The investigator will document how he or she will ensure staff are adequately trained before they perform the infusion, and he or she will ensure that there is a system in place that will guarantee supervision of the study therapy administration process and patient safety (eg, study therapy will only be administered to patients under supervision of an investigator). Source documentation should clearly indicate who administered the infusion. When a local HHC agency has been employed by the national HHC vendor contracted by the sponsor, the national HHC vendor will also be responsible for ensuring that the local agency adheres to the above documentation and training requirements. The national HHC agency will work closely with the investigator to ensure the Delegation of Authority log remains current and training of local HHC staff is provided and documented prior to HHC staff administering study therapy.

Records of IV study therapy usage should include the identification of the person to whom the IV study therapy was administered, the quantity and date of administration, and a record of unused IV study therapy. The investigator/pharmacist is responsible for maintaining accurate IV study therapy accountability records throughout the study on the relevant forms provided by AstraZeneca/ . Each administration of IV study therapy will be documented in the eCRF.

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

- Deliveries of such products are correctly received by a responsible person (eg, pharmacist).
- Deliveries are recorded.
- Intravenous study therapy is handled and stored safely and properly.
- Intravenous study therapy provided for this study is used only as directed in the study protocol.
- Study center personnel account for all therapy received at the study center, dispensed for the patient, and returned to the pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved.

The unblinded representative performs complete IV study therapy accountability during each monitoring visit, including verifying documentation of receipt, dispensing, return, and

destruction of IV study therapy and consistency of this documentation with physical inventory and IVRS/IWRS.

At the end of the study, the study center must account for all study drugs and labels received at the site and for all unused study drugs; these must be reconciled and/or destroyed appropriately. Destruction of unused test material can be performed at study sites, according to local procedures, provided AstraZeneca has approved the destruction. The investigator or pharmacist should sign certificates of delivery and return.

5.8 Discontinuation of investigational product

Patients may be prematurely discontinued from IP (ie, prior to cure) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE (eg, risk to patients, as judged by the investigator and/or safety review committee, , or AstraZeneca)
- Positive pregnancy test at any time during the study treatment period.
- In the absence of any alternative explanation for an increase in the following abnormalities, individual patients should be withdrawn if the following criteria are met (see also Appendix G):
  - ALT or AST >8 × ULN
  - ALT or AST >3 × ULN and either total bilirubin >2 × ULN or evidence of coagulopathy. Evidence of coagulopathy should be discussed with the Physician where possible.
  - ALT or AST >3 × ULN and with appearance of symptoms suggestive of new or progressive liver disease. Symptoms suggestive of new or progressive liver disease should be discussed with the Physician where possible
- Severe noncompliance to study protocol, as judged by the investigator and/or or AstraZeneca
- Treatment failure
- In the opinion of the investigator, it is not in the best interest of the patient to continue the IV study therapy or at the request of the representative or AstraZeneca that the patient stops participation.

For patients who discontinue IP early, their FU assessments should be collected. Liver eCRF modules should be completed for patients discontinued after meeting hepatic/liver criteria.

The patient should be scheduled for the EOT visit within 24 hours after IV study therapy discontinuation.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of discontinuation from the IP and at the LFU visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and Section 6.4.5); and all IV study drugs (CAZ-AVI plus metronidazole, and meropenem) should be returned by the investigator.

If a patient is withdrawn from the study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of withdrawal and at the LFU visit. Adverse events and SAEs will be followed up (See Sections 6.4.3 and 6.4.5).

Withdrawn patients will not be replaced. When a patient is withdrawn from the study, study center personnel should call the IVRS/IWRS and register the patient withdrawal information.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

For this study, patient data will be collected by electronic data capture (EDC).

The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the instructions provided. He or she will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study center.

6.1.1 Electronic data capture

Data will be collected electronically for each study patient by an EDC data management and workflow system. Source data supporting all EDC entries will be recorded in the study patient's medical records as per the site's standard practice. Investigators and study center personnel will be responsible for the data capture and will respond to queries within the EDC data management system.

Correction of any data errors and other such changes will be made by changing or updating the data in the system which also requires the entry of the user's name and a password for each change that will be captured in the electronic audit trail.

Clinical data (including AEs and concomitant medications) will be entered into a data management system that is compliant with Title 21 of the US Code of Federal Regulations Part 11 and provided by . The data system includes password protection and internal quality checks, such as automatic verification range checks, to identify data that appear to be out of the specified ranges. Programmed edit specifications identify discrepancies in the data that may be addressed by the study center personnel.

6.2 Data collection and enrollment

Every effort should be made to collect all the data, blood samples, and cultures and to complete all assessments required for each visit as detailed in the Study Plan (Table 1) and discussed by visit in Sections 6.2.1 to 6.2.6.

Clinical information obtained as part of standard clinical care before the informed consent is signed may be used as part of the screening and evaluation process. Specimens collected for culture prior to consent may be used for central laboratory confirmation only after the informed consent has been signed.

6.2.1 Visit 1 eligibility/screening (Days –1 to 0) assessment procedures

Procedures for Visit 1 will vary depending on the timing of surgery relative to the visit.

At Eligibility/Screening (Day –1 to Day 0), each potential patient will provide informed consent prior to starting any study-specific procedures. Visit 1 (eligibility/screening) may occur pre- or postoperatively as described in Figure 2 in Section 3.1.

Each patient will undergo screening assessment procedures less than 24 hours prior to the first dose of IV study therapy. Study center personnel will calculate the estimated creatinine clearance at Screening using serum creatinine results from the local laboratory. See Appendix E for the calculation of the estimated creatinine clearance.

Screening assessments will consist of:

1. Obtaining informed consent.
2. Reviewing of the inclusion and exclusion criteria with the patient.
3. Collecting demographics.
4. Collecting medical and surgical history.
5. Reviewing prior and current medications (including prior antibiotic therapy).
6. Performing complete physical examination as defined in Section 6.4.8.
7. Assessing abdominal signs and symptoms.

8. Measuring vital signs including supine BP, heart rate, RR, and body temperature as defined in Section 6.4.10. Height and weight will only be measured at Screening. After the screening visit, weight should be measured as clinically indicated. Body mass index (kg/m^2) will be calculated as the ratio of weight in kg/(height in $cm/100)^2$.

9. Collecting AEs.

10. Determining APACHE II score (see Appendix F) using the most recent parameters available.

11. Obtaining blood cultures (Note: this assessment is mandatory at Visit 1).

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

13. Estimating creatinine clearance using the serum creatinine results from the local laboratory. Refer to Appendix E for details on estimating the creatinine clearance.

14. Obtaining blood sample for serum β-hCG for women of childbearing potential. If the results of the serum β-hCG cannot be obtained prior to dosing of IP, a patient may be enrolled on the basis of a negative urine pregnancy test obtained locally, though serum β-hCG must still be obtained. If either test is positive, the patient must be excluded. If a study center cannot do serum β-hCG testing, a urine β-hCG test must be obtained.

15. Recording radiologic examination results if done as part of the patient's diagnosis. Radiologic examinations include plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

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

16. Abdominal wound examinations postoperatively.

17. Must have obtained culture from site of abdominal infection during surgical procedure.

18. Collecting description of operative procedures (including study entry and subsequent procedures).

6.2.2 Visit 2 (Day 1 [Baseline]) assessment procedures

Procedures for Visit 2 will vary depending on the timing of Visits 1 and 2 relative to surgery. Visit 2 may occur pre- or postoperatively as described in Figure 2 in Section 3.1.

Local laboratory test results will be used to qualify patients for randomization, although samples will also be sent to the central reference laboratory for testing. All samples for laboratory assessments should be collected prior to dosing.

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

1. Reviewing of the inclusion and exclusion criteria with the patient.

2. Reviewing prior and concomitant medications.

3. Measuring vital signs including supine BP, heart rate, RR, and temperature as defined in Section 6.4.10.

4. Performing a digital 12-lead electrocardiogram (ECG) prior to dosing (the patient should be resting in a supine position for at least 10 minutes prior to the evaluation). The ECG measurement should be repeated in triplicate.

5. Collecting new AEs and reviewing ongoing AEs.

6. Obtaining a blood sample for blood culture (as clinically indicated) and direct Coombs test (to be performed locally).

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

8. Description of the operative procedure (if not already collected at Visit 1).

9. No longer applicable as of Amendment 2.

10. No longer applicable as of Amendment 2.

11. Randomizing eligible patient to treatment group using the IVRS/IWRS.

12. Administering IV study therapy. Note all other baseline assessments should be complete before the patient receives the first dose of IV therapy. The exception to this is that patients may receive study therapy before obtaining abdominal cultures if Visit 2 occurs pre-operatively, see Figure 2).

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

13. Assessing abdominal signs and symptoms plus abdominal wound examinations postoperatively.

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

15. Estimating creatinine clearance using the serum creatinine results from the local laboratory (as clinically indicated). Refer to Appendix E for details on estimating the creatinine clearance.

6.2.3 Visits 3 to 15 (Days 2 to 14) assessment procedures

The total number of days of combined treatment with IV study therapy will be a minimum of 5 and a maximum of 14 days. Those patients who remain on IV study therapy after 5 days (15 doses for patients with normal renal function or mild renal impairment) will receive their IV study therapy by study center personnel while in the hospital or qualified health care provider (eg, agency) as an outpatient. The patient is to return to the study center for their scheduled visits following discharge from the hospital. The following assessment procedures will be performed during treatment with IV study therapy:

1. Reviewing concomitant medications (daily).

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

3. Measuring vital signs (daily) including supine BP, heart rate, RR, and body temperature as defined in Section 6.4.10.

4. On Day 3 only - 2 ECG measurements: one measurement at the end of a meropenem/meropenem placebo infusion and one measurement at the end of the corresponding CAZ-AVI/CAZ-AVI placebo infusion. Each ECG measurement should be performed in triplicate.

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

6. Obtaining culture from site of abdominal infection (as clinically indicated).

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

8. Obtaining blood and urine samples for safety analysis (every 3 days) (central reference laboratory).

9. Estimating creatinine clearance using the serum creatinine results from the local laboratory (as clinically indicated). Refer to Appendix E for details on estimating the creatinine clearance.

10. On Day 3 only - obtaining blood samples for PK analysis (refer to Section 6.5.1 for sample collection times).

11. No longer applicable as of Amendment 2.

12. Collecting description of operative procedures (any postbaseline procedures).

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

6.2.4 Visit 16 end of IV therapy (EOT) visit assessment procedures

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

1. Reviewing concomitant medications.

2. Performing complete physical examination, to include assessing abdominal signs and symptoms plus abdominal and wound examinations postoperatively as defined in Section 6.4.8.

3. No longer applicable as of Amendment 2.

4. Measuring vital signs including supine BP, heart rate, RR, and body temperature as defined in Section 6.4.10.

5. Performing a digital 12-lead ECG (the patient should be resting in a supine position for at least 10 minutes prior to the evaluation). The ECG measurement should be repeated in triplicate.

6. Collecting new AEs and reviewing ongoing AEs. Should a patient experience significant diarrhea during or after IV study therapy, the investigator should consider obtaining a stool sample and testing for *C. difficile* toxin.

7. Obtaining culture from site of abdominal infection (as clinically indicated).

8. If repeat blood culture results have not been finalized negative by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit.

9. Obtaining blood and urine samples for safety analysis (central reference laboratory) and direct Coombs test (performed locally).

10. No longer applicable as of Amendment 2.

11. Collecting description of operative procedures (any postbaseline procedures).

12. Determining clinical response assessment.

    Note: if a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

13. Obtaining investigator case summary, operative notes and hospital discharge summary (ongoing as available).

6.2.5 Visit 17 Test of Cure (TOC) visit assessment procedures (Day 28 visit)

If it is not possible to perform the TOC on study Day 28 (eg, the patient is on holiday), then the allowed visit window is Day 28 to 35.

TOC visit assessment procedures include:

1. Reviewing concomitant medications.

2. Performing complete physical examination, to include assessing abdominal signs and symptoms plus abdominal and wound examinations postoperatively as defined in Section 6.4.8.

3. No longer applicable as of Amendment 2.

4. Measuring vital signs including supine BP, heart rate, RR, and body temperature as defined in Section 6.4.10.

5. Collecting new AEs and reviewing ongoing AEs. Should a patient experience significant diarrhea during or after IV study therapy, the investigator should consider obtaining a stool sample and testing for *C. difficile* toxin.

6. Obtaining culture from site of abdominal infection (as clinically indicated).

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

8. Obtaining blood and urine samples for safety analysis (central reference laboratory) and Coombs test (performed locally).

9. Obtaining blood sample for serum β-hCG for women of childbearing potential.

10. Collecting description of operative procedures (any postbaseline procedures).

11. Determining clinical response assessment.

    Note: if a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

12. Obtaining investigator case summary, operative notes and hospital discharge summary (ongoing as available).

6.2.6 Visit 18 Late Follow-Up (LFU) visit assessment procedures (Day 42 visit):

If it is not possible to perform the LFU on study Day 42 (eg, the patient is on holiday), then the allowed visit window is Days 42 to 49.

LFU visit assessment procedures include:

1. Reviewing concomitant medications.

2. Performing complete physical examination, to include assessing abdominal signs and symptoms plus abdominal and wound examinations postoperatively as defined in Section 6.4.8.

3. No longer applicable as of Amendment 2.

4. Measuring vital signs including supine BP, heart rate, RR, and body temperature as defined in Section 6.4.10.

5. Collecting new AEs and reviewing ongoing AEs. Should a patient experience significant diarrhea during or after IV study therapy, the investigator should consider obtaining a stool sample and testing for *C. difficile* toxin.

6. Obtaining culture from site of abdominal infection (as clinically indicated).

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

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

9. Obtaining blood sample for serum β-hCG for females of childbearing potential.

10. Collecting description of operative procedures (any postbaseline procedures).

11. Determining clinical response assessment.

    Note: if a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

12. Submitting investigator case summary, operative notes and hospital discharge summary.

6.3 Efficacy

6.3.1 Clinical response

Clinical response definitions at the EOT, TOC, and LFU visits are cure, failure, and indeterminate. Reasons for failure will be indicated according to the clinical response definitions in Table 6.

Table 6 Definitions of clinical response at the EOT, TOC, and LFU visits

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention is necessary. Note: Patients who receive coverage for MRSA or *Enterococcus* spp., as allowed per protocol, can still have a response definition of cure.
Failure	Patients who meet any one of the criteria below will be considered a treatment failure: • Death related to intra-abdominal infection • Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively • Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or nonroutine wound care • Patient who receives treatment with additional antibiotics for ongoing symptoms of intra-abdominal infection (including patients prematurely discontinued from study drug due to an AE who require additional antibiotics for cIAI) • Patient previously met criteria for failure.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response cannot be made • Death where cIAI is clearly noncontributory • Circumstances that preclude classification as a cure or failure.

Abbreviations: AE, adverse event; cIAI, complicated intra-abdominal infection; EOT, End of Treatment; IV, intravenous; LFU, Late Follow-Up; MRSA, methicillin-resistant *Staphylococcus aureus*; TOC, Test of Cure.

6.3.2 Microbiological response assessments

The per-patient and per-pathogen microbiologic response of CAZ-AVI plus metronidazole compared to meropenem in the microbiological modified intent-to-treat (mMITT), ME, and extended ME analysis sets for patients with cIAI at the EOT, TOC, and LFU visit is a secondary outcome.

Microbiological response will be assessed per-pathogen and per-patient according to the definitions listed in Sections 6.3.2.1 and 6.3.2.2, respectively. Microbiological outcome per-patient is assessed in a blinded manner. It is based on outcome per-pathogen isolated at the initial visit (considered as causative) and on the isolation of pathogens during the course of treatment or the posttreatment period.

6.3.2.1 Per-pathogen microbiological assessments after completion of all follow-up visits

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 7. Microbiological responses other than "indeterminate" will be classified as "favorable" or "unfavorable." Favorable microbiological response assessments include "eradication" and "presumed eradication." Unfavorable microbiological response assessments include "persistence," "persistence with increasing MIC," and "presumed persistence." Patients with a microbiological response assessment of "indeterminate" will be considered to be nonevaluable for the ME analysis set. "Superinfection" and "new infection" will be considered separately.

6.3.2.2 Per-patient (overall) microbiological response assessments

Overall microbiological response will also be assessed as "favorable" or "unfavorable" for each patient. For patients from whom only 1 causative pathogen is isolated, the overall microbiological response assessment will be based on the microbiological response assessment for that pathogen.

For patients from whom more than 1 baseline pathogen is isolated, the overall microbiological response assessment will be "favorable" only if the microbiological response assessment for each of the baseline pathogens isolated is "favorable."

6.3.2.3 Microbiological response

Each baseline pathogen will be categorized according to the definitions in Table 7.

Table 7 Microbiological response categories for each pathogen identified at initial/prestudy culture, EOT, TOC, and LFU

Microbiological response	Definition
Eradication	Absence of causative pathogen from appropriately obtained specimens at the site of infection
Presumed eradication	Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure.
Persistence	Causative organism still present at or beyond the EOT visit from a culture of intra-abdominal abscess, peritonitis, or surgical wound infection.
Persistence with increasing MIC	Continued presence of the causative organism in a culture of the intra-abdominal abscess, peritonitis, or surgical wound infection obtained during or upon completion of treatment with IV study therapy that displays a ≥4-fold higher MIC to IV study therapy after treatment with IV study therapy.
Presumed persistence	Patient was previously assessed as a clinical failure and repeat cultures were not performed/clinically indicated
Indeterminate microbiological response	Study data are not available for evaluation of efficacy, for any reason including: • Patient lost to follow-up such that a determination of microbiologic response cannot be made • Death where cIAI is clearly noncontributory • Circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence • Patient with no pathogen isolated from a cIAI culture obtained at Baseline or for whom a culture was not obtained.

Abbreviations: cIAI, complicated intra-abdominal infection; EOT, End of Treatment; IV, intravenous; LFU, Late Follow-Up; MIC, minimum inhibitory concentration; TOC, Test of Cure.

Microbiologic response for blood pathogens should be classified similarly to the classifications for baseline pathogens noted in Table 7.

6.3.2.4 MIC among pathogens

The favorable per-pathogen microbiologic response at the EOT, TOC, and LFU visits will be evaluated for MIC categories. The MIC categories to be used are: <0.008, 0.015, 0.03, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and >256 μg/mL.

6.3.2.5 Emergent infections

Pathogens first appearing after baseline in patients with a baseline pathogen are categorized in Table 8 and will be summarized separately**.**

Table 8 Emergent infections

Emergent infection	Definition
Superinfection	Isolation of a new pathogen or pathogens (other than the original baseline pathogen[s]) from intra-abdominal cultures which is accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy during the period up to and including EOT
New infection	Isolation of a new pathogen or pathogens (other than the original baseline pathogen[s]) from intra-abdominal cultures which is accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy in the time period after EOT

Abbreviation: EOT, End of Treatment.

6.3.3 Primary efficacy outcome variable

The primary efficacy outcome variable is the proportion of patients with clinical cure (as defined in Section 6.3.1, Table 6) at the TOC visit in the mMITT analysis set.

6.3.4 Secondary efficacy outcome variables

The secondary efficacy outcome variables include the following:

- Proportion of patients with clinical cure at the TOC visit in the ME and extended ME analysis sets
- Proportion of patients with clinical cure at the EOT and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with clinical cure at EOT, TOC, and LFU in the CE analysis set
- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets
- Favorable per-pathogen microbiologic response at the EOT, TOC, and LFU visits by MIC categories in the mMITT, ME, and extended ME analysis sets
- Favorable per-patient clinical response and favorable per-patient microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with a favorable per-pathogen microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME, and extended ME analysis sets

- Time to first defervescence while on IV study therapy in the CE, ME, and extended ME analysis sets for patients who have fever at study entry.

6.3.5 Exploratory variables

- Signs and symptoms associated with cIAIs at recorded time points

Exploratory health utilization variables (to be reported outside the CSR), include the following:

- Length of hospital stay
- Length of intensive care unit (ICU) stay and/or transfer to the ICU
- Length of IV therapy
- Mortality caused by cIAIs (up to the LFU visit)

6.3.6 Safety and tolerability outcome variables

Safety and tolerability will be assessed by the incidence and severity of AEs and SAEs, exposure, mortality, reasons for discontinuations of IV study therapy and study, vital sign measurements (BP and heart rate), physical examination findings, 12-lead ECG parameters (QRS, RR interval, heart rate, QT interval [QT], corrected QT (QTc) interval using Bazett formula [QTcB] and Fridericia formula [QTcF]), and clinically important changes in clinical chemistry, hematology, and urinalysis laboratory values.

6.3.7 Pharmacokinetic outcome variables

Ceftazidime and avibactam compartmental PK parameters derived from population PK analysis and potential PK/PD relationships will be reported separately. Summary statistics and listing of ceftazidime and avibactam plasma concentrations at specified sampling windows will be reported in the CSR.

6.3.8 Pharmacogenetic outcome variables

No longer applicable as of Amendment 2.

6.3.9 Biomarker outcome variables

No longer applicable as of Amendment 2.

6.4 Safety

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

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time after the patient has signed informed consent, even if no IV study therapy has been administered.

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

6.4.2 Definitions of serious adverse event

An SAE is an AE occurring during any study period (ie, Treatment, Follow-up) that fulfills 1 or more of the following criteria:

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

For further guidance on the definition of an SAE, see Appendix B.

Cases of liver dysfunction that meet Hy's Law criteria are defined and reported as SAEs, using the "important medical event" serious criterion if no other criteria are applicable (see Appendix G).

6.4.3 Recording of adverse events

Time period for collection of adverse events

Nonserious AEs and SAEs will be collected for each patient from the time when informed consent is obtained at Screening (Day –1 to 0) through the LFU visit.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IV study therapy (yes or no)
- Action taken with regard to IV study therapy
- Outcome of the AE

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

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

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

  – Date of death

  – Autopsy performed

  – Primary/secondary cause of death

(b) Life threatening

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

  - Date of hospitalization
  - Date of discharge

(d) Congenital abnormality or birth defect

(e) Important medical event

(f) Suspected transmission via a medicinal product of an infectious agent

- Causality assessment in relation to study procedures
- Causality assessment in relation to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

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

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in Appendix B.

Adverse events based on signs and symptoms

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

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital sign measurements will be summarized in the CSR. Deterioration as compared with Day 1 (Baseline) in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IV study therapy.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE or SAE.

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

6.4.4 Exceptions from standard adverse event collection

6.4.4.1 Lack of effect

Where there is deterioration in the condition for which the IV study therapy is being used, there may be uncertainty as to whether this is lack of efficacy, disease progression, or constitutes an AE. In such cases, unless the AstraZeneca or reporting physician considers that the IV study therapy contributed to the deterioration or local regulations state to the contrary, the deterioration should be considered to be lack of efficacy and not an AE.

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

6.4.4.2 Disease progression

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

6.4.5 Reporting of serious adverse events

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

If any SAE occurs during the course of the study, then investigators or other study center personnel will inform appropriate AstraZeneca/ representatives within 24 hours of awareness.

The designated AstraZeneca/ representatives will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 3 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately by the investigator. Investigators or other study center personnel will inform the AstraZeneca/ representatives of any FU information on a previously reported SAE within 24 hours of awareness.

6.4.6 Laboratory safety assessments

Blood and urine samples will be sent to. For transfer to Covance, samples will be labeled, stored, and shipped according to AstraZeneca or Covance standard operating procedures, as appropriate. Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in Table 1.

The following laboratory variables will be measured:

Table 9 Laboratory variables

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

Table 9 Laboratory variables

Clinical chemistry	Hematology	Urinalysis
Other	**Coagulation**	
Blood cultures	Partial thromboplastin time	
Coombs test (direct) to be performed by local laboratory when possible	Prothrombin time International normalized ratio	

Abbreviation: β-hCG, β-human chorionic gonadotropin.

For blood volume see Section 7.1.

6.4.7 Actions required in cases of increases in liver chemistry values

The investigator is responsible for, without delay, determining whether the patient meets potential Hy's law criteria; AST or ALT ≥3 × ULN **and** total bilirubin ≥2 × ULN at any point during the study, irrespective of the value of the patient's alkaline phosphatase. The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe. Details regarding the actions required in the cases of increases in ALT, AST, and total bilirubin can be found in Appendix G.

If a patient reaches an ALT or AST = 5 × ULN, the patient may continue with the IP as planned unless discontinuation criteria as described in Section 5.8 are met. The patient should be seen within 48 hours to instigate enhanced follow-up and monitoring. Enhanced follow-up should include collection of clinical and historical information to determine the cause of ALT and/or AST elevations. Additional testing for liver laboratory test results must be done every 48 hours until the peak value has been reached as documented by a decline in the values and/or until the patient is feeling better. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or study drug has been discontinued and the patient is asymptomatic. The patient should be followed until resolution (including laboratory testing).

6.4.8 Physical examination

The timing of individual examinations is indicated in Table 1.

A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen including wound examination, musculoskeletal, and neurological systems. The use of negative pressure wound therapy in an open skin wound is permissible. Surgical wound examination should occur daily even if inspection is limited by the presence of a negative pressure wound therapy device. A thorough wound evaluation should occur when a full dressing change is performed.

Assessment of abdominal signs and symptoms plus postoperative abdominal and wound examinations (infection-related focused physical examination) will be conducted at Screening, Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, and LFU visits as outlined in the study plan (Table 1).

If pathologic findings emerge or worsen from the baseline physical examination, a nonserious AE page of the eCRF should be completed for these findings. If the findings meet the criteria for an SAE, procedures for reporting such events should be followed (refer to Section 6.4.5).

Height and weight will be measured at the Screening visit. Body mass index will be calculated. After the screening visit, weight should be measured as clinically indicated.

6.4.9 Resting ECG

Triplicate digital 12-lead ECGs will be recorded within 1 to 2 minutes of each other, at the time points specified in Table 1 using equipment provided by the central ECG laboratory eResearch Technology, Inc (eRT). The reports for the triplicate repeat ECGs will consist of the mean data from 3 beats (heartbeats or intervals) reported during each separate ECG. Patients must relax in a recumbent position for at least 10 minutes prior to the ECG reading being recorded. Central processing of ECGs and data storage will be provided by eRT. Each ECG will define heart rate, RR interval, QRS duration, corrected QT (QTc) interval, QTcF and QTcB, T-wave morphology (normal versus abnormal), and overall interpretation.

If any significant increase of QTcF (ie, increase from baseline of ≥30 msec or QTcF >460 msec) is observed, then additional ECG assessments must be performed. Electrocardiograms should be performed after the next dose of study drug then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to baseline (Day 1 prior to receiving any study drug). Assessments should be performed after the completion of study drug administration and be recorded as unscheduled assessments.

If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment.

All ECGs will be sent to the central reader who will judge the overall interpretation as normal or abnormal. If abnormal, the central reader will decide whether or not the abnormality is clinically significant and the reason for the abnormality will be recorded. The date, time, and central reader's interpretation (normal, abnormal clinically significant, or abnormal not clinically significant) for the ECGs will be entered in the eRT database. The study center will be contacted by eRT if alert criteria are found on any ECG. Specific procedures for use of the ECG recorder and transfer process, as well as detailed alert criteria, will be provided in separate study documentation.

Abnormal values should not be recorded as AEs unless they result in discontinuation from the study or they fulfill the criteria for an SAE.

6.4.10 Vital signs

6.4.10.1 Heart rate and blood pressure

Supine BP will be measured using a semiautomatic BP recording device with an appropriate cuff size. The patients will be required to rest in a supine position for at least 10 minutes prior to heart rate and BP measurements. The timing of these assessments is included in Table 1.

6.4.10.2 Body temperature

Body temperature will be measured using an automated thermometer at the times indicated in Table 1. The patient's body temperature will also be evaluated at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature collection will be recorded. Fever will be defined as a body temperature >38°C. For each individual patient, the method of temperature measurement ideally should be consistent for the duration of the study.

6.4.10.3 Respiratory rate

Respiratory rate will be collected in breaths per minute.

6.5 Pharmacokinetics

6.5.1 Collection of samples

Blood samples will be taken from all patients on Day 3 following a dose administration that is convenient for collection of the plasma samples at the times presented in the study plan (Table 1) and summarized below:

- Anytime within the 15 minutes prior to or after stopping CAZ-AVI/CAZ-AVI placebo infusion
- Anytime between 30 minutes and 90 minutes after stopping CAZ-AVI/CAZ-AVI placebo infusion
- Anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI/CAZ-AVI placebo infusion.

Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient.

If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose.

Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual. The date and time of sample collection will be recorded, as well as the date and time of the immediately preceding dose of IV study therapy.

For blood volume see Section 7.1.

6.5.2 Determination of drug concentration

Samples for determination of avibactam and ceftazidime concentrations in plasma will be analyzed on behalf of AstraZeneca using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

6.6 Pharmacodynamics

6.6.1 Collection of pharmacodynamic markers

Ceftazidime is a β-lactam antimicrobial agent, and it is expected that the time that the plasma concentration of ceftazidime exceeds the MIC (percentage of time above a threshold concentration [%T] >MIC) of the infecting organism will be correlated with efficacy. Thus, the %T >MIC, will be calculated from an appropriate PK model after the ceftazidime plasma concentrations are collected and analyzed. The collection of ceftazidime plasma concentrations is described in Section 6.5.1, and the detailed method to calculate %T >MIC will be included in the separate PK/PD analysis plan.

It is assumed that the percentage above a threshold concentration of avibactam is associated with avibactam's effect on inhibiting β–lactamase. An appropriate PK/PD index for avibactam, such as the percentage of time above a threshold concentration (%T >the critical threshold concentration of avibactam), will be calculated with a PK model after avibactam plasma concentrations are collected and analyzed. The collection of avibactam plasma concentration is described in Section 6.5.1, and the detailed method to calculate avibactam exposure measures will be included in the separate PK/PD analysis plan.

Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

For the blood volume that will be collected, see Section 7.1.

6.7 Pharmacogenetics

No longer applicable as of Amendment 2.

6.8 Collection of samples for biomarker research

No longer applicable as of Amendment 2.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is presented in Table 10.

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	6	30
	Hematology	3	6	18
	Coagulation	4.5	5	22.5
Pharmacokinetic sample		4	3	12
Blood culture		10 – 15	4[a]	40 – 60
Total				122.5 – 142.5

[a] If the screening blood culture is negative, 4 samples will be collected; if the screening blood culture is positive, additional samples will be collected.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on CAZ-AVI become available. However, the maximum volume to be drawn from each patient over approximately 60 days should not exceed 500 mL.

7.2 Handling, storage, and destruction of biological samples

For information on handling, storage, and destruction of microbiological samples see Section 3.1.2. The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Pharmacokinetic and pharmacodynamic samples

Incurred sample reproducibility analysis may be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses.

Key samples for investigation of metabolite identification and/or analysis may be retained at AstraZeneca, at the central laboratory, or possibly a contract research organization on behalf of AstraZeneca for a maximum of 5 years following the finalization of the CSR. The results from the investigation will not be reported in the CSR but separately in a metabolism report.

7.2.2 Pharmacogenetic samples

No longer applicable as of Amendment 2.

7.3 Labeling and shipment of biohazard samples

The investigator will ensure that samples are labeled and shipped in accordance with the laboratory manual and the Infections Substances, Category B regulations (materials containing

or suspected to contain infectious substances that do not meet Category A criteria [see Appendix C]).

Any samples identified as Infectious Substances, Category A materials, are not to be shipped and no further samples will be taken from the patient unless agreed upon by AstraZeneca and the appropriate labeling, shipping, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout the sample life cycle.

The investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

keeps oversight of the samples during the study through monitoring and AstraZeneca keeps oversight of the entire life cycle through internal procedures and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

No longer applicable as of Amendment 2.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1) Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document that incorporates) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An ethics committee (EC) or institutional review board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC, and to the study center personnel.

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca/ before randomizing any patient into the study. The EC should approve all advertising used to recruit patients for the study.

AstraZeneca/ should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be reapproved by the EC annually.

Before randomizing any patient into the study, the national regulatory authority approves the final study protocol, including the final version of the ICF or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca/ will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca/ will provide regulatory authorities, ECs, and investigators with safety updates/reports according to local requirements, including suspected and unexpected serious adverse reactions, where relevant.

8.4 Informed consent

The investigator(s) at each center will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study
- Ensure that each patient is notified that he or she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that patients who are unconscious or considered by the investigator clinically unable to consent at Screening and who are entered into the study by the consent of a legally acceptable representative provide their own written informed

consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

- Ensure that the original, signed ICF(s) is/are stored in the investigator's study file
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

8.5 Changes to the protocol and informed consent form

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

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

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

AstraZeneca/ will distribute any subsequent amendments and new versions of the protocol to each investigator. For distribution to EC, see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca/ and the center's EC is to approve the revised ICF before the revised form is used.

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

If local regulations require, any administrative change will be communicated to or approved by each EC.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT

9.1 Prestudy activities

Before the first patient is entered into the study, it is necessary for representative to visit the investigational study center to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of AstraZeneca/ . This will be documented in a CSA between AstraZeneca/ and the investigator.

9.2 Training of study center personnel

Before the first patient is entered into the study, a representative will conduct an on site initiation visit to review and discuss the requirements of this protocol and the related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized and review training of staff for the EDC system utilized in the study.

The investigator will ensure that appropriate training relevant to the study is given to all of the study center personnel, and that any new information relevant to the performance of this study is forwarded to the study center personnel involved.

The investigator will maintain a record of all individuals involved in the study (medical, nursing, and other study center personnel).

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the study center personnel are adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the laboratory manual, and that IV study therapy accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This

will require direct access to all original records for each patient (eg, clinic charts and electronic and paper medical records)

- Ensure withdrawal of informed consent to the use of the patients' biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The representative will be available between visits if the investigator(s) or other study center personnel at the center need information and advice about the study conduct.

9.3.1 Unblinded monitoring

In order to maintain the integrity of the study blind, separate unblinded monitoring visits will be conducted as outlined in the study clinical monitoring plan.

9.3.2 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the CSA, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca/ and the investigator should be in place before any study-related procedures can take place or patients are randomized to IV study therapy.

9.4.1 Archiving of study documents

The investigator will follow the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as the last visit of the last patient participating in the study.

The study is expected to start in fourth quarter 2011 and to end by third quarter 2013.

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

Completion of the study

Upon terminating the study, the investigator/subinvestigator will report in writing the completion of the study as well as the summary of the results to the head of the study center in accordance with the institution's rules. The head of the study center, who is informed of the

termination by the investigator, will provide a written notification of the results to the EC and AstraZeneca. Notification of study termination should be timed in a manner that will allow sites to access patients' records for study purposes after last patient last visit in order to address any potential data queries.

10. DATA MANAGEMENT

Data management will be performed by .

The data collected through third party sources will be obtained and reconciled against study data. Adverse events and medical and surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by .

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

The data will be validated as defined in the data validation manual. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and verified, the investigator will electronically sign the data, a clean file will be declared by data management, and the data will be locked. Any treatment-revealing data may thereafter be added and the final database will be frozen.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze samples.

11. CALCULATION OF VARIABLES

For the calculation of the variables in this section, with the exception of microbiological cultures, baseline will be defined as the last nonmissing assessment before the start of IV study therapy. For microbiologic cultures the initial culture (required at time of surgical intervention) will be defined as baseline. Refer to Section 3.1 for definitions of EOT, TOC, and LFU. Study randomization will be defined as the Day 1 (Baseline) visit.

11.1 Calculation or derivation of efficacy variables

The primary efficacy variable is clinical cure as assessed at the TOC visit in the mMITT analysis set. The primary efficacy variable will be based on the definitions in Section 6.3.1. The proportion of patients with clinical cure is defined as the number of patients with clinical cure divided by the number of patients in the corresponding analysis sets (mMITT, CE, ME, and extended ME) at each visit.

The other efficacy outcome variables will be based on the definitions in Section 6.3. The proportion of patients with favorable per-patient microbiologic response is defined as the number of patients with a favorable microbiological response (eradication and presumed eradication) divided by the number of patients in the corresponding analysis set (mMITT, ME, and extended ME).

The proportion of favorable microbiologic response for each pathogen (per-pathogen) is defined as the number of patients with a favorable microbiological response (eradication and presumed eradication) for the specific pathogen divided by the number of patients with the same baseline pathogen in the corresponding analysis set (mMITT, ME, and extended ME).

Identification of pathogens and susceptibility results will be recorded by both the local microbiology laboratory and the central reference laboratory. The identification and susceptibility results of the central reference laboratory will be regarded as definitive.

Time to first defervescence will be calculated for patients with a fever (>38ºC) at Baseline. Defervescence (≤37.8ºC) will be defined as absence of fever based on the highest temperature within 24 hours. Time to first defervescence while on IV study therapy in the CE, ME, and extended ME analysis sets for patients who have fever at study entry will be defined as time from the first dose of IV study therapy to first absence of fever. For patients with unresolved fever at the EOT visit, the time to defervescence will be censored at the day of the EOT visit.

The length of hospital stay and length of ICU stay will be calculated as the difference between the discharge date and the study entry date converted to days plus 1 day.

11.2 Calculation or derivation of safety variables

All nonserious AEs and SAEs will be collected for each patient from the time when informed consent is obtained at Screening (Day –1 to 0) up to and including the LFU visit. Adverse events that occur before dosing will be reported separately.

With the exception of microbiological cultures, baseline will be defined as the last nonmissing assessment before the start of IV study therapy. For microbiologic cultures, the initial culture (required at time of surgical intervention) will be defined as baseline. The change-from-baseline variables will be calculated for the following safety variables, as the posttreatment value minus the value at Baseline.

- Clinical laboratory tests including clinical chemistry, hematology, and urinalysis as defined in Section 6.4.6.

- Vital signs: heart rate, body temperature, and BP.

- ECG test such as heart rate, RR interval, QRS, corrected QT (QTc) interval, QTcF, and QTcB intervals.

11.2.1 Other significant adverse events

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

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

11.3 Calculation or derivation of pharmacokinetic variables

Descriptive statistics of individual plasma concentrations for ceftazidime and avibactam will be summarized and listed according to the nominal sampling windows after dosing for the PK analysis set and will be reported in the CSR. Ceftazidime and avibactam compartmental PK parameters derived from population PK analysis, and potential PK/PD relationships will be reported separately. The pharmacokinetics of avibactam and ceftazidime will be assessed by population PK modeling. The actual dosing and plasma sampling times will be used in the population PK modeling.

The avibactam and ceftazidime concentration, patient demographic, disease status data, etc, will be combined with the data from appropriate previous clinical studies for the population PK modeling analysis. Individual compartmental PK parameters for patients with available avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters such as C_{max}, minimum concentration, AUC at steady state, and elimination half-life will be derived from the predicted avibactam and ceftazidime concentration time courses. The appropriate avibactam and ceftazidime exposure outcome variables predicted by the population PK modeling will be used for PK/PD modeling analysis for appropriate microbiological or clinical cure outcome variables.

11.4 Calculation or derivation of pharmacodynamic variables

The outcome variables to be used in the population PK/PD analysis will be the per-patient microbiological and clinical response.

11.4.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

The relationship between the PD or clinical response variables and the ceftazidime exposure such as %T>MIC, and relevant covariates will be conducted and reported as a separate population PK and PK/PD analysis.

11.4.2 Population analysis of pharmacokinetic/pharmacodynamic variables

The population PK analysis and PK/PD analysis for some selected outcome variables, if appropriate, will be reported and listed separately.

11.5 Calculation or derivation of pharmacogenetic variables

No longer applicable as of Amendment 2.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

The analysis of data will be based on different analysis sets according to the purpose of analysis, ie, for safety and efficacy. The decision regarding validity of data for each of the analysis sets will be based on a blinded review of data, which will occur prior to declaring database lock.

12.1.1 Efficacy analysis sets

The efficacy analysis of data will be based on different subsets according to the purpose of analysis. Efficacy analyses will be based on 1 or more of the analysis sets defined in Sections 12.1.1.1 through 12.1.1.2 below. Patients who receive both study therapies will be excluded from CE and ME analysis sets. Patients in the CE, ME, and extended ME analysis sets will be analyzed according to the treatment they receive, while patients in the mMITT set will be analyzed according to the randomized treatment.

12.1.1.1 Microbiological modified intent-to-treat analysis set

The mMITT analysis set includes all patients who:

1. Met the disease definition of cIAI and have at least 1 Gram negative pathogen identified at study entry (regardless of isolate susceptibilities). Patients with a bacterial species typically not expected to respond to both study drugs (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.) will be excluded.

12.1.1.2 Clinically evaluable analysis set at the EOT, TOC, and LFU visits

The CE analysis set at the EOT, TOC, and LFU visits includes all patients meeting the following criteria:

1. Had an appropriate diagnosis of cIAI. As an exception, patients with a bacterial species typically not expected to respond to both study drugs (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.) will be excluded.

2. **EITHER**

   (a) Received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered

   OR

   (b) Received therapy <48 hours before discontinuing treatment due to an AE.

3. Was evaluated at the EOT, TOC, or LFU visit with a clinical response of cure or failure.

4. Had no important protocol deviations that would affect assessment of efficacy.

5. Did not receive any prior antibiotics other than protocol allowed antibiotics with specified duration in Section 4.2 exclusion criterion 17.

6. Did not receive concomitant antibiotic therapy with potential activity against any of the baseline pathogens between the time of randomization and the time of the EOT, TOC, or LFU culture, respectively, except for protocol allowed antibiotics for the coverage of *Enterococcus* spp. and MRSA. This does not include patients who have failed and require additional antibiotic therapy. Topical antibacterials and antifungals are permitted except that they may not be applied to the surgical site.

7. Considered to have had adequate initial infection source control (see definition of source control in Section 3.1.1).

12.1.1.3 Microbiologically evaluable analysis set at the EOT, TOC, and LFU visits

The ME analysis set at the EOT, TOC, and LFU visits includes all patients meeting the following criteria:

1. Included in a subset of CE patients at EOT, TOC, or LFU, respectively.

2. Had at least 1 Gram negative pathogen in the initial/prestudy culture that is susceptible to both study agents.

12.1.1.4 Extended microbiologically evaluable analysis set at the EOT, TOC, and LFU visits

The extended ME analysis set at the EOT, TOC, and LFU visits includes all patients meeting the following criteria:

1. Included in a subset of CE patients in EOT, TOC, or LFU, respectively.

2. Had at least 1 Gram negative pathogen in the initial/prestudy culture regardless of susceptibility.

12.1.2 Safety analysis set

The safety analysis set will include all patients who received any amount of IV study therapy.

12.1.3 PK analysis set

The PK analysis set will include all patients who had at least 1 plasma concentration data value available for either ceftazidime or avibactam.

12.2 Methods of statistical analyses

12.2.1 General considerations

The primary efficacy objective will be to assess the noninferiority of CAZ-AVI plus metronidazole compared to meropenem with respect to the proportion of patients with clinical cure at the TOC. The primary efficacy outcome variable will be assessed in the mMITT analysis set.

Statistical analyses as specified for each variable will be conducted and all comparisons will be between CAZ-AVI plus metronidazole and meropenem. The 2-sided 95% confidence intervals (CIs) will be produced. Descriptive statistics, including numbers, means, standard deviations, medians, minimums and maximums for continuous variables, and number and percentages for categorical variables will be presented by treatment. For the reporting of descriptive statistics, the mean and median values will be presented to 1 more decimal precision as the source data, SD will be presented to 2 more decimal precision, minimum and maximum values will be presented to the same precision as the source data, and percentages will be presented with 1 decimal precision. Listings of individual patients' data will also be produced.

For the safety analysis, the patients will be presented under the treatment they received. Project standard output templates will be used to produce standard summaries and plots for patient characteristics, safety and tolerability, and efficacy results.

Missing data will result in a reduced sample size for that parameter. Since the safety analyses will be predominantly presentations in tables and individual data listings, no action will be taken to handle missing data. A patient who withdraws prior to the last planned observation in a study period will be included in the safety analyses up to the time of discontinuation. Refer to Section 6.3 for handling of missing data for efficacy variables.

Further details on the methods of statistical analyses will be provided via a comprehensive statistical analysis plan to be issued before unblinding of the data. As a consequence of differing regulatory requirements for the statistical analyses of this study, 2 separate regional analysis plans will be produced.

12.2.2 Analysis of study population and patient characteristics

Enrollment, important protocol deviations, and discontinuations from IV study therapy as well as from the study will be summarized by CAZ-AVI plus metronidazole and meropenem. Protocol deviations are defined as any variations from the protocol, including enrollment of a patient who did not meet all inclusion and exclusion criteria and failed to perform the key assessments and procedures within the required time frame that may impact on evaluating treatment efficacy (see the statistical analysis plan for details). The number of patients in each analysis population will be reported overall and by treatment group.

Demographics (age, sex, race), medical and surgical history, description of cIAI, baseline assessments of clinical signs and symptoms, microbiological assessment of primary infection site or blood, and IV study therapy administration will also be summarized. The summarizations will be presented for mMITT, ME at TOC, extended ME at TOC, and safety analysis sets overall and by treatment group.

Efficacy

General considerations: Refer to Section 12.2.1 for descriptions of treatment comparisons and summarizations. The analysis of clinical cure at TOC in the mMITT analysis set is the primary analysis.

Primary alternative hypothesis: CAZ-AVI plus metronidazole will demonstrate clinical efficacy comparable with that of meropenem as a treatment for hospitalized patients with cIAI.

This hypothesis will assess whether the treatment effect measured by the primary efficacy variable for CAZ-AVI plus metronidazole will be noninferior to meropenem. The sponsor will conclude noninferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) is greater than –12.5%, however, noninferiority may be assessed using a 10% margin in regions where this is a regulatory requirement.

Primary efficacy variable: The primary efficacy variable will be the proportion of patients with clinical cure as defined in Section 6.3.1 at TOC in the mMITT analysis set. The number and percentage in each treatment group will be tabulated. Indeterminates will be included in the denominator for calculating the percentages. A 2-sided 95% CI for the observed difference in the proportion of clinical cure (CAZ-AVI plus metronidazole – meropenem) will be computed using the unstratified method of Miettinen and Nurminen (Miettinen and Nurminen 1985). A sensitivity analysis stratified by the prespecified stratification factors will also be performed for the primary outcome variable in the mMITT analysis set. The stratification factors are baseline severity of disease (APACHE II score; levels: ≤10 or >10 to ≤30) and region (North America and Western Europe, Eastern Europe, and the rest of the world).

The analysis for clinical cure at TOC will be presented by subgroups according to baseline characteristics. The subgroups to be analyzed will include, but not be limited to:

- baseline severity of disease
- primary site of infection (eg, stomach)
- the diagnosis of perforated appendix/appendiceal abscess
- infectious process (eg, single abscess, multiple abscess)
- initial operative procedure (ie, open laparotomy, laparoscopic surgery, drainage of abscess)
- baseline postoperative and nonpostoperative infections
- prior antibiotic use (including pre- and postsurgery, and ≤24-hour antibiotics vs prior treatment regimen failures)
- monomicrobial or polymicrobial infection
- baseline pathogens (total isolates, abdominal isolates, blood isolates)
- age (≥18 to 45, 46 to 64, 65 to 74, ≥75 to ≤90), sex, race, and region.

Forest plots will used to present the point estimate and the associated 2-sided 95% CI for difference in proportion for the subgroups.

Secondary efficacy variables: The numbers and percentages in each treatment group for clinical response recorded as cure, failure, and indeterminate as defined in Section 6.3 will be tabulated. Indeterminate or missing assessments will be included in the denominator for calculating the percentages for only the mMITT set, but they will be excluded from the denominator for the CE, ME, and extended ME sets. Secondary efficacy outcome variables considering proportions will be analyzed by determining 2-sided 95% CIs for the observed difference in the outcome proportion between CAZ-AVI plus metronidazole and meropenem (using the unstratified Miettinen and Nurminen method as described for the primary outcome variable).

The secondary variables assessing the outcomes are:

- Proportion of patients with clinical cure at the TOC visit in the ME and extended ME analysis sets
- Proportion of patients with clinical cure at the EOT and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of patient with clinical cure at EOT, TOC, and LFU in the CE analysis set

- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

The definitions for the outcomes are presented in Section 6.3. The clinical cure analyses will be presented for the mMITT, ME, extended ME, and CE analysis sets. The microbiologic response analyses will be presented for the mMITT, ME, and extended ME analysis sets. A cross-tabulation for a clinical response and baseline pathogens will also be presented for the mMITT, ME, and extended ME analysis sets. If a patient has more than 1 unique baseline pathogen identified and has a response of clinical cure, then the patient's clinical response will be a clinical cure for all of the baseline pathogens. Conversely, if the patient is a clinical failure, the patient's clinical response will be clinical failure for all of the baseline pathogens.

Additionally, the per-pathogen response at TOC and clinical cure at TOC will be summarized by treatment group for patients whose reason for exclusion from the ME analysis set is that the patient did not have at least 1 Gram negative pathogen susceptible to both arms but did have 1 Gram negative pathogen susceptible to the treatment they received.

The analysis of time to event secondary variable is as follows:

- Time to first defervescence while on IV study therapy in patients in the CE, ME, and extended ME analysis sets who have fever at study entry.

The treatment difference in the time to event variable (eg, first defervescence) will be assessed using a log-rank test. Median time to event will be computed using Kaplan-Meier method for each treatment group.

The analysis of other secondary variables is as follows:

- Proportion of patients with a favorable clinical response and per-patient microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME, and extended ME analysis sets

- Proportion of patients with a favorable per-pathogen microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME, and extended ME analysis sets

- Favorable per-pathogen microbiologic response at EOT, TOC, and the LFU visits by MIC categories in the mMITT, ME, and extended ME analysis sets.

Clinical cure, per-patient microbiological response, and per-pathogen microbiological response will be presented by treatment group for patients infected by ceftazidime-resistant pathogen. Clinical cure and per-pathogen microbiological response will be presented by MIC

among pathogens considered to be causative in the CAZ-AVI and meropenem treatment groups.

In each treatment group of the study, MIC frequencies for each infecting species isolated from either the abdominal site or blood for which the number is 10 or more will be reported separately. Descriptive statistics for MIC will be reported for each infecting species at MIC range and the MIC to inhibit the growth of 50% of organisms (MIC50). Additionally, for infecting species for which the number is 10 or more, the MIC to inhibit the growth of 90% of organisms (MIC90) will be reported.

To understand the relationship between the pathogens in the study and the same species in general circulation, frequency distributions of MICs of study therapies will be graphed for the following groups (where the numbers are sufficiently large): Enterobacteriaceae, *P. aeruginosa*, other nonfermenting aerobes, anaerobes, and facultative Gram-positive cocci.

PK variables

Individual plasma concentrations for ceftazidime and avibactam will be listed and summarized using the descriptive statistics as well as geometric mean and coefficient of variation according to the nominal sampling windows after dosing.

Exploratory variables

Proportion of patients with resolution of signs and symptoms associated with cIAI at recorded time points will be presented in mMITT and ME analysis sets.

Exploratory health utilization variables include the following:

- Length of hospital stay
- Length of ICU stay and/or transfer to the ICU
- Length of IV therapy
- Mortality caused by cIAI (up to the LFU visit)

The health economics variables such as length of hospital stay, length of ICU stay, percent of patients who transferred to the ICU, length of IV therapy, and mortality for the duration from first dose of IV study therapy to the LFU visit will be tabulated for treatment cure versus treatment failure in the mMITT and ME at TOC analysis set. The results of these health utilization variables will be reported separately and will not be included in the CSR for this study.

12.3 Safety and tolerability

General considerations: In addition to earlier description of the methods of summarization under Section 12.2.1, graphical presentations will be used as appropriate. Examples may

include line graphs showing individual or mean development over time, and shift plots showing pretreatment values on horizontal axis and posttreatment values on vertical axis.

For the reporting of descriptive statistics of safety variables (ie, clinical laboratory values, vital sign values, and ECG values), the mean and median values will be presented to 1 more decimal precision as the source data, SD will be presented to 2 more decimal precision, and minimum and maximum values will be presented to the same precision as the source data, and percentages will be presented with 1 decimal precision. The safety analysis set will be used for the listings and tabulations.

All AEs, ECG outliers, and clinical laboratory outliers that occur following the first dose of IV study therapy will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

Safety hypothesis: The safety and tolerability profile of CAZ-AVI plus metronidazole administered intravenously is acceptable.

This hypothesis will be assessed based on the following analysis of safety variables using the safety analysis set.

All nonserious AEs and SAEs will be collected for each patient from the time when informed consent is obtained at Screening (Day –1 to 0) up to and including the LFU visit. Any AEs that are unresolved at the patient's last AE assessment will be followed up by the investigator for as long as medically indicated. Adverse events that occur before dosing will be reported separately.

Adverse events occurring from the first dose of IV study therapy up to the TOC visit will be summarized by preferred term and system organ class using MedDRA vocabulary (Version 12.0 or higher) by dose group for the primary hypothesis. Adverse events will also be summarized for events occurring from the first dose of IV study therapy up to the LFU visit. These summaries will also be presented by relationship to IV study therapy and severity. Adverse events leading to discontinuation will be summarized. The same summarizations will also be presented for SAEs and OAEs.

Summaries and listings of death, SAEs, AEs, OAEs, and AEs that led to withdrawal will be presented.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical examination findings will be presented. Where applicable, data will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For clinical laboratory tests, listings of values for each patient will be presented with abnormal or out-of-range values flagged. Clinically significant changes in the laboratory test will be summarized and listed by treatment groups. Clinical laboratory data will be reported in Système International units in the CSR.

For ECG variables, the QT correction factor will be based on the Bazett and Fridericia formula. Categorical summaries of absolute QT and QTcF values (≥450 ms, ≥480 ms, ≥500 ms) and change from Day 1 (Baseline) values in QT and QTcF values (≥30 ms, ≥60 ms) will also be presented. All other ECG variables will be listed.

12.3.1 Interim analyses

Not applicable.

12.4 Determination of sample size

Synthesis of historical trials has indicated that a 12.5% margin is appropriate for assessment of noninferiority in cIAI trials; however, there are regional variations in the regulatory requirements for noninferiority trials. In order to meet these requirements globally this trial has been sized to provide 90% power for a 10% noninferiority margin, required in some regions (therefore providing >95% power to assess noninferiority using a 12.5% margin). Assuming that both treatments have an underlying clinical cure rate of 70% in the mMITT analysis set, in order to provide 90% power for a 10% noninferiority margin using the lower limit of a 2-sided 95% CI, 442 randomized patients per treatment group will be needed for the mMITT analysis set. Assuming that 80% of the randomly assigned patients will be included in the mMITT analysis set, 553 randomized patients per treatment group based on the mMITT rate will be needed. Consequently, a total of approximately 1106 eligible patients will be randomized in the study. The sample size was calculated using nQuery® version 7 (Statistical Solutions Ltd Cork, Ireland) using the Newcombe-Wilson (Newcombe 1998) score method (uncorrected). For large samples, this method is approximately the same as the Miettinen and Nurminen (Miettinen and Nurminen 1985).

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

12.5 Data monitoring committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in close consultation with the . Issues identified will be addressed; this could involve for instance amendments to the study protocol and letters to the investigators.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and SAE contacts

The investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.5. In the case of urgent safety concerns, the investigator should contact the physician via the numbers listed below for the appropriate region.

In the event of an SAE-related question, the investigator should contact the Hotline number for the appropriate region.

Region	Role in the study	Address and telephone number
	Medical Monitor	
	24-hour Service	
	Medical Monitor	
	24-hour Service	
	Medical Monitor	
	24-hour Service	
	Medical Monitor	
	24-hour Service	

13.2 Overdose

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

Recording an overdose will be done according to the following:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca IV study therapy occurs in the course of the study, then investigators or other study center personnel will inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **the end of the next business day** from when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca patient safety data entry site.

For overdoses associated with an SAE, standard reporting time lines apply, see Section 6.4.5. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

If a patient becomes pregnant during the course of the study, CAZ-AVI should be discontinued immediately. All outcomes of pregnancy should be reported to AstraZeneca and .

13.3.1 Maternal exposure

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

If any pregnancy occurs in the course of the study, then investigators or other study center personnel will inform appropriate AstraZeneca/ representative within 1 day, ie, immediately but no later than the end of the next business day from when he or she becomes aware of it.

The designated AstraZeneca/ representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca patient safety data entry site within 1 or 3 days for SAEs (see Section 6.4.5) and within 30 days for all other pregnancies.

The same time lines apply when outcome information is available.

All outcomes of pregnancy should be reported to AstraZeneca/ . Any patient who becomes pregnant during the course of the study will be followed so that pregnancy outcome can be determined and reported to AstraZeneca and the regulatory authorities.

The PREGREP module is used to report the pregnancy and is entered into the clinical database. The PREGOUT module (a paper CRF) is used to report the outcome of the pregnancy, but is not entered into the clinical database.

13.3.2 Paternal exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of any pregnancy occurring from the date of the first dose of study drug until 3 months after the last dose of study drug must be reported to AstraZeneca within 5 days and documented as specified in Section 13.3.1.

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