Clinical Study Protocol

Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00006
Edition Number	1
Date	[redacted]

An Open-Label, Randomized, Multicenter, Phase III Study of Ceftazidime-Avibactam (CAZ-AVI, formerly [redacted]) and Best Available Therapy for the Treatment of Infections Due to Ceftazidime Resistant Gram-Negative Pathogens

Sponsor: AstraZeneca AB, S-151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

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

[redacted] 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 [redacted] and AstraZeneca.

AstraZeneca

PROTOCOL SYNOPSIS

An Open-Label, Randomized, Multicenter, Phase III Study of Ceftazidime-Avibactam (CAZ-AVI, formerly [redacted] and Best Available Therapy for the Treatment of Infections Due to Ceftazidime Resistant Gram-Negative Pathogens

International Coordinating Investigator

[redacted]

Study centers and number of patients planned

This will be a multicenter study enrolling approximately 400 hospitalized patients (≥18 years of age) with a diagnosis of complicated urinary tract infection (including patients with acute pyelonephritis, which will be referred to collectively as cUTI) or complicated intra-abdominal infection (cIAI) who are known to have a ceftazidime resistant, Gram-negative pathogen as the etiology of their study qualifying infection.

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

Objectives

Primary objective

- To estimate the per-patient clinical response to ceftazidime-avibactam (CAZ-AVI, formerly [redacted]) and Best Available Therapy (BAT) at Test of Cure (TOC) in the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens

Secondary objectives

- To further evaluate the clinical response to CAZ-AVI and BAT at different visits and in patient subgroups (including entry diagnosis, pathogen, resistance mechanism, and previously failed treatment class)
- To estimate the microbiological response to CAZ-AVI and BAT in the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens
- To evaluate the reasons for treatment change and/or discontinuation for CAZ-AVI and BAT
- To estimate the 28-day, all-cause mortality among patients treated with CAZ-AVI and BAT
- To evaluate the safety and tolerability profile of CAZ-AVI and BAT for the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens
- To evaluate the pharmacokinetics (PK) of the individual components of CAZ-AVI in this population with selected serious infections, and to characterize the relationship between the PK and clinical and microbiological response for CAZ-AVI

Exploratory objectives

- To assess the change in symptoms from Baseline while on study therapy
- To collect blood samples for DNA extraction and storage for future possible exploratory research into genes that may include response, ie, distribution, safety, tolerability, and efficacy of CAZ-AVI and BAT and/or susceptibility to bacterial infections. The results of any genetic research will not form part of the clinical study report (CSR) for this study. Blood samples for DNA extraction will not be collected in all countries (eg, China).
- To collect and store plasma and serum samples from patients for possible biomarker analysis. The results of any biomarker analysis research will not be included in the CSR for this study.
- To collect data to allow an exploratory evaluation of health utilization

Study design

This is a Phase III, prospective, open-label, randomized, multicenter, study to evaluate the efficacy, safety, and tolerability of CAZ-AVI and BAT in the treatment of hospitalized adults with cIAIs or cUTIs caused by ceftazidime-resistant Gram-negative pathogens. For this

study, ceftazidime resistance is defined as those bacterial isolates whose susceptibility results are intermediate or resistant using Clinical Laboratory Standards Institute methodology and isolates that are resistant using European Committee on Antimicrobial Susceptibility Testing methodology. The duration of treatment is 5 to 21 days, where a full day is defined as a 24-hour period. The precise duration of therapy will be determined by the investigator based on the patient's response. Each patient is expected to complete the study, including FU visits. The entire study duration is expected to be approximately 30 months unless enrollment is extended. The patient must remain hospitalized during the first 5 days of treatment. Those patients who remain on study therapy after 5 days (15 doses for those patients randomized to CAZ-AVI) will receive their study therapy by study center personnel while in the hospital or qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT, TOC, FU1, and FU2 visits following discharge from the hospital.

Approximately 400 hospitalized patients (≥18 years of age) diagnosed with cIAI or cUTI caused by ceftazidime-resistant Gram-negative pathogens will be enrolled in the study. The diagnosis of infection will be based on the patient's clinical syndrome and the study-qualifying culture results. The patient must have a ceftazidime-resistant Gram-negative bacterial organism as the causative pathogen on the study-qualifying culture. A supplementary culture is required for all patients entering with a cUTI diagnosis. The supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy.

After obtaining written informed consent and confirming eligibility, the investigator will determine the BAT that the patient would be expected to receive based on assessment of the local resistance panel for the patient's isolate. Once the BAT has been chosen and documented, patients will be randomized in a 1:1 ratio according to the central randomization schedule to receive either CAZ-AVI or BAT. The randomization schema will be designed to ensure equal distribution in both treatment groups by entry diagnosis (patients with cIAI and cUTI) and by region (North America and Western Europe, Eastern Europe, and the rest of the world. Determination of BAT for a patient must be documented in the source documents by the investigator prior to randomization.

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 22 (Days 2 to 21)	While on therapy
End of Treatment (EOT with study therapy)	Within 24 hours after the completion of the last infusion of study therapy[a]
Follow-Up Period	
Test of Cure Visit (TOC)[b]	
cUTI	7 days after the last infusion of study therapy
cIAI	7 days after the last infusion of study therapy
Follow-Up 1 (FU1)[c]	
cUTI	Day 21[d]
cIAI	Day 28[e]
Follow-Up 2 (FU2)	
cUTI[f]	Day 28[g]
cIAI	No additional visit required

[a] Patients who discontinue 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 infusion of study therapy.
[b] The TOC visit may occur 7 to 10 days after the last infusion of study therapy.
[c] If it is not possible to perform the FU1 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 21 to Day 25 and for cIAI is Day 28 to Day 35.
[d] The designated windows for the TOC (7 to 10 days after the last infusion of study therapy) and FU1 (Day 21 to Day 25) visits may overlap depending upon the number of days the cUTI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU1 visits need to be performed only once.
[e] The designated windows for the TOC (7 to 10 days after last infusion of study therapy) and FU1 (Day 28 to Day 35) visits may overlap depending upon the number of days the cIAI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU1 visits need to be performed only once.
[f] If it is not possible to perform the FU2 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 28 to Day 32.
[g] The designated windows for the TOC (7 to 10 days after last infusion of study therapy) and FU2 (Day 28 to Day 32) visits for a cUTI patient may overlap depending upon the number of days the patient receives study therapy. In those instances, the TOC and FU2 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU2 visit only need to be performed once.

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection.

Target patient population

Approximately 400 (200 per treatment group, CAZ-AVI or BAT) hospitalized patients (≥18 years of age) diagnosed with cIAI or cUTI caused by ceftazidime-resistant Gram-negative pathogens will be enrolled in the study.

Certain specific organisms or specific resistance mechanisms or both are critical to meeting the outlined study objectives. Based on the changing resistance landscape at each site, the exact number anticipated for each of the organisms or resistance mechanisms of interest can not be predetermined. In the event that critical numbers of key organisms or specific resistance mechanisms are not obtained with the enrollment of the planned 400 patients, this trial may over-enroll up to an additional 100 patients so that the critical objectives can be met.

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

Patients randomized to receive CAZ-AVI will receive an infusion of CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) every 8 hours administered by intravenous (IV) infusion in a volume of 100 mL at a constant rate over 120 minutes. Patients randomized to receive CAZ-AVI for cIAI will also receive metronidazole (500 mg) administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes immediately following the CAZ-AVI infusion. No additional Gram-negative antibiotic coverage is allowed for patients randomized to the CAZ-AVI group.

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 or severely impaired renal function are described in the dose regimen adjustments section of the protocol.

Best Available Therapy, dosage, and mode of administration

Patients randomized to receive the investigator-determined BAT will receive doses based on the investigator's standard of care and the local label recommendation. The preferred BAT options are meropenem, imipenem, doripenem, tigecycline, and colistin (colistin does not cover anaerobes, if colistin is the therapy of choice, then the addition of metronidazole should be considered for anaerobic coverage). If a compound other than the 5 preferred options is chosen, or more than 1 antibacterial is chosen to be co-administered, then the investigator must document in the electronic case report form the reason a nonpreferred therapy was chosen. Patients randomized to the BAT group may receive combination therapy for Gram-negative coverage (such as with an aminoglycoside) as per the investigator's standard of care. All components of combination therapy must be selected and documented prior to randomization. If randomized to BAT, all components must be initiated at the start of study therapy.

Best available therapy must not consist solely of the original failed therapy. Switching therapy within the carbapenem class should be considered carefully by investigators as this may not represent best clinical practice. Details for dose and frequency of administration of

BAT can be found in the local package inserts for the specific BAT antibacterial selected by the investigator.

Coverage of Gram-positive, anaerobic, and fungal pathogens

Patients with polymicrobial infections may be entered into the study. If *Enterococcus* spp. or methicillin-resistant *Staphylococcus aureus* (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 as per the usual practice of the investigator. If vancomycin, linezolid, or daptomycin is started empirically to cover MRSA or *Enterococcus* spp., and if subsequent culture results did not isolate MRSA or *Enterococcus* spp., then the investigator should discontinue the additional Gram-positive coverage that was empirically added.

Metronidazole may be added for anaerobic coverage (Note: cIAI patients in the CAZ-AVI group will automatically receive metronidazole).

Patients with concurrent fungal infections may receive antifungal therapy.

Duration of treatment

Study therapy will be continued for a period of 5 to 21 days as deemed appropriate by the investigator based upon resolution of fever and improvement/resolution of other signs and symptoms that demonstrate clear evidence of local and systemic improvement. After 5 full days of 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 outcome variable

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

- Secondary efficacy outcome variables

  The secondary efficacy outcome variables include the following:

  – Proportion of patients with clinical cure at the EOT, FU1, and FU2 visits in the MITT analysis set and at the EOT, TOC, FU1, and FU2 visits in the extended microbiologically evaluable (ME) analysis set

  – Proportion of patients with clinical cure at the TOC visit, by pathogen (eg, *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*), by resistance mechanism (eg, *Klebsiella pneumoniae* carbapenemase [KPC] producer, extended spectrum β-lactamase [ESBL] producer), and by entry diagnosis (cIAI/cUTI), in the MITT and extended ME analysis sets

- Proportion of patients with clinical cure by previously failed treatment class (eg, quinolone, β-lactam/β-lactamase inhibitor, third- or fourth-generation cephalosporin, carbapenem), at the TOC visit in the MITT analysis set, and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set

- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits in the MITT and extended ME analysis sets

- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, FU1, and FU2 visits in the MITT and extended ME analysis sets

- Proportion of patients with a favorable microbiological response at the TOC visit by resistance mechanism (eg, KPC producer, ESBL producer) in the MITT and extended ME analysis sets

- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits, by minimum inhibitory concentration (MIC) categories in the MITT and extended ME analysis sets

- Reasons for treatment change and/or discontinuation in the MITT analysis set

- 28-day mortality rate in the MITT and extended ME analysis sets

- Safety and tolerability outcome variables

  Safety and tolerability will be assessed by the incidence and severity of adverse events (AEs) and serious AEs, exposure, mortality, reasons for discontinuation 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 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 outcome variables

  - Change in symptoms from Baseline at recorded time points in the MITT and extended ME analysis sets

Exploratory health utilization variables (to be reported outside of the CSR) in the MITT analysis set and in the extended ME at TOC analysis set include the following:

- Length of hospital stay
- Length of intensive care unit stay and/or transfer to the intensive care unit
- Length of study therapy
- Mortality caused by cIAIs and cUTIs (up to the TOC visit)

Statistical methods

The primary efficacy objective will be to estimate the per-patient clinical response to CAZ-AVI and BAT at the TOC visit. The primary efficacy outcome variable will be assessed in the MITT analysis set. Additional analysis sets are defined for the secondary efficacy outcome variables and for the safety analysis.

Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal power calculations have been performed for this study; therefore, the sample size is based on practical considerations.

The TOC, FU1, and FU2 visit dates are calculated from date of randomization and are different for each diagnosis. For patients entering with a cUTI diagnosis, TOC is 7 days after last study therapy, FU1 is Day 21 to Day 25, and FU2 is Day 28 to Day 32. For patients entering with a cIAI diagnosis, TOC is 7 days after last study therapy, FU1 is Day 28 to Day 35 and FU2 is not required.

- **Modified intent-to treat analysis set**

  The MITT analysis set includes all patients who:

  - Have a diagnosis of cIAI or cUTI with a ceftazidime-resistant pathogen on the study-qualifying culture and who received at least 1 dose of study therapy

- **Extended microbiologically evaluable analysis set at the EOT, TOC, FU1 and FU2 visits**

  The extended ME analysis set at the EOT, TOC, FU1, and FU2 visits includes all patients meeting the following criteria:

  - Were included in the MITT analysis set
  - Received at least 5 days of study therapy or received <48 hours of therapy before discontinuing due to an AE

- Had no important protocol deviations that would affect the assessment of efficacy

- Received no additional systemic, Gram-negative antibacterial therapy (other than study therapy as designated at randomization) for treatment of a non-cIAI or non-cUTI infection. This does not include antibiotic therapy taken for the treatment of cIAI or cUTI by patients who were considered failures.

- For cUTI patients only, had a microbiological assessment from a quantitative urine culture at the EOT, TOC, FU1, and FU2 visits, respectively, with a microbiological response other than indeterminate

Note: The extended ME analysis set terminology is used for consistency with the broader clinical CAZ-AVI program. An ME analysis set is not defined for this study.

- **Safety analysis set**:

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

- **Pharmacokinetic 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.

Timing of analysis:

The entire study duration is expected to be approximately 30 months and, therefore, this study is not expected to be completed until after completion of the pivotal Phase III cIAI and cUTI studies. Consequently, the data from the resistant pathogens study are intended to supplement the CAZ-AVI pivotal Phase III program and, therefore, will be included in any future regulatory submissions. The results of this study will be analyzed at 3 or more different time points including (a) in a time frame to allow the submission of these resistant pathogens data with the pivotal Phase III cIAI and cUTI data in the regulatory submissions, (b) in a time frame to allow the latest resistant pathogens data to be included in breakpoint discussions, and (c) at the end of this study.

As no formal statistical comparisons will be performed for this study, no adjustment for these multiple time points will be applied.

Analyses:

Two-sided 95% Wilson confidence intervals (CIs) for the proportion of patients with clinical cure within each treatment group (CAZ-AVI and BAT) at TOC will be calculated (Wilson 1927).

The primary efficacy objective of this study is to estimate the per-patient clinical response to CAZ-AVI and BAT at the TOC visit, in the MITT analysis set. This will be achieved by assessing the 2-sided 95% Wilson CIs for the proportion of patients with clinical cure at TOC for CAZ-AVI in the MITT analysis set. Results will be presented for the entire study population and separately by entry diagnosis. Corresponding CIs for the efficacy of the BAT will provide a context for these estimates of the efficacy of CAZ-AVI. Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Secondary efficacy outcome variables considering proportions will be analyzed by determining 2-sided 95% Wilson CIs for the outcome proportion within each treatment group (CAZ-AVI and BAT). Analyses of other secondary efficacy variables, baseline characteristics, and health utilization variables 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 study therapy. For microbiological cultures, the study-qualifying culture is the culture that documented the ceftazidime resistance that made the patient eligible for the trial and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit.

Pharmacokinetic analysis

The collected ceftazidime and avibactam concentrations will be listed and descriptively summarized at specified sampling windows in the CSR. Individual compartmental PK parameters of ceftazidime and avibactam for cIAI patients will be derived via a population modeling approach. The ceftazidime and avibactam 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 ceftazidime and avibactam plasma concentration data available will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, such as maximum concentration, minimum concentration, area under the plasma concentration-time curve at steady state, and terminal half-life, will be derived from the predicted ceftazidime and avibactam concentration time courses. All of the derived PK parameters will be descriptively summarized. The appropriate ceftazidime and avibactam exposure outcome variables predicted by the population PK modeling will be used for PK/PD modeling for appropriate microbiological or clinical cure outcome variables. A separate population PK and PK/PD modeling analysis plan will be prepared and the results will be reported separately.

Safety and tolerability analysis

The safety analysis will be performed using the safety analysis set. Safety parameters include AEs, clinical laboratory parameters, vital signs, 12-lead ECG parameters (QRS, RR, heart rate, QT, QTc, QTcB, and QTcF), and physical examinations. For each safety parameter, the

last assessment made prior to the first dose of study therapy will be used as the Baseline for all analyses. For the safety analysis, the patients will be presented under the treatment they received. The safety analysis will be presented by treatment group and diagnosis (cIAI, cUTI, and a combination of both). No statistical inference will be made for safety analysis.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
β-hCG	β-human chorionic gonadotropin
%T	Percentage of time above a threshold concentration
AE	Adverse event
ALT	Alanine aminotransferase
AmpC	A Class C β-lactamase (Amp = ampicillin)
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	Aspartate aminotransferase
BAT	Best Available Therapy
BP	Blood pressure
CAZ-AVI	Ceftazidime-avibactam
CFU	Colony-forming unit
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CLSI	Clinical Laboratory Standards Institute
CrCl	Creatinine clearance
CSA	Clinical study agreement
CSR	Clinical study report
C_T	Threshold concentration
cUTI	Complicated urinary tract infection
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
ESBL	Extended-spectrum β-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FU1	Follow-up 1
FU2	Follow-up 2
GCP	Good Clinical Practice
HHC	Home healthcare

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IP	Investigational product
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KPC	*Klebsiella pneumoniae* carbapenemase
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MITT	Modified intent to treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
PD	Pharmacodynamic
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PTA	Probability of target attainment
[redacted]	[redacted]
QT	QT interval
QTc	Corrected QT interval
QTcB	Corrected QT interval by Bazett formula
QTcF	Corrected QT interval by Fridericia formula
RR	R-R interval
SAE	Serious adverse event
SRP	Surgical review panel
TOC	Test of Cure
ULN	Upper limit of normal
WBC	White blood cell

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 Surgical Infection Society and 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* or *Pseudomonas* 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 Urinary tract infections

It is estimated that 2 million patients per year in the United States acquire infections while in hospitals, approximately 350000 (10% to 20%) of these infections involve the bloodstream, and 90000 (4.5%) are fatal (D'Agata 2004, Kang et al 2003, Cosgrove et al 2002, Karlowsky et al 2004). Gram-negative pathogens are responsible for a substantial proportion of infections in the community.

Among the Gram-negative pathogens, coliform (*Escherichia* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp.) and *Proteus* bacilli currently cause 29% of nosocomial infections in the United States. This group of nosocomial pathogens is responsible for 46% of urinary tract infections (UTIs), 24% of surgical site infections, 17% of bacteremia cases, and 30% of pneumonia cases (Guentzel 1996).

Among community-acquired infections, *Escherichia coli* is the major cause of UTIs, including prostatitis, pyelonephritis (hospitalization due to pyelonephritis), and septicemia. *Proteus* spp., *Klebsiella* spp., and *Enterobacter* spp. are also common urinary tract pathogens. *Proteus mirabilis* is the most frequent cause of infection-related kidney stones (Go et al 2004).

1.1.3 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 (eg, 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 a Class C β-lactamase (Amp = ampicillin) (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).

1.1.4 Other clinical trials in patients with serious infections due to resistant Gram-negative organisms

Industry-sponsored clinical trials involving patients with infections caused by resistant Gram-negative pathogens have not been conducted frequently. Wyeth conducted an open-label, Phase III, noncomparative, multicenter study to assess the efficacy and safety of intravenous (IV) tigecycline in hospital patients with serious infections, including patients with cIAI, caused by resistant Gram-negative bacteria, or failures who had received prior antimicrobial therapy or were unable to tolerate other antimicrobials (Vasilev et al 2008). All infections were due to resistant Gram-negative organisms, including extended-spectrum β-lactamase (ESBL)-producing strains. The primary efficacy endpoint was clinical response in the extended microbiologically evaluable (ME) population at Test of Cure (TOC). The clinical cure rate in the extended ME population at TOC was 72.2% with a microbiological eradication rate of 66.7%. The most commonly isolated resistant Gram-negative pathogens

were *Acinetobacter baumannii* (47%), *Escherichia coli* (25%), *Klebsiella pneumoniae* (16.7%), and *Enterobacter* spp. (11.0%). The mortality rate for the trial was 20 of 112 (17.9%) patients. The investigators did not consider the deaths to be related to tigecycline treatment but were considered to be consistent with the patient's underlying disease or a concomitant medical condition. These factors were taken into consideration when designing the endpoints, outcomes definitions, and expected mortality for this protocol.

1.1.5 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 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 et al 2004).

Infections due to ESBL-producing organisms are increasing across Europe (Coque et al 2008) and 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* infections. Resistance to carbapenems is rare but occurs in strains that produce serine-carbapenemases (*Klebsiella pneumoniae* carbapenemase [KPC] enzymes). Over the past decade a group of serine-carbapenemases has been increasingly reported from around the world (Hirsch et al 2010). As one example of this observation, resistance has been reported for imipenem in strains of *Enterobacter cloacae* (Fraser et al 2010). Hyperproduction (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).

1.1.6 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.

1.1.7 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, IV 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 patients with different degrees of renal impairment (Study NXL104/1003). The relationship between avibactam renal clearance and calculated creatinine clearance (CrCl) 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, formerly [redacted] that are consistent with those already recommended for ceftazidime (see Section 5.5.2.2).

Overall, preliminary data indicate that there were no major safety and tolerability concerns identified in this study. Additional details can be found in Section 5.1 of the CAZ-AVI Investigator's Brochure.

In addition, 2 other Phase 1 studies have been conducted:

- A Phase I double-blind, randomized, placebo-controlled, 4-way crossover thorough QT interval (QT) study to assess PK and safety in healthy volunteers (Study D4280C00007)

- A Phase I single and multiple dose study in healthy male Japanese subjects (Study D4280C00010)

Data from Study D4280C00007 indicate that a single supratherapeutic IV dose of CAZ-AVI (3000 mg ceftazidime plus 2000 mg avibactam) does not prolong the QTc (corrected QT interval) corrected by Fridericia formula (QTcF) beyond 10 ms. There were no QTcF values greater than 450 ms nor were there any QTcF changes from Baseline greater than 30 ms after a single supratherapeutic IV dose of CAZ-AVI.

In Study D4280C00010, avibactam alone and in combination with ceftazidime were well tolerated at the doses tested when administered as single and multiple doses to healthy male Japanese subjects. There were no clinically significant electrocardiogram (ECG) measurements, physical examination findings, or intestinal flora measurements following either treatment. Liver function parameter values were noteworthy for 1 subject, a healthy 41-year-old Japanese male (randomized to avibactam alone), who experienced transaminase elevations that were classified as other significant adverse events (AEs). After receiving multiple doses of avibactam, his highest transaminase results were: alanine aminotransferase (ALT) 522 U/L (reference range: 17 to 63 U/L) and aspartate aminotransferase (AST) 246

U/L (reference range: 15 to 41 U/L). His transaminase levels decreased but had not normalized at the time of the last follow-up visit. The subject had no symptoms at the time of the transaminase elevations. According to the investigator, the increases in the transaminase values were considered mild in severity and related to the investigational product. Given these findings, drug-induced liver injury is now considered an important potential risk for which appropriate clinical study program [redacted] and risk mitigation measures have been outlined. Details pertaining to these measures are specified in each individual clinical study protocol (eg, targeted follow-up study case report forms [CRFs] for potential Hy's Law reports). While increases in transaminase levels are not currently considered expected adverse drug reactions with avibactam alone, increases in transaminase levels are noted as expected adverse drug reactions for ceftazidime alone and ceftazidime combined with avibactam. Currently, this finding does not alter the benefit-risk profile for CAZ-AVI.

The PK of avibactam alone or in combination with ceftazidime was similar in Japanese subjects to that observed in studies of Western subjects.

1.1.8 Human experience – Phase II

A prospective, multicenter, double-blind, randomized, 2-arm, 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 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 ME patients (ie, patients with at least 1 pathogen isolated that was susceptible to both study therapies) with cIAI at the TOC visit, 2 weeks after treatment 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 AEs reported (>7.5% incidence overall) were nausea, vomiting, pyrexia, increased ALT, increased 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 therapy. 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 therapies). 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 after treatment) compared with imipenem. Similar microbiological response rates were seen in both treatment groups; at the TOC visit, 19 of 27 patients (70.4%) in the CAZ-AVI group and 25 of 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 Section 5.2.2 of the CAZ-AVI Investigator's Brochure.

1.2 Rationale for conducting this study

This is a Phase III study designed to evaluate the efficacy, safety, and tolerability of CAZ-AVI in the treatment of patients with cIAI and cUTI (including patients with acute pyelonephritis, which will be referred to collectively as cUTI) caused by ceftazidime-resistant Gram-negative pathogens. The results are intended to supplement the pivotal Phase III program. As discussed in Section 1.1.4, clinical studies in the resistant Gram-negative bacterial population are rare. This study is designed to obtain further information regarding these increasingly prevalent pathogens. This protocol also offers an opportunity to study patients who are typically excluded from or not recruited to pivotal Phase III trials (eg, patients with infections due to pathogens that are resistant to the chosen comparator and patients with multiple comorbidities).

The preferred Best Available Therapy (BAT) options for this protocol are defined as meropenem, imipenem, doripenem, tigecycline, and colistin. These agents were selected because they have established efficacy against the Gram-negative pathogens isolated in cIAIs and cUTIs and provide a context for estimates of efficacy in these clinical settings.

1.3 Benefit/risk and ethical assessment

Patients enrolled into this clinical study will have cIAIs or cUTIs that are of sufficient severity to require hospitalization and treatment with IV antibiotics. These patients may have limited options for antibiotic therapy. The potential benefit to patients participating in this study is that they would 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 and cUTIs, 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 or cUTIs. This risk is mitigated in that the 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 ceftazidime and avibactam, as well as the risks associated with other treatments that might be administered as described in

this protocol. As the risks for the BAT 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 intraarterial 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 or severe intensity in the CAZ-AVI group, who also received IV metronidazole (17 of 101 patients, 16.8%) versus the meropenem group (11 of 102 patients, 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 therapy per dose.

In the Phase II study (NXL104/2001) examining CAZ-AVI versus imipenem cilastatin followed by appropriate oral therapy as a comparator in cUTIs, approximately 35% of patients

in the CAZ-AVI group and 41% of patients in the imipenem cilastin group experienced a local reaction at the IV infusion site. The majority of these were mild or moderate in intensity. One patient in the imipenem cilastatin experienced a severe local reaction (induration, swelling). The most common infusion-related events across treatment arms were erythema, pain, and tenderness. Of note, patients in the CAZ-AVI group received 3 infusions per day, while patients in the imipenem group received 4 infusions per day.

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 study therapy 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 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 and cUTIs, it is possible that efficacy will not be demonstrated. For each patient in the trial, appropriate treatment of the cIAI or cUTI 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 estimate the per-patient clinical response to CAZ-AVI and BAT at TOC in the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens.

2.2 Secondary objectives

The secondary objectives of this study are:

- To further evaluate the clinical response to CAZ-AVI and BAT at different visits and in patient subgroups (including entry diagnosis, pathogen, resistance mechanism, and previously failed treatment class)

- To estimate the microbiological response to CAZ-AVI and BAT in the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens

- To evaluate the reasons for treatment change and/or discontinuation for CAZ-AVI and BAT
- To estimate the 28-day, all-cause mortality among patients treated with CAZ-AVI and BAT
- To evaluate the safety and tolerability profile of CAZ-AVI and BAT for the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens
- To evaluate the pharmacokinetics (PK) of the individual components of CAZ-AVI in this population with selected serious infections, and to characterize the relationship between the PK and clinical and microbiological response for CAZ-AVI

2.3 Exploratory objectives

The exploratory objectives of this study are

- To assess the change in symptoms from Baseline while on study therapy
- To collect blood samples for DNA extraction and storage for future possible exploratory research into genes that may include response, ie, distribution, safety, tolerability, and efficacy of CAZ-AVI and BAT and/or susceptibility to bacterial infections. The results of any genetic research will not form part of the clinical study report (CSR) for this study. Blood samples for DNA extraction will not be collected in all countries (eg, China).
- To collect and store plasma and serum samples from patients for possible biomarker analysis. The results of any biomarker analysis research will not be included in the CSR for this study.
- To collect data to allow an exploratory evaluation of health utilization

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, open-label, randomized, multicenter, study to evaluate the efficacy, safety, and tolerability of CAZ-AVI and BAT in the treatment of hospitalized adults with cIAIs and cUTIs caused by ceftazidime-resistant Gram-negative pathogens. For this study, ceftazidime resistance is defined as those bacterial isolates whose susceptibility results are classified as “intermediate” or “resistant” using Clinical Laboratory Standards Institute

(CLSI) methodology or isolates that are classified as "resistant" using European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology. The duration of treatment is 5 to 21 days, where a full day is defined as a 24-hour period. The precise duration of therapy will be determined by the investigator based on the patient's response. Each patient is expected to complete the study, including FU visits. The entire study duration is expected to be approximately 30 months unless enrollment is extended. The patient must remain hospitalized during the first 5 days of treatment. Those patients who remain on study therapy after 5 days (15 doses for those patients randomized to CAZ-AVI) will receive their study therapy by study center personnel while in the hospital or qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT, TOC, FU1, and FU2 visits following discharge from the hospital. The assessments at the FU1 and FU2 visits would provide data from this study that could be put into context with data from other Phase III CAZ-AVI trials conducted in patients with cUTI and cIAI.

Approximately 400 hospitalized patients (≥18 years of age) diagnosed with cIAI or cUTI caused by ceftazidime-resistant Gram-negative pathogens will be enrolled in the study. The diagnosis of infection will be based on the patient's clinical syndrome and the study-qualifying culture results. The patient must have a ceftazidime-resistant Gram-negative bacterial organism as the causative pathogen on the study-qualifying culture.

Certain specific organisms or specific resistance mechanisms or both are critical to meeting the outlined study objectives. Based on the changing resistance landscape at each site, the exact number anticipated for each of the organisms or resistance mechanisms of interest can not be predetermined. In the event that critical numbers of key organisms or specific resistance mechanisms are not obtained with the enrollment of the planned 400 patients, this trial may over-enroll up to an additional 100 patients so that the critical objectives can be met.

After obtaining written informed consent and confirming eligibility, the investigator will determine the BAT that the patient would be expected to receive based on assessment of the local resistance panel for the patient's isolate. Once the BAT has been chosen and documented, patients will be randomized in a 1:1 ratio according to the central randomization schedule to receive either CAZ-AVI or BAT. The randomization schema will be designed to ensure equal distribution in both treatment groups by entry diagnosis (patients with cIAI and cUTI) and by region (North America and Western Europe, Eastern Europe, and the rest of the world). Determination of BAT for a patient must be documented in the source documents by the investigator prior to randomization.

Intravenous study therapy (CAZ-AVI or BAT) will be continued for a period of time (5 to 21 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 of study therapy and at the discretion of the investigator, all study therapies may then be discontinued. Those patients who remain on study therapy will receive their study therapy by study center personnel while in the hospital or qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to

return to the study center for their EOT, TOC, FU1, and FU2 visits following discharge from the hospital.

An overall clinical assessment, vital sign measurement, and assessment of infection-related signs and symptoms will be performed at Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, FU1, and FU2 visits. For cIAI patients, clinical signs and symptoms will include abdominal signs and symptoms plus abdominal and wound examinations. For cUTI, clinical signs and symptoms include fever or chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, suprapubic pain, and nausea or vomiting. The investigator is responsible for determining the appropriate duration of study therapy and assessing the relationship of AEs to study therapy.

If a patient experiences diarrhea during or after 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 study therapy under certain circumstances that are described in detail in Section 5.8. Patients withdrawn from the 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 study therapy must be recorded in the electronic CRF (eCRF) and in the patient's medical records. If the patient is withdrawn from study therapy due to an AE, the AE must be reported in accordance with the procedures in Section 6.4. All patients should be followed, whenever possible, until the FU visits for the final outcome assessment and safety. If withdrawal from treatment with study 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 Day 0) up to and including the FU1 visit for cIAI patients and the FU2 visit for cUTI patients (see study periods table).

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 22 (Days 2 to 21)	While on therapy
End of Treatment (EOT with study therapy)	Within 24 hours after the completion of the last infusion of study therapy[a]
Follow-Up Period	
Test of Cure Visit (TOC)[b]	
cUTI	7 days after the last infusion of study therapy
cIAI	7 days after the last infusion of study therapy
Follow-Up 1 (FU1)[c]	
cUTI	Day 21[d]
cIAI	Day 28[e]
Follow-Up 2 (FU2)	
cUTI[f]	Day 28[g]
cIAI	No additional visit required

[a] Patients who discontinue 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 infusion of study therapy.

[b] The TOC visit may occur 7 to 10 days after the last infusion of study therapy.

[c] If it is not possible to perform the FU1 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 21 to Day 25 and for cIAI is Day 28 to Day 35.

[d] The designated windows for the TOC (7 to 10 days after the last infusion of study therapy) and FU1 (Day 21 to Day 25) visits may overlap depending upon the number of days the cUTI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU1 visits need to be performed only once.

[e] The designated windows for the TOC (7 to 10 days after last infusion of study therapy) and FU1 (Day 28 to Day 35) visits may overlap depending upon the number of days the cIAI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU1 visits need to be performed only once.

[f] If it is not possible to perform the FU2 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 28 to Day 32.

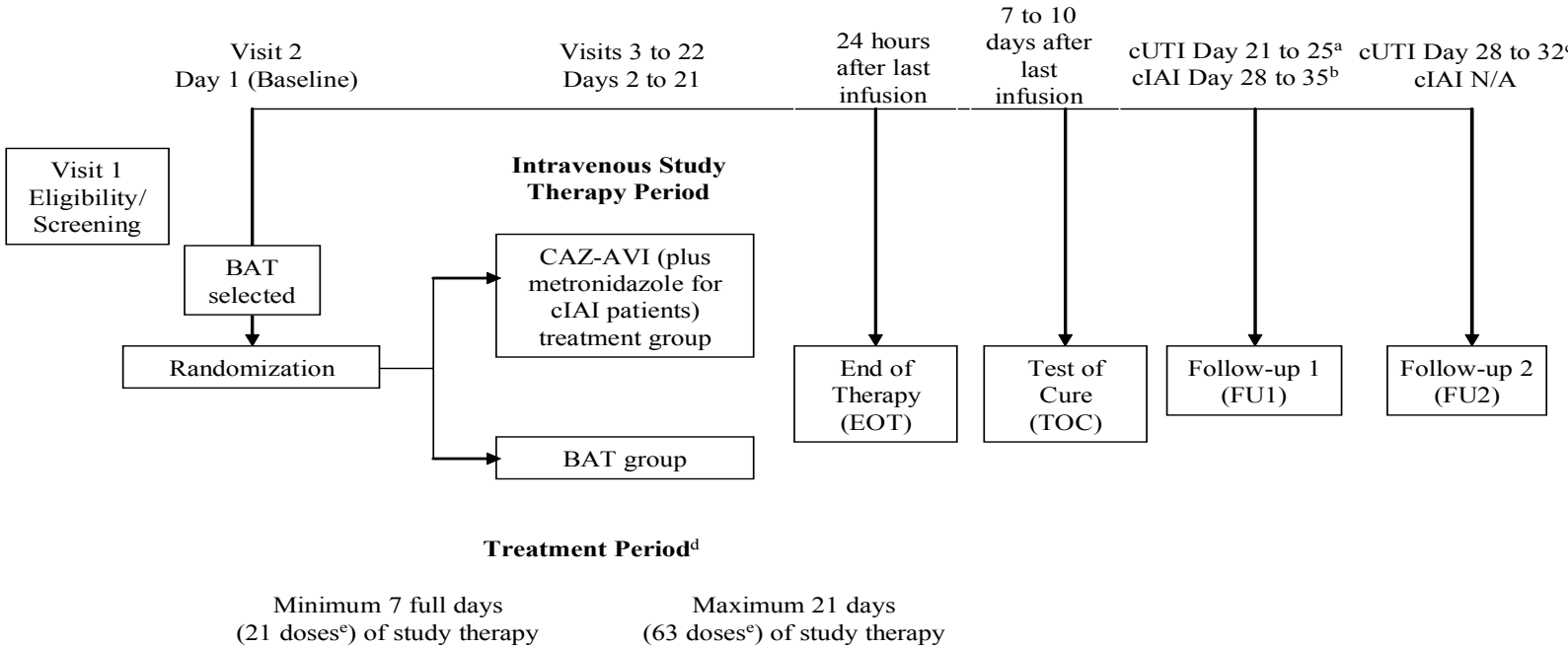
[g] The designated windows for the TOC (7 to 10 days after last infusion of study therapy) and FU2 (Day 28 to Day 32) visits for a cUTI patient may overlap depending upon the number of days the patient receives study therapy. In those instances, the TOC and FU2 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU2 visit only need to be performed once.

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection.

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. Details of the study plan are provided in Table 1.

Figure 1 Study flow chart



[a] The designated windows for the TOC (7 to 10 days after last dose of study therapy) and FU1 (Day 21 to Day 25) visits may overlap depending upon the number of days the cUTI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day.

[b] The designated windows for the TOC (7 to 10 days after last dose of study therapy) and FU1 (Day 28 to Day 35) visits may overlap depending upon the number of days the cIAI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day.

[c] The designated windows for the TOC (7 to 10 days after last dose of study therapy) and FU2 (Day 28 to Day 32) visits may overlap depending upon the number of days the cUTI patient receives study therapy. In those instances, the TOC and FU2 visits may be combined on the same day.

[d] Treatment Period doses are only for patients randomized to CAZ-AVI. Dosing intervals for BAT will be per the local standard of care.

[e] For patients with creatinine clearance >50 mL/min

Abbreviations: BAT, Best Available Therapy; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; N/A, not applicable.

Table 1 Study plan

	Eligibility/ Screening	Baseline[a]	Treatment Period[b]				
	Visit 1	Visit 2	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Informed consent[e]	X						
Inclusion and exclusion criteria	X	X					
Demographics	X						
Medical history[f]	X						
Review prior and concomitant medications (including prior antibiotic therapy)	X	X	Daily	X	X	X	X
Complete physical examination[g]	X			X	X	X	X
Assess infection-related signs and symptoms and perform focused physical examination[h]	X	X	Daily	X	X	X	X
Assess urinary device status (as appropriate for cUTI patients only)		X	X	X	X	X	X
Vital sign measurements[i]	X	X	Daily	X	X	X	X
12-Lead digital ECG[j]		X	X	X			
Monitor adverse events[k]	X	X	Daily	X	X	X	X
APACHE II score (see Appendix F)[l]	X						
Obtain isolate from study-qualifying culture and send to central laboratory[m]	X						

Table 1 Study plan

	Eligibility/ Screening	Baseline[a]	Treatment Period[b]				
	Visit 1	Visit 2	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Blood cultures[n] (if not previously documented as negative)		X[o]	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
Intra-abdominal culture (cIAI patients only)[p]		As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Quantitative urine culture (cUTI patients only)[q]		X		X	X	X	X
Urine for microscopic white blood cell count (cUTI patients only)[r]		X					
Blood and urine for safety analysis[s]	X	X	Every 3 days	X	X	X	X
Estimate creatinine clearance[t]	X	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
Serum β-hCG for women of childbearing potential[u]	X					X (for cIAI patients)	X (for cUTI patients)
Determination of Best Available Therapy prior to randomization[v]		X					
Randomization		X[w]					
Pharmacokinetic sample[x]			X				
Pharmacogenetic blood sample[y]		X					
Biomarker sample[z]		X		X			
Description of operative procedures (cIAI patients only)[aa]	As available	As available	As available	As available	As available	As available	

Table 1 Study plan

	Eligibility/ Screening	Baseline[a]	Treatment Period[b]				
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Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Administer study therapy[bb]		X	X				
Clinical response assessment				X	X	X	X
Record radiologic examination if performed (for cIAI patients only)[cc]	X						
Investigator case summary/operative notes/hospital discharge summary (for cIAI patients only)[dd]				X		X	
Mortality assessment			X	X	X	X	X

[a] Repeat assessments are not required for visits that occur on the same calendar day as the Eligibility/Screening visit.

[b] A minimum of 5 full days of treatment to a maximum of 21 days, where a full day is defined as a 24-hour period.

[c] Visit to be completed within 24 hours of last infusion of study treatment. Patients who discontinue study therapy should be scheduled for the EOT visit within 24 hours after the last infusion of study therapy, and should continue the study schedule as planned whenever possible.

[d] The TOC visit may occur 7 to 10 days after the last infusion of study therapy. If it is not possible to perform the FU1 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 21 to Day 25 and for cIAI is Day 28 to Day 35. The FU2 visit for cUTI patients may likewise be performed on Day 28 to Day 32 and is not required for cIAI patients. Depending on the number of days of study therapy, the FU1 or FU2 visit may fall within the window for the TOC visit, in which case the FU1 or FU2 visit may be combined with the TOC visit. All assessments for both visits must be performed. Assessments that are required at both the TOC and FU visits need to be performed only once.

[e] The overall consent covers sending the qualifying microbiological isolate obtained per routine standard of care to the central microbiology vendor for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics. A separate informed consent form must be signed for the pharmacogenetics and biomarker assessments prior to these assessments being conducted. Declining participation in the pharmacogenetics and biomarkers portion of the study will not exclude the patient from participating in the main study.

[f] History will include surgical history for cIAI patients.

[g] A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head, eyes, ears, nose, throat, and lymph nodes, and respiratory, cardiovascular, abdominal, musculoskeletal, and neurological systems. Height and weight will be measured at Screening only. Weight will be measured as necessary to calculate the patient's estimated CrCl.

[h] Infection-related signs and symptoms should be assessed daily while the patient is receiving study therapy. For cUTI patients, clinical signs and

Table 1 Study plan

	Eligibility/ Screening	Baseline[a]	Treatment Period[b]				
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Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**

symptoms include fever or chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, suprapubic pain, and nausea or vomiting. For cIAI patients, clinical signs and symptoms include abdominal signs and symptoms plus abdominal and wound examinations.

i Vital sign measurements include blood pressure, heart rate, respiratory rate, and body temperature. The patient should be resting in a supine position for at least 10 minutes before measuring blood pressure. Body temperature should be evaluated at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature measurement recorded. Height and weight will be measured at Screening only.

j A digital ECG must be performed prior to dosing on Day 1 (Baseline) and on Day 3 at the end of study infusion CAZ-AVI and BAT). The 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 ms or QTcF >460 ms) is observed, then additional ECG assessments must be performed (see Section 6.4.9).

k 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 FU visits. Should a patient experience significant diarrhea during or after study therapy, the investigator should consider obtaining a stool sample and testing for *C. difficile* toxin.

l See Appendix F for calculation. Patients with an Apache II score >30 must be excluded.

m Study-qualifying microbiological isolate demonstrating ceftazidime resistance as per local susceptibility testing within 5 days prior to study entry. Submission of this isolate to the central microbiology vendor is critical for study objectives: thus, the isolate must be sent to the central microbiology vendor for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics.

n When obtaining samples for blood cultures, 2 sets should be collected. If a blood culture prior to study entry also grew the same pathogen as the study-qualifying microbiological isolate from the disease under study, then this blood culture study-qualifying isolate will be utilized as the isolate to determine microbiological response for positive blood cultures.

o If blood cultures had not been performed previously or if previous blood cultures were positive, but repeat cultures had not yet shown clearance of bacteremia, an additional blood culture must be obtained at Baseline/Randomization as described in Section 3.1.2.1.

p For cIAI patients with surgical specimens collected on or after the Baseline visit, 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.

q A urine culture must be obtained at Baseline prior to the first dose of study therapy for cUTI patients.

r A microscopic analysis on centrifuged urine must be performed to confirm the presence of pyuria. A urine sample must also be submitted to the central laboratory.

s Local laboratory test results will be used to qualify patients for randomization. Laboratory specimens will be obtained prior to dosing and sent to the central reference laboratory. For any clinically significant abnormal laboratory results at FU visits, additional laboratory tests should be performed and results followed until resolution or stabilization. Abnormal laboratory results at TOC should be followed-up as clinically indicated. Local laboratory

Table 1 Study plan

	Eligibility/ Screening	Baseline[a]	Treatment Period[b]				
	Visit 1	Visit 2	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**

test results will be used to qualify patients for eligibility and randomization.

t Study center personnel will calculate the estimated creatinine clearance at Screening and when clinically indicated using serum creatinine results from the local laboratory. Appendix E provides details for the calculation of the estimated creatinine clearance.

u Serum β-hCG results must be available within 1 day of study entry per the inclusion criteria. If the results of the serum β-hCG cannot be obtained prior to dosing of the investigational product, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained. If a study center cannot do a serum β-hCG test, a urine β-hCG must be obtained.

v Investigator to choose BAT (including dose and dose interval) based on local susceptibility testing and document in the source documents prior to randomizing the patient. If a compound other than 1 of the 5 preferred options (meropenem, imipenem, doripenem, tigecycline, and colistin) is chosen, or more than 1 antibacterial is chosen to be co-administered, the investigator must document in the source documents the reason a nonpreferred therapy was chosen.

w Randomization will occur before dosing but after BAT is documented in the eCRF as noted in footnote "v."

x Plasma samples for pharmacokinetic assessments will be collected on Day 3 following a dose administration that is convenient for plasma sample collection at the following time points: anytime within 15 minutes prior to or after stopping any infusion, anytime between 30 minutes and 90 minutes after stopping any infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping any infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient.

y The pharmacogenetic sample should only be taken from consented patients prior to commencement of study therapy. If this sample is not taken prior to study therapy it may be taken at any point until the patient leaves the study.

z Biomarker samples should only be taken from consented patients. Biomarker samples should be taken at Baseline and at the following times: 8 hours after the beginning of study therapy infusion, 24 hours after the beginning of study therapy infusion, and at the EOT visit.

aa For cIAI patients, this includes any report from the procedure when the study-qualifying isolate was obtained and with any subsequent surgical procedures.

bb If necessary for patients receiving CAZ-AVI, a 1-time dosing interval adjustment can be made after the first dose of study therapy to create a suitable dosing schedule. For patients with normal renal function or with mild renal impairment (CrCl >50 mL/min), 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. 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. See Section 5.5.2.2 for additional guidance for patients with moderate or severe renal impairment (CrCl 50 to 6 mL/min).

cc For cIAI patients only, radiological examinations are not required for the study but the results should be recorded if assessed as part of the diagnosis. Radiological examinations include plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

Table 1 Study plan

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Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**

[dd] For cIAI patients only, all documentation including surgical reports and imaging studies for any surgical intervention performed during the study must be submitted as soon as it becomes available. For those patients whose surgical intervention was percutaneous abscess drainage, 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.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; β-hCG, β-human chorionic gonadotropin; BAT, Best Available Therapy; cIAI, complicated intra-abdominal infection; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; ECG, electrocardiogram; eCRF, electronic case report form; EOT, End of Treatment; FU1, Follow-up 1; FU2, Follow-up 2; N/A, not applicable; PK, pharmacokinetic; QTcF, corrected QT interval by Fridericia; TOC, Test of Cure.

3.1.1 Surgical review panel (cIAI patients only)

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 review while blinded to study therapy. For all patients classified as a clinical failure (after study randomization and receipt of study therapy or BAT) and all patients classified as cure at TOC who undergo another procedure subsequent to randomization, 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 reclassified as indeterminate and will be excluded from the extended ME analysis set.

3.1.2 Microbiological assessments

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

For microbiological cultures, the study-qualifying culture is the culture that documented the ceftazidime resistance, which made the patient eligible for the trial, and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit. For an organism to be considered a pathogen on the study-qualifying culture, it must be a Gram-negative bacterial organism and be resistant to ceftazidime (eg, all Enterobacteriaceae including *E. coli*, *Klebsiella* spp., *Proteus* spp., *Providencia* spp., *Citrobacter* spp., and *Serratia* spp. as well as nonfermentative Gram-negative pathogens such as *P. aeruginosa*). Gram-negative organisms not considered to be pathogens are presumed to be contaminants and are not appropriate for study entry.

For this study, ceftazidime resistance is defined as those isolates whose susceptibility results are intermediate or resistant using CLSI methodology and isolates that are resistant using EUCAST methodology.

3.1.2.1 Specimen collection

Abdominal culture for patients with cIAI

The ceftazidime-resistant Gram-negative bacterial isolate from the study-qualifying culture must be sent to the central microbiology vendor for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics. Any subsequent abdominal culture specimen should be sent to the local laboratory for culture, identification, and in vitro susceptibility testing and be processed according to recognized methods that culture for both aerobic and anaerobic bacterial 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 at Baseline and abdominal culture specimens should be obtained at the time of any surgical procedure. All Gram-negative cultured isolates that are resistant to ceftazidime 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.

Urine culture for patients with cUTI

The ceftazidime-resistant Gram-negative bacterial isolate from the study-qualifying culture must be sent to the central microbiology vendor for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics. An adequate urine specimen for microbiological evaluation must be obtained from all cUTI patients and sent to the local laboratory for culture, identification, and in vitro antibacterial susceptibility testing. The specimens should be processed according to recognized methods (Murray et al 2007) and following the standard operating procedures of the clinical microbiology laboratory at each study center. Urine culture specimens should be taken at Baseline (the supplementary culture) and at the EOT, TOC, FU1, and FU2 visits. All cultured isolates of Gram-negative uropathogens at $\geq 10^5$ colony-forming units (CFU)/mL at Baseline (the supplementary culture) and at the EOT, TOC, FU1, and FU2 visits as well as any Gram-negative uropathogen isolated at Baseline regardless of quantification in urine that are resistant to ceftazidime 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 laboratory.

Urine samples should not be obtained from urinary catheter bags. Preferred methods of collection of urine for culture include:

- Straight catheterization using sterile technique (preferred for female patients)
- Midstream clean catch
- Suprapubic specimen collection using sterile technique

- Whenever possible, urine specimens should not be obtained from indwelling catheters. When necessary, urine specimens in patients with indwelling bladder catheters should be obtained by sterile aspiration through the catheter port or by puncturing the catheter tubing with a needle and syringe if a port is not present.

The urine specimen should be plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, this test may be performed within 24 hours of collection if the specimen is stored at 2°C to 8°C before processing. The specimen for microscopic evaluation (eg, evidence of persisting pyuria) and culture obtained at Baseline should be collected before randomization and administration of study therapy.

Blood cultures for all patients (cIAI and cUTI)

If blood cultures had not been performed prior to study entry or if blood cultures were positive, but repeat cultures had not yet shown clearance of bacteremia, a blood culture must be obtained at Baseline/Randomization. Additional specimens for blood cultures will be collected as clinically indicated after randomization. Two sets of blood cultures should be collected from 2 different sites (ie, 4 tubes) 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. At least 1 set of blood cultures must be obtained through a venipuncture. Organisms isolated in the blood from a blood study-qualifying culture will be assigned a microbiological response similar to those given for pathogens isolated from abdominal cultures (cIAI) and to those given for uropathogens isolated from urine cultures as noted in Table 5, except that specification for quantity will not apply for blood isolates. The blood study-qualifying microbiological isolate will be utilized as the isolate to determine microbiological response. Details concerning the collection of blood cultures are provided in the laboratory manual.

Cultures from patients discontinuing or altering study therapy

It is recognized that some patients may need to discontinue study therapy earlier than planned secondary to treatment failure or for other reasons. For cUTI patients, any time the antibacterial therapy for the disease under study is changed; an appropriate specimen for culture should be obtained after stopping the initial treatment but before the new treatment is administered. This is to ensure accuracy of the database and assist with microbiological assessments. Other scheduled EOT assessments should also be performed. For patients with cUTI, the eCRF should indicate collection date and time for the urine sample.

Patients with cIAI who have study therapy discontinued early because the patient is failing therapy and the patient requires another surgery, an appropriate specimen for culture should be obtained, ideally after stopping study therapy 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 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 [redacted] representative.

3.1.2.3 Analysis of isolates

For patients with cIAI, 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. All isolated Gram-negative organisms, including the study-qualifying isolate, that are resistant to ceftazidime should be sent to the central reference laboratory for confirmation of identification and susceptibility testing. All anaerobic bacterial pathogens, including the study-qualifying isolate, must be identified to at least the genus level. All anaerobic isolates should be sent to the central reference laboratory for confirmation of identification and susceptibility testing.

For patients with cUTI, all Gram-negative pathogens resistant to ceftazidime meeting the criteria of $\geq 10^5$ CFU/mL from study-qualifying cultures and at EOT, TOC, FU1, and FU2 and all Gram-negative pathogens resistant to ceftazidime isolated from urine cultures collected at Baseline (the supplementary culture) regardless of quantification, must be identified to the genus and species level using confirmatory, not presumptive, identification methods. All isolated Gram-negative pathogens resistant to ceftazidime 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 reported Gram-negative isolates that are resistant to ceftazidime and shipped by the local laboratory. If discrepancies occur between the results obtained at the central reference laboratory and those obtained at the study center's local laboratory, a [redacted] 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 [redacted] 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 from the local laboratory to the central reference laboratory, or a microorganism is not recoverable from the local laboratory and therefore cannot be reshipped to the central reference laboratory.

3.2 Rationale for study design, doses, and control groups

This study is open-label and patients will be randomized in a 1:1 ratio to receive either CAZ-AVI or BAT. Patients randomized to receive investigator-determined BAT will receive doses based on the investigator's standard of care and the local label recommendation. The preferred BAT options are meropenem, imipenem, doripenem, tigecycline, and colistin (colistin does not cover anaerobes, if colistin is the therapy of choice, then the addition of

metronidazole should be considered for anaerobic coverage). If a compound other than the 5 preferred options is chosen, or more than 1 antibacterial is chosen to be co-administered, then the investigator must document in the eCRF the reason a nonpreferred therapy was chosen. Patients randomized to this BAT group may receive combination therapy for Gram-negative coverage (such as with an aminoglycoside) as per the investigator's standard of care. All components of combination therapy must be selected and documented prior to randomization. If randomized to BAT, all components must be initiated at the start of study therapy.

The BAT must not consist solely of the original failed therapy. Switching therapy within the carbapenem class should be considered carefully by investigators as this may not represent best clinical practice. Details for dose and frequency of administration of BAT can be found in the local package inserts for the specific BAT antibacterial selected by the investigator.

Given the target patient population for this study and the requirement to have a Gram-negative organism resistant to ceftazidime, many of the isolates will have multiple class resistance and resistance mechanisms including those not mediated by β-lactamases. Thus, the selection of a single antibiotic and dose that could be an appropriate control group for all patients is not possible. This study will be conducted in hospitalized patients with a diagnosis of cIAI or cUTI. The infections must be ceftazidime resistant on the study-qualifying culture and must be presumed CAZ-AVI susceptible.

The dose of ceftazidime approved for the treatment of serious Gram-negative infections for patients with a CrCl >50 mL/min is 2000 mg for 30 minutes intravenously every 8 hours and for patients with a CrCl ≥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. See Table 3 for full CAZ-AVI doses, regimens, and infusion times for patients with renal impairment.

Complicated intra-abdominal infections are typically polymicrobial, potentially involving anaerobes such as the *Bacteroides 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.

Gram-negative pathogens, including those producing ESBLs and AmpC β-lactamases, are important causes of cUTIs. The spectrum of activity of CAZ-AVI is well suited for the treatment of pathogens commonly responsible for cUTIs.

The drugs considered as BAT for this study are often used as treatment for cIAIs or cUTIs with resistant pathogens. Refer to local label for the dosing information.

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 ceftazidime as well as 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 (C_T) 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 minimum inhibitory concentration (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 ceftazidime and avibactam 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 ceftazidime plasma concentrations above an MIC of 8 mg/L for at least 50% of the dosing interval
- maintains unbound avibactam plasma concentrations above the C_T (1 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 with 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 1.1.8). 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.

For the Phase II study in patients with cUTI (Study NXL104/2001), a dose of 500 mg ceftazidime every 8 hours plus 125 mg avibactam every 8 hours was used. This was based on the US labeling text for ceftazidime (FORTAZ® prescribing information), with an assumption that high urinary concentrations of ceftazidime and avibactam would be yielded due to predominately renal excretion of both compounds and based on the preclinical data available at the time. While this dosage regimen was considered sufficient to cover the majority of bacteria in the urine, it did not take into account the importance of adequate drug concentrations at extra urinary sites. Patients with cUTI can have associated bacteremia, pyelonephritis, renal parenchymal abscess, and perinephric abscess. Thus Phase III dose regimen selection was based on PTA simulations (see Section 3.2.1.1) of plasma rather than urinary concentrations.

The PTA simulations ascertained that a higher dose and infusion time would be required to achieve the PD targets and joint PTA threshold of ≥0.9 described in Section 3.2.1.1. The joint PTA with the 500 mg ceftazidime/125 mg avibactam regimen used in Phase II (<0.05) was far from the desired joint PTA of ≥0.9. Based on these simulations, in order to achieve a joint PTA ≥0.9 a revised dose of 2000 mg ceftazidime/500 mg avibactam given every 8 hours and infused over a period of 2 hours is proposed for Phase III studies in patients with cUTI.

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 into the study or receive study therapy. There can be no exceptions to this rule. Patients discontinued from the study should be followed for safety.

Where patients that 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 [redacted] physician immediately (see Section 5.3). The patient may continue to receive study therapy or be discontinued from study therapy at the investigator's discretion. The [redacted] physician is to ensure all such contacts are appropriately documented.

4.1 Inclusion criteria

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

All Patients

1. Patient must be ≥18 years of age

2. 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 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. 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:

- Had normal menstrual periods for the 3 months prior to study entry, and
- Has a negative serum pregnancy test (serum β-human chorionic gonadotropin [β-hCG]) within 1 day prior to study entry (if the results of the serum β-hCG cannot be obtained prior to dosing of the IP, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained), and
- Must be willing, during treatment and for at least 28 days after last infusion of study therapy, to practice highly effective methods of birth control such as intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), 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. Patient has a ceftazidime-resistant Gram-negative pathogen that was isolated from an appropriate culture within 5 days prior to study entry (ie, the study-qualifying culture), which was determined to be the causative agent of the entry infection and there is an isolate available to be sent to the central laboratory. For this study, ceftazidime resistance is defined as those bacterial isolates whose susceptibility results are intermediate or resistant using CLSI methodology and isolates that are resistant using EUCAST methodology.

   All ceftazidime-resistant Gram-negative isolate(s) from the study-qualifying culture(s) must be sent to the central laboratory.

5. Patients who have received appropriate prior empiric antibacterial therapy for a ceftazidime-resistant pathogen must meet at least 1 of the following criteria (Note: therapy is considered appropriate if microbiological susceptibility test results show that all ceftazidime-resistant pathogens are susceptible to the empiric antibacterial[s] received):

(a) Worsening of objective symptoms or signs of infection after at least 48 hours of appropriate therapy

(b) Lack of improvement of objective symptoms or signs of infection after at least 72 hours of appropriate therapy

(c) Persistent positive cultures from the site of infection or from blood

Note: Symptomatic patients (see inclusion criteria 9 and 12) with an isolated causative pathogen that was not susceptible to the prior empiric therapy received or who received no prior empiric therapy are eligible for this trial.

For inclusion in the genetic component of the study, patients must fulfill the following additional criterion:

6. Patient provides signed, written, and dated informed consent for genetic research. If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the volunteer. The patient will not be excluded from other aspects of the study described in this clinical study protocol, so long as he or she provides a signed written informed consent to participate in the main study.

Additional Inclusion Criteria - cIAI Patients

7. Patient must have a ceftazidime-resistant Gram-negative pathogen isolated from an abdominal source during a surgical intervention. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery.

8. Patients 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 and 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 or chronic ascites)

(g) Tertiary peritonitis (based on failure entry criteria defined above)

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

9. Patient has at least 1 of the following signs/symptoms from each of the following 2 groups:

(a) Group A:

- Fever (defined as body temperature >38°C)
- Hypothermia with a core body temperature <35°C
- Elevated white blood cell count (>12000 cells/mm^3)
- Chills

(b) Group B:

- Abdominal pain
- Nausea
- Vomiting
- Tenderness to palpation
- Rebound tenderness
- Guarding

Additional Inclusion Criteria - cUTI Patients

10. Patient had a positive urine culture in the 5 days prior to Screening, containing $\geq 10^5$ CFU/mL of at least 1 Gram-negative uropathogen known to be ceftazidime resistant, ie, the isolate from the study-qualifying culture

11. Patient had pyuria in the 5 days prior to Screening as determined by a midstream clean catch or catheterized urine specimen with ≥10 white blood cells (WBCs) per high-power field on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine

12. Patient demonstrates either acute pyelonephritis or complicated lower UTI without pyelonephritis as defined by the following criteria:

(a) Acute pyelonephritis indicated by flank pain (which must have onset or worsened within 7 days of enrollment) or costovertebral angle tenderness on examination and at least 1 of the following:

- Fever, defined as body temperature >38°C (with or without patient symptoms of rigor, chills, or warmth) documented within 12 hours of entry into the study
- Nausea and/or vomiting

OR

(b) Complicated lower UTI, as indicated by qualifying symptoms plus at least 1 complicating factor as follows:

- Qualifying symptoms: patient must have at least 2 of the following symptoms with at least 1 symptom from Group A:
  - Group A symptoms include dysuria, urgency, frequency, and or suprapubic pain
  - Group B symptoms include fever (defined as body temperature >38°C with or without patient symptoms of rigor, chills, warmth), nausea, and/or vomiting
- Complicating factors: patient must have at least 1 of the following complicating factors:
  - Documented history of urinary retention (male patients)
  - Obstructive uropathy that is scheduled to be medically or surgically relieved during study therapy and before the EOT
  - Functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a postvoid residual urine volume of at least 100 mL
  - Use of intermittent bladder catheterization or presence of an indwelling bladder catheter for at least 48 hours prior to obtainment of study-qualifying culture
  - Urogenital procedure (such as cystoscopy or urogenital surgery) within the 7 days before study entry prior to obtainment of study qualifying-culture

4.2 Exclusion criteria

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

All Patients

1. Patient has an APACHE II score >30
2. Patient has an infection due to Gram-negative bacterial species that is unlikely to respond to CAZ-AVI treatment (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.)
3. Patient has a rapidly progressive or terminal illness, including acute hepatic failure or respiratory failure with a high risk of mortality due to other causes
4. Patient has a history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to carbapenem or cephalosporin or other β-lactam antibiotics
5. Patient is unlikely to respond to 5 to 21 days of study treatment
6. Patient has a concurrent infection that may interfere with the evaluation of response to the study antibacterials
7. Patient has a need for effective concomitant systemic antibacterials in addition to those allowed per protocol
8. Patient is receiving hemodialysis or peritoneal dialysis
9. Patient has an estimated CrCl <6 mL/min by Cockcroft-Gault formula (Cockcroft and Gault 1976). Refer to Appendix E for the formula for calculating CrCl.
10. Presence of hepatic disease as indicated by ALT or AST >3 × upper limit of normal (ULN) at Screening. Patients with AST and/or ALT up to 5 × ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.
11. Patient has a bilirubin >3 × ULN, unless isolated hyperbilirubinemia is directly related the acute process
12. Patient has acute hepatic failure or acute decompensation of chronic hepatic failure
13. Patient has a perinephric infection
14. Patient has any illness (eg, significant immunosuppression) that, in the opinion of the investigator, may confound the results of the study or pose additional risks in administering the study therapy to the patients.
15. Patient has an absolute neutrophil count <500/mm^3

16. Patient has previously been treated with the CAZ-AVI

17. 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 the 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.

18. Patient has been previously enrolled in this study

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

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

21. Patient is unlikely to comply with protocol, eg, uncooperative attitude, inability to return for FU visits, and unlikelihood of completing the stud.

In addition, the following are considered criteria for exclusion from the genetic research:

22. Patient received nonleukocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection

23. Patient had previous allogenic bone marrow transplant

Additional Exclusion Criteria - cIAI Patients

24. Patient has infections limited to the hollow viscous, such as simple cholecystitis, gangrenous cholecystitis without rupture, and simple appendicitis

25. Patient has acute suppurative cholangitis, infected necrotizing pancreatitis, or pancreatic abscess

26. Patient has abdominal wall abscess or small-bowel obstruction without perforation or ischemic bowel without perforation

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

28. 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 re-operation is planned.

29. Patient has a history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to metronidazole

Additional Exclusion Criteria - cUTI Patients

30. More than 2 pathogens are isolated from the patient's study-qualifying urine culture regardless of the colony count

31. Patient had a renal transplant

32. Patient has a complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, or prostatitis

33. Patient has a permanent urinary diversion (eg, ileal loops, cutaneous ureterostomy) or vesicoureteral reflux

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 healthcare provider's specific recommendations for effective use of these methods after completing 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. However, if a patient is unable to consent, 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 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. Determine and document the proposed BAT in the source documents

7. After written informed consent has been obtained and eligibility established, the study center's 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 randomized to treatment in a 1:1 ratio to CAZ-AVI (plus metronidazole for cIAI patients) or BAT. The BAT dose and dosing interval must be recorded in the source documents prior to randomizing the patient. The investigator will determine BAT based on assessment of the local resistance panel for the patient's isolate. The randomization schema will be stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe and the rest of the world) to ensure equal distribution in both treatment arms.

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

5.3 Procedures for handling patients incorrectly enrolled or randomized

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

Where patients that 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 [redacted] physician immediately. The [redacted] physician is to ensure that all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study (not applicable)

This is an open-label study. Blinding procedures are not applicable.

5.5 Treatments

5.5.1 Identity of investigational products

CAZ-AVI contains both ceftazidime and avibactam, 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 100 mL saline.

Information on the IP (CAZ-AVI [plus metronidazole for cIAI patients]) dosage, form, and strength is provided in Table 2. Investigational product and metronidazole (for cIAI patients only) will be supplied by AstraZeneca. The BAT will be supplied by the study centers.

Table 2 Investigational products: dosage, form, and strength

Investigational product	Dosage, form, and strength
CAZ-AVI (single-vial product supply)	Sterile crystalline powder, 2000 mg ceftazidime/500 mg avibactam for solution for infusion
Metronidazole intravenous[a]	Metronidazole 500 mg/100 mL solution for infusion

[a] All cIAI patients will receive metronidazole in addition to CAZ-AVI.
Abbreviations: CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intra-abdominal infection.

5.5.2 CAZ-AVI doses and treatment regimens

All patients randomized to receive CAZ-AVI will receive IV CAZ-AVI as outlined in Sections 5.5.2.1 and 5.5.2.2. For patients with cIAI, this will be followed immediately by IV metronidazole (500 mg). Patients randomized to receive BAT will be treated according to locally accepted standard of care and local label. No additional Gram-negative antibiotic coverage is allowed for patients randomized to the CAZ-AVI group.

5.5.2.1 CAZ-AVI dosing intervals in patients with normal renal function and patients with mild renal impairment (creatinine clearance >50 mL/min)

Treatment with CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) will be repeated every 8 hours (±30 minutes) administered by IV infusion in a volume of 100 mL at a constant

rate over 120 minutes. If necessary, a 1-time dosing interval adjustment can be made after the first dose of 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 CAZ-AVI dose regimen adjustments for patients with moderate to severe renal impairment (creatinine clearance 50 to 6 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 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. 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.

Dose adjustments for CAZ-AVI for patients with an estimated CrCl between 50 and 6 mL/min are outlined in Table 3. Since decreased renal function does not alter the PK of metronidazole, dosing adjustments for metronidazole are not needed for patients with cIAI as the entry diagnosis.

Table 3 CAZ-AVI dose, regimens, and infusion times for patients with renal impairment (creatinine clearance 50 to 6 mL/min)

Estimated creatinine clearance (mL/min)[a]	Ceftazidime and avibactam dose, interval, duration
50 to 31	1000 mg ceftazidime and 250 mg avibactam every 12 hours ±30 minutes over 120 minutes at a constant rate of infusion
30 – 16	1000 mg ceftazidime and 250 mg avibactam every 24 hours ±30 minutes over 120 minutes at a constant rate of infusion
15 – 6	500 mg ceftazidime and 125 mg avibactam every 24 hours ±30 minutes over 120 minutes at a constant rate of infusion

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

Note: Metronidazole infusion time = 60 min (for cIAI patients). Dosing adjustments for metronidazole are not needed.

5.5.2.3 Metronidazole dosing for patients with complicated intra-abdominal infections

Dosing adjustments for metronidazole are not needed since decreased renal function does not alter the PK of metronidazole. For patients with cIAI, metronidazole will be administered immediately following completion of each CAZ-AVI infusion at a constant dose of 500 mg/100 mL over a 60-minute time period.

5.5.3 Best Available Therapy doses and treatment regimens

Patients randomized to receive the investigator-determined BAT will receive doses based on the investigator's standard of care and the local label recommendation. The preferred BAT options are meropenem, imipenem, doripenem, tigecycline, and colistin (colistin does not cover anaerobes, if colistin is the therapy of choice, then the addition of metronidazole should be considered for anaerobic coverage). If a compound other than the 5 preferred options is chosen, or more than 1 antibacterial is chosen to be co-administered, then the investigator must document in the source document the reason a nonpreferred therapy was chosen. Patients randomized to this BAT group, may receive combination therapy for Gram-negative coverage (such as with an aminoglycoside) as per the investigator's standard of care. Only those patients treated with BAT may receive additional Gram-negative coverage. All components of combination therapy must be selected and documented prior to randomization. If randomized to BAT, all components must be initiated at the start of study therapy.

The BAT must not consist solely of the original failed therapy. Switching therapy within the carbapenem class should be considered carefully by investigators as this may not represent best clinical practice. Details for dose and frequency of administration of BAT can be found in the local package inserts for the specific BAT antibacterial selected by the investigator.

5.5.3.1 Dose adjustments for patients receiving Best Available Therapy with renal impairment

The investigator should follow dose adjustments for patients with renal impairment as established by the locally accepted standard of care and local label.

5.5.4 Additional study therapy

No additional study therapy will be provided during this study.

5.5.5 Labeling

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

5.5.6 Storage

All study therapy should be kept in a secure place under appropriate storage conditions. The storage conditions will be stated on the study therapy 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 FU visits (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 FU visits).

In patients with cIAI, 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 of cIAI patients.

Patients with polymicrobial infections may be entered into the study. If *Enterococcus* spp. or methicillin-resistant *Staphylococcus aureus* (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 as per the usual practice of the investigator. If vancomycin, linezolid, or daptomycin is started empirically to cover MRSA or *Enterococcus* spp., and if the subsequent culture results did not isolate MRSA or *Enterococcus* spp., then the investigator should discontinue the additional Gram-positive coverage that was empirically added.

Metronidazole may be added for anaerobic coverage (Note: cIAI patients in the CAZ-AVI group will automatically receive metronidazole). Simultaneous administration of 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 co-administration of study therapy with an oral anticoagulant agent, as per local practice.

Patients with concurrent fungal infections may receive antifungal therapy.

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 study therapy, the investigator should contact the AstraZeneca physician or [redacted] 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 study therapy and are in the FU period should remain in the study as they are not actively on study therapy but being followed for outcomes.

For those receiving BAT, the investigator should refer to the local label(s) to assess and understand pertinent drug-to-drug interactions for the BAT option(s) selected.

5.7 Treatment compliance

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

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

5.7.1 Accountability

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

Intravenous study therapy will be dispensed to the investigator or medically qualified personnel by the study center pharmacist. Intravenous study therapy will only be prepared and administered to patients by the study center pharmacists and medically qualified personnel who have been appropriately trained to prepare and administer study therapy. Written authorization of study personnel to administer IP must be documented for both hospital staff and, when applicable, home healthcare (HHC) staff, on the Delegation of Authority Log in 1 of 2 ways:

- All study staff trained and authorized by the investigator to administer 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 and pharmacy staffs are appropriately trained on study therapy preparation and administration prior to preparing and administering it, and for maintaining current and complete training documentation at all times.

Written documentation of training of 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 that the 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 study therapy usage should include the identification of the person to whom the study therapy was administered, the quantity and date of administration, and a record of unused study therapy. The investigator and pharmacist are responsible for maintaining accurate study therapy accountability records throughout the study on the relevant forms provided by AstraZeneca [redacted]. Each administration of 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 (specifically CAZ-AVI and metronidazole [for patients with cIAI in the CAZ-AVI group]), 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 [redacted] representative performs complete study therapy accountability during each monitoring visit, including verifying documentation of receipt, dispensing, return, and destruction of study therapy and consistency of this documentation with physical inventory and IVRS/IWRS.

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

For patients randomized to the BAT group, the investigator or medically qualified personnel will only be required to document the name of the BAT, the dose administered, who administered it, and when it was administered.

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
- Adverse event (eg, risk to patients, as judged by the investigator and/or safety review committee, [redacted] 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 [redacted] 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 [redacted] Physician where possible.

- Severe noncompliance to study protocol, as judged by the investigator and/or [redacted] or AstraZeneca
- Treatment failure
- In the opinion of the investigator, it is not in the best interest of the patient to continue the study therapy or at the request of the [redacted] representative or AstraZeneca that the patient stops participation in the study.

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 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 TOC visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and Section 6.4.5).

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 (study therapy 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 FU 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's 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 patient's medical records as per the study center'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 [redacted] 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 (see Table 1) and discussed by visit in Sections 6.2.1 to 6.2.7.

6.2.1 Visit 1 Eligibility/Screening (Days –1 to 0) assessment procedures

At Eligibility/Screening (Day –1 to Day 0), each potential patient will provide informed consent prior to starting any study-specific procedures.

Each patient will undergo screening assessment procedures less than 24 hours prior to the first dose of study therapy.

Screening assessments will consist of:

1. Obtaining informed consent
2. Reviewing inclusion and exclusion criteria with the patient
3. Ensuring that the isolate from the study-qualifying culture is still available at the local microbiology laboratory and that it will be retained to be sent to the central microbiology vendor should the patient successfully qualify for the study
4. Collecting demographics
5. Collecting medical history
6. Reviewing prior and current medications (including prior antibiotic therapy)

7. Performing complete physical examination as defined in Section 6.4.8. Height will be measured at Screening only. Weight will be measured as necessary to calculate the patient's estimated CrCl.

8. Assessing infection-related signs and symptoms

9. Measuring vital signs including supine blood pressure (BP), heart rate, respiratory rate, 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 $cm/100)^2$.

10. Monitoring for AEs

11. Determining APACHE II score (see Appendix F)

12. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (central reference laboratory)

13. Obtaining a urine sample for routine urinalysis (central reference laboratory)

14. Estimating CrCl using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)

15. Obtaining a 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 the investigational product, 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 can not do serum β-hCG testing, a urine β-hCG test must be obtained.

16. Collecting a description of the operative procedure(s) (as available for cIAI patients only)

17. Recording radiologic examination results (for cIAI patients only) if assessed 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.

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

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 inclusion and exclusion criteria with the patient
2. Reviewing prior and concomitant medications
3. Assessing infection-related signs and symptoms
4. Performing focused physical examination
5. Assessing urinary device status (as appropriate for cUTI patients only)
6. Measuring vital signs including supine BP, heart rate, respiratory rate, and temperature as defined in Section 6.4.10
7. Performing a digital 12-lead 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.
8. Monitoring for new AEs and reviewing ongoing AEs
9. Obtaining a blood sample for blood culture if a blood culture had not been previously obtained or if blood cultures were positive, but repeat blood cultures had not yet shown clearance of bacteremia
10. Obtaining an intra-abdominal culture from the infection site (as clinically indicated for cIAI patients only)
11. Obtaining a urine sample for quantitative urine culture (cUTI patients only)
12. Obtaining a urine sample for microscopic WBC count to assess for presence of persisting pyuria (cUTI patients only)
13. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (central reference laboratory)
14. Obtaining a urine sample for routine urinalysis (central reference laboratory)
15. Estimating CrCl (as clinically indicated) using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)
16. Determining appropriate BAT and documenting selected BAT in the source documents (prior to randomization). Level of detail on BAT should include name of drug and dose and frequency of administration for the therapy.
17. Randomizing eligible patient to treatment group using the IVRS/IWRS

18. Collecting a blood sample for pharmacogenetic (PGx) research analysis (only from patients who signed the separate PGx informed consent and will receive study therapy). If this sample is not taken prior to study therapy, it may be taken at any point until the patient leaves the study.

19. Obtaining a blood sample for biomarker analysis (only from those patients consenting to biomarker sample collection/analysis)

20. Collecting a description of operative procedure(s) (as available, for cIAI patients only)

21. Administering study therapy. Note all other baseline assessments should be complete before the patient receives the first dose of study therapy.

6.2.3 Visits 3 to 22 (Days 2 to 21) assessment procedures

The total number of days of combined treatment with study therapy will be a minimum of 5 and a maximum of 21 days. Those patients who remain on study therapy after 5 days (15 doses for patients randomized to the CAZ-AVI group with normal renal function or mild renal impairment) will receive their study therapy from study center personnel while in the hospital or from a qualified healthcare 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 study therapy:

1. Reviewing concomitant medications (daily)

2. Assessing infection-related signs and symptoms (daily)

3. Performing focused physical examination (daily)

4. Assessing urinary device status (as appropriate for cUTI patients only)

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

6. Performing a digital 12-lead ECG at the end of dosing on Day 3 (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.

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

8. Obtaining a blood sample for blood culture (as clinically indicated)

9. Obtaining an intra-abdominal culture from the infection site (as clinically indicated for cIAI patients only)

10. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments every 3 days (central reference laboratory)

11. Obtaining a urine sample for routine urinalysis every 3 days (central reference laboratory)

12. Estimating CrCl (as clinically indicated) using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)

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

14. Collecting a description of operative procedure(s) (any postbaseline procedures, as available for cIAI patients only)

15. Administering study therapy (daily for a minimum of 5 full days to a maximum of 21 full days, where a full day is defined as a 24-hour period)

16. Assessing mortality

6.2.4 EOT visit assessment procedures

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

1. Reviewing concomitant medications

2. Performing complete physical examination as defined in Section 6.4.8

3. Assessing infection-related signs and symptoms

4. Assessing urinary device status (as appropriate for cUTI patients only).

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

6. 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.

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

8. Obtaining a blood sample for blood culture (as clinically indicated)

9. Obtaining an intra-abdominal culture from the infection site (as clinically indicated for cIAI patients only)

10. Obtaining a urine sample for quantitative urine culture (cUTI patients only)

11. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (central reference laboratory)

12. Obtaining a urine sample for routine urinalysis (central reference laboratory)

13. Estimating CrCl (as clinically indicated) using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)

14. Obtaining a blood sample for biomarker analysis (only from those patients consenting to biomarker sample collection/analysis)

15. Collecting a description of operative procedure(s) (as available for cIAI patients only)

16. Determining clinical response assessment

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

17. Obtaining investigator case summary, operative notes, and hospital discharge summary (ongoing as available for cIAI patients only)

18. Assessing mortality

6.2.5 TOC visit assessment procedures

The TOC visit may occur between 7 and 10 days after the last infusion of study therapy.

The following procedures will be performed at the TOC visit:

1. Reviewing concomitant medications

2. Performing complete physical examination as defined in Section 6.4.8

3. Assessing infection-related signs and symptoms

4. Assessing urinary device status (as appropriate for cUTI patients only)

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

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

7. Obtaining a blood sample for blood culture (as clinically indicated)

8. Obtaining an intra-abdominal culture from the infection site (as clinically indicated for cIAI patients only)

9. Obtaining a urine sample for quantitative urine culture (cUTI patients only)

10. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (central reference laboratory)

11. Obtaining a urine sample for routine urinalysis (central reference laboratory)

12. Estimating CrCl (as clinically indicated) using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)

13. Collecting a description of operative procedure(s) (as available for cIAI patients only)

14. Determining clinical response assessment

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

15. Assessing mortality

6.2.6 FU1 visit assessment procedures

The FU1 visit dates are calculated from the date of randomization and are different for each diagnosis. For patients entering the study with a diagnosis of cUTI, the FU1 visit should be conducted on Day 21 with a visit window of Day 21 to Day 25. For patients entering with a diagnosis of cIAI the FU1 visit should be conducted on Day 28 with a visit window of Day 28 to Day 35. Depending on the number of days of study therapy, it is possible for the FU1 visit window to overlap with the TOC (7 to 10 days after last study therapy) visit window. In those instances where the TOC and FU1 windows overlap, the 2 visits may be combined into 1 visit. All assessments for the TOC and FU1 visit must be completed, but any duplicate assessments only need to be completed 1 time.

The following procedures will be performed at the FU1 visit:

1. Reviewing concomitant medications

2. Performing complete physical examination as defined in Section 6.4.8

3. Assessing infection-related signs and symptoms

4. Assessing urinary device status (as appropriate for cUTI patients only)

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

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

7. Obtaining a blood sample for blood culture (as clinically indicated)

8. Obtaining an intra-abdominal culture from the infection site (as clinically indicated for cIAI patients only)

9. Obtaining a urine sample for quantitative urine culture (cUTI patients only)

10. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (central reference laboratory)

11. Obtaining a urine sample for routine urinalysis (central reference laboratory)

12. Estimating CrCl (as clinically indicated) using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)

13. Obtaining a blood sample for serum β-hCG for women of childbearing potential (for cIAI patients only)

14. Collecting a description of operative procedure(s) (as available for cIAI patients only)

15. Determining clinical response assessment

16. Obtaining investigator case summary, operative notes, and hospital discharge summary (ongoing as available for cIAI patients only)

17. Assessing mortality

6.2.7 FU2 visit assessment procedures (cUTI patients only)

The FU2 visit is only required for the cUTI patients. The FU2 visit should be conducted on Day 28. If it is not possible to conduct the visit on Day 28, the FU2 visit window is Day 28 to Day 32. Depending on the number of days of study therapy, it is possible for the FU2 visit window to overlap with the TOC (7 to 10 days after last study therapy) visit window. In those instances where the TOC and FU2 windows overlap, the 2 visits may be combined into 1 visit. All assessments for the TOC and FU2 visit must be completed, but any duplicate assessments only need to be completed 1 time.

The following procedures will be performed at the FU2 visit:

1. Reviewing concomitant medications

2. Performing complete physical examination as defined in Section 6.4.8

3. Assessing infection-related signs and symptoms

4. Assessing urinary device status (as appropriate for cUTI patients only)

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

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

7. Obtaining a blood sample for blood culture (as clinically indicated)

8. Obtaining a urine sample for quantitative urine culture (cUTI patients only)

9. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (central reference laboratory)

10. Obtaining a urine sample for routine urinalysis (central reference laboratory)

11. Estimating CrCl (as clinically indicated) using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)

12. Obtaining a blood sample for serum β-hCG for women of childbearing potential (for cUTI patients only)

13. Determining clinical response assessment

14. Assessing mortality

6.3 Efficacy

6.3.1 Clinical response assessment

Clinical response definitions at the EOT, TOC, FU1, and FU2 visits are cure, failure, and indeterminate. Reasons for failure will be indicated according to the clinical response definitions in Table 4.

Table 4 Definitions of clinical response at the EOT, TOC, FU1, and FU2 visits

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antimicrobial therapy, drainage, or surgical intervention is necessary.
Failure	Patients who meet any 1 of the following criteria will be considered a treatment failure: • Death related to the index infection • Patient who received treatment with additional antibiotics for ongoing symptoms of index infection (including patients prematurely discontinued from study therapy due to an adverse event who require additional antibiotics for the index infection) • Patient previously met criteria for failure (not applicable for EOT). In addition, patients with cIAI will be considered a treatment failure in the following conditions: • 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
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 index infection is clearly noncontributory • Circumstances that preclude classification as a cure or failure.

Abbreviations: cIAI, complicated intra-abdominal infection; EOT, End of Treatment (with study therapy); FU1, Follow-up 1; FU2, Follow-up 2; TOC, Test of Cure.

6.3.2 Microbiological response assessments

The per-patient and per-pathogen microbiological response of CAZ-AVI and BAT in the modified intent-to-treat (MITT) and extended ME analysis sets for patients with the index infection at the EOT, TOC, FU1, and FU2 visits 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. It is based on outcome per-pathogen isolated from the study-qualifying culture 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 5. 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 extended 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 causative pathogen is isolated, the overall microbiological response assessment will be "favorable" only if the microbiological response assessment for each of the causative pathogens isolated is "favorable."

6.3.2.3 Microbiological response

Each causative pathogen will be categorized according to the definitions in Table 5.

Table 5 Microbiological response categories for each pathogen identified at initial/prestudy (study-qualifying) culture, EOT, TOC, FU1, and FU2

Microbiological response	Definition
Eradication	Absence (or urine quantification $<10^4$ CFU/mL for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved.
Presumed eradication	Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).
Persistence	Causative organism is still present at or beyond the EOT visit from a specimen at the site of infection. For cUTI patients, the organism must be present at $\geq 10^4$ CFU/mL.
Persistence with increasing MIC	Continued presence of the causative organism originally susceptible to study therapy in a culture taken after at least 2 full days of treatment displays a ≥4-fold higher MIC to study therapy after treatment with study therapy. For cUTI patients, the culture taken after at least 2 full days must also demonstrate $\geq 10^4$ CFU/mL.
Presumed persistence	Patient was previously assessed as a clinical failure and repeat cultures were not performed/clinically indicated (specific to cIAI population).
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 microbiological response cannot be made • Death where the index infection is clearly noncontributory • Circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence

Abbreviations: CFU, colony-forming unit; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; EOT; End of Treatment; FU1, Follow-up 1; FU2, Follow-up 2; MIC, minimum inhibitory concentration; TOC, Test of Cure.

Microbiological response for blood pathogens should be classified similarly to the classifications for causative pathogens noted in Table 5.

6.3.2.4 Minimum inhibitory concentration among pathogens

The favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 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 that appear after Baseline are categorized in Table 6 and will be summarized separately.

Table 6 Emergent infections

Emergent infection	Definition
Superinfection	Emergence of new pathogen during treatment with study therapy, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.
New infection	Emergence of new pathogen after completion of treatment with study therapy, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.

6.3.3 Primary efficacy outcome variable

The primary efficacy outcome variable is the proportion of patients with clinical cure at the TOC visit in the MITT analysis set as defined in Section 6.3.1, Table 4.

6.3.4 Secondary efficacy outcome variables

The secondary efficacy outcome variables include the following:

- Proportion of patients with clinical cure at the EOT, FU1, and FU2 visits in the MITT analysis set and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set
- Proportion of patients with clinical cure at the TOC visit, by pathogen (eg, *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*), by resistance mechanism (eg, KPC producer, ESBL producer), and by entry diagnosis (cIAI/cUTI), in the MITT and extended ME analysis sets
- Proportion of patients with clinical cure by previously failed treatment class (eg, quinolone, β-lactam/β-lactamase inhibitor, third- or fourth-generation cephalosporin, carbapenem), at the TOC visit in the MITT analysis set, and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set
- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits in the MITT and extended ME analysis sets
- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, FU1, and FU2 visits in the MITT and extended ME analysis sets
- Proportion of patients with a favorable microbiological response at the TOC visit by resistance mechanism (eg, KPC producer, ESBL producer) in the MITT and extended ME analysis sets

- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits, by MIC categories in the MITT and extended ME analysis sets
- Reasons for treatment change and/or discontinuation in the MITT analysis set
- 28-day mortality rate in the MITT and extended ME analysis sets

6.3.5 Exploratory outcome variables

The exploratory outcome variables include the following:

- Change in symptoms from Baseline at recorded time points in the MITT and extended ME analysis sets
- Exploratory health utilization variables (to be reported outside the CSR) in the MITT analysis set and in the extended ME at TOC analysis set, include the following:
  - Length of hospital stay
  - Length of ICU stay and/or transfer to the ICU
  - Length of study therapy
  - Mortality caused by cIAIs and cUTIs (up to the TOC 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 discontinuation of 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, QTc interval using Bazett formula [QTcB] and QTcF), and clinically important changes in clinical chemistry, hematology, and urinalysis laboratory values.

6.3.7 Pharmacokinetic outcome variables

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

6.3.8 Pharmacogenetic outcome variables

Patients will be offered the possibility to participate in optional genetic exploratory research. After signing a separate consent for optional genetic research, a blood sample will be collected as per the inclusion criteria and Table 1. Genotype is a stable parameter; therefore, if for any reason the blood sample is not drawn on the first day in the Treatment Period (Day 1,

Baseline), it may be taken at any point until patients leave the study. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

6.3.9 Biomarker outcome variables

Patients will be offered the possibility of participating in optional biomarker research. After signing a separate consent for optional biomarker research, a blood sample will be collected as per the inclusion criteria and Table 1. The biomarker blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

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 study therapy has been administered. Adverse events may also include complications that occur as a result of protocol-mandated procedures and are distinguished as such.

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 study therapy of an infectious agent

Appendix B provides further guidance on the definition of an SAE.

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 FU visits.

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 [redacted] 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 study therapy (yes or no)
- Action taken with regard to 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 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 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 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 AEs.

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 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 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 or increases in the symptoms of the disease or both. Expected progression of the disease under study and 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 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 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/[redacted] representatives within 24 hours of awareness.

The designated AstraZeneca [redacted] 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 [redacted] representatives of any FU information on a previously reported SAE within 1 calendar day, ie, immediately but no later than the end of the next business day, or when he or she becomes aware of it.

Once the investigator or other study center personnel indicate an AE is serious in the EDC system, an automated e-mail alert will be sent to the designated AstraZeneca/[redacted] representative.

If the EDC system is not available, then the investigator or other study center personnel should report the SAE to the appropriate AstraZeneca [redacted] representative by telephone (see Section 13.1).

The AstraZeneca [redacted] representative will advise the investigator or study center personnel how to proceed.

6.4.6 Laboratory safety assessments

Blood and urine samples will be sent to [redacted] For transfer to [redacted], samples will be labeled, stored, and shipped according to AstraZeneca or

[redacted] 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.

Table 7 presents the safety laboratory variables that will be measured.

Table 7 Laboratory variables

Clinical chemistry	Hematology	Urinalysis
Alanine aminotransferase	Hematocrit	Appearance (color, clarity)
Albumin	Hemoglobin	Bilirubin
Alkaline phosphatase	Platelet count	Glucose
Aspartate aminotransferase	Red blood cell count	Ketones
β-hCG	White blood cell count (total and differential)	Leukocyte esterase
Bicarbonate		Nitrite
Blood urea nitrogen		pH
Calcium		Protein
Chloride		Specific gravity
Creatinine		Urobilirubin
Gamma-glutamyltransferase		Microscopic examination
Glucose (nonfasting)		Red blood cells
Inorganic phosphorus		White blood cells
Potassium		Casts
Sodium		Crystals
Bilirubin (total, direct and indirect)		Bacteria, yeast cells, or parasites
Total protein		
Other	**Coagulation**	
Biomarker samples (banked specimen)	Partial thromboplastin time	
Blood cultures	Prothrombin time	
Coombs test (direct) to be performed by local laboratory when possible	International normalized ratio	

Note: Local laboratory test results will be used to qualify patients for randomization.
Abbreviations: 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 time frame. 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 of at least 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 therapy 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, eyes, ears, nose, throat, and lymph nodes, and respiratory, cardiovascular, abdominal, musculoskeletal, and neurological systems.

Daily infection-related signs and symptoms assessments will be conducted as outlined in the study plan (see Table 1).

Infection-related focused physical examinations will be conducted as outlined in the study plan (see Table 1).

- The cIAI-focused physical examination will include an assessment of the abdominal wound. A detailed abdominal assessment will be performed at Screening, Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, FU1, and FU2 visits. 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.

- The cUTI-focused physical examination will include an assessment for suprapubic pain and costovertebral angle tenderness.

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 (see 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 [redacted]. 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 [redacted]. Each ECG will define heart rate, RR, QRS interval, 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 ms or QTcF >460 ms) is observed, then additional ECG assessments must be performed. Electrocardiograms should be performed after the next dose of study therapy then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to Baseline (Day 1 prior to receiving any study therapy). Assessments should be performed after the completion of study therapy 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) of the ECGs will be entered in the [redacted] database. The study center will be contacted by [redacted] 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. If any medication with antipyretic properties has been taken by the patient, 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.

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 in the CAZ-AVI group on Day 3 following a dose administration that is convenient for collection of the plasma samples at the times presented in the study plan (see Table 1) and summarized as follows:

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

For blood volume, see Section 7.1.

6.5.2 Determination of drug concentration

Samples for determination of ceftazidime and avibactam 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 C_T [%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 C_T of avibactam is associated with avibactam's effect on inhibiting β-lactamase. An appropriate PK/PD index for avibactam, such as the %T concentration (%T >the critical C_T 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

For details of PGx sampling, see Appendix D.

Blood samples for PGx sampling will be shipped periodically from the study center to the central laboratory. All samples received by the central laboratory will be shipped to AstraZeneca or the AstraZeneca-approved laboratory at agreed intervals.

6.8 Collection of samples for biomarker research

Blood samples for biomarker research will be collected as per the inclusion criteria and study plan (Table 1). The samples will be processed to serum and plasma as directed in the laboratory manual.

Tubes will be labeled with the study number, sample description, randomization number, and date and time of collection. The date of the blood sample collection will be recorded in the appropriate section of the eCRF. The biomarker blood sample would ideally be drawn through the same cannula used to draw blood samples required for the main study.

6.8.1 Sample processing and shipping

Samples must be shipped frozen (–20°C or below) and transported to the relevant storage site, as indicated in the laboratory manual. Samples should be shipped in batches and coordinated with [redacted] to ensure their arrival during working hours. A requisition sheet should accompany the shipment that details the study number, center number, enrollment number, randomization number, date of sample collection, and unique identifier for each of the samples in the shipment. Refer to the laboratory manual for detailed instructions for sample processing and shipping.

6.8.2 Summary of biomarker assessments and analysis

The purpose of the biomarker research is to enable the generation of data for possible use in future retrospective analysis. The results of the biomarker research will not form part of the CSR for this study. The results may be pooled with biomarker data from other studies on CAZ-AVI to generate hypotheses to be tested in future studies.

Blood samples for biomarkers will be shipped periodically from the study center to the central laboratory. All samples received by the central reference laboratory will be shipped to AstraZeneca or the AstraZeneca-approved laboratory at agreed intervals.

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 8.

Table 8 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	12[a]	60[a]
	Hematology	3	12[a]	36[a]
	Coagulation	4.5	12[a]	54[a]
Pharmacokinetic sample		4	3	12
Biomarker sample		10	4	40
Blood culture		20	4[a]	80
Pharmacogenetic sample		10	1[b]	10
Total				292

[a] This is the maximum number of samples and total blood volume (mL) if the patient received the maximum 21 days of study therapy. These values could be less depending on the number of days the patient receives study therapy.

[b] If no previous blood cultures were obtained or if blood cultures prior to Baseline were positive, but repeat cultures have not yet shown clearance of bacteremia, then a blood culture must be done at Baseline. For all remaining visits, blood cultures should only be obtained as clinically indicated.

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.

Biological samples for future exploratory genetic research will be retained at the research and development site, on behalf of AstraZeneca for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR.

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

For details of PGx sample handling, storage, and destruction, see Appendix D.

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 Infectious 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 biological samples collected from the patients and stored at the center until shipment or disposal (where appropriate). The investigator at each center will also keep documentation of receipt of arrival.

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

[redacted] 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

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research. As collection of the biological samples (for the genetic and biomarker research) is an optional part of the study, the patient may continue in the study.

The investigator:

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

AstraZeneca verifies that the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or destroyed and the action documented and returned to the study center.

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) 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/[redacted] efore randomizing any patient into the study. The EC should approve all advertising used to recruit patients for the study.

AstraZeneca [redacted] 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 [redacted] will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca [redacted] 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 [redacted] 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 [redacted] 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 [redacted], 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/[redacted] 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 [redacted] 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 [redacted]. This will be documented in a CSA between AstraZeneca [redacted] and the investigator.

9.2 Training of study center personnel

Before the first patient is entered into the study, a [redacted] 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 [redacted] 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 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 [redacted] 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 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 [redacted] and the investigator should be in place before any study-related procedures can take place or patients are randomized to 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 the second quarter of [redacted] and to end by the fourth quarter of [redacted].

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

study centers to access patients' records for study purposes after the last patient last visit in order to address any potential data queries.

10. DATA MANAGEMENT

Data management will be performed by [redacted].

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 of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by [redacted].

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.

The results of any genetic or biomarker research will not form part of the CSR for this study.

Some or all of the clinical data sets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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 study therapy. For microbiological cultures, the study-qualifying culture is the culture that documented the ceftazidime resistance, which made the patient eligible for the trial and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a

cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit. Refer to Section 3.1 for definitions of EOT, TOC, FU1, and FU2. 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 MITT 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 (MITT 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 microbiological 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 (MITT and extended ME).

The proportion of favorable microbiological 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 pathogen in the corresponding analysis set (MITT 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.

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 FU visits. 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 study therapy. 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 results such as heart rate, RR, QRS interval, QTc interval, QTcF, and QTcB.

11.2.1 Other significant adverse events

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

Examples of these are marked 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

The collected ceftazidime and avibactam concentration data will be listed and descriptively summarized at specified sampling windows in the CSR. The PK of ceftazidime and avibactam will be assessed by population PK modeling. The actual dosing and plasma sampling times will be used in the population PK modeling.

The ceftazidime and avibactam 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 ceftazidime and avibactam plasma concentration data will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, such as maximum concentration, minimum concentration, area under the plasma concentration-time curve at steady state, and elimination half-life, will be derived from the predicted ceftazidime and avibactam concentration time courses. The appropriate ceftazidime and avibactam 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. A separate population PK and PK/PD modeling analysis plan will be prepared and the results will be reported separately.

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 and avibactam 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

Pharmacogenetic analysis to investigate potential genetics effects on response to CAZ-AVI or susceptibility to disease may be performed as appropriate.

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 review of data, which will occur prior to 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 and 12.1.1.2. Patients in the extended ME analysis set will be analyzed according to the treatment they receive while patients in the MITT set will be analyzed according to the randomized treatment.

12.1.1.1 Modified intent-to-treat analysis set

The MITT analysis set includes all patients who:

- Have a diagnosis of cIAI or cUTI with a ceftazidime-resistant pathogen on the study-qualifying culture and who received at least 1 dose of study therapy

12.1.1.2 Extended microbiologically evaluable analysis set at the EOT, TOC, FU1, and FU2 visits

The extended ME analysis set at the EOT, TOC, FU1, and FU2 visits includes all patients meeting the following criteria:

- Were included in the MITT analysis set
- Received at least 5 days of therapy or received <48 hours of therapy before discontinuing due to an AE
- Had no important protocol deviations that would affect the assessment of efficacy

- Received no additional systemic, Gram-negative antibacterial therapy (other than study therapy as designated at randomization) for treatment of a non-cIAI or non-cUTI infection. This does not include antibiotic therapy taken for the treatment of cIAI or cUTI by patients who were considered failures.

- For cUTI patients only, had a microbiological assessment from a quantitative urine culture at the EOT, TOC, FU1, and FU2 visits, respectively, with a microbiological response other than indeterminate

Note: The extended ME analysis set terminology is used for consistency with the broader clinical CAZ-AVI program. An ME analysis set is not defined for this study.

12.1.2 Safety analysis set

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

12.1.3 Pharmacokinetic 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 estimate the per-patient clinical response to CAZ-AVI and BAT with respect to the proportion of patients with clinical cure at TOC. The primary efficacy outcome variable will be assessed in the MITT analysis set. Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Statistical analyses as specified for each variable will be conducted. Two-sided 95% confidence intervals (CIs) for the primary and secondary efficacy analyses will be produced. Results will be presented for the whole study population and separately by pathogen and by entry diagnosis.

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, 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. 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.

Timing of analysis:

The entire study duration is expected to be approximately 30 months and therefore this study is not expected to be completed until after completion of the pivotal Phase III cIAI and cUTI studies. Consequently, the data from the resistant pathogens study are intended to supplement the CAZ-AVI pivotal Phase III program and therefore will be included in any future regulatory submissions. The results of this study will be analyzed at 3 or more different time points including (a) in a time frame to allow the submission of these resistant pathogens data with the pivotal Phase III cIAI and cUTI data in the regulatory submissions, (b) in a time frame to allow the latest resistant pathogens data to be included in breakpoint discussions, and (c) at the end of this study.

As no formal statistical comparisons will be performed for this study, no adjustment for these multiple time points will be applied.

12.2.2 Analysis of study population and patient characteristics

The number of patients randomized, important protocol deviations, and number of patients completing and discontinuing from the study therapy as well as the study, along with reasons for withdrawal will be tabulated by treatment group (CAZ-AVI and BAT), diagnosis (cIAI, cUTI), and a combination of both. Important protocol deviations are defined as any important variations from the protocol that could affect the assessment of efficacy. The number of patients in each analysis population will be reported overall, by treatment group, and by entry diagnosis.

Demographics (age, sex, and race), medical and surgical history, baseline assessments of clinical signs and symptoms, microbiological assessment, and study therapy administration will also be summarized. The summarizations will be presented for MITT, extended ME at TOC, and safety analysis sets, overall, by treatment group, and by entry diagnosis.

Efficacy

General considerations: Refer to Section 12.2.1 for descriptions of summarizations by treatment group. The analysis of the proportion of patients with clinical cure at TOC in the MITT analysis set is the primary analysis.

Primary efficacy outcome variable: The primary efficacy outcome variable is the proportion of patients with clinical cure at the TOC visit in the MITT analysis set. For derivation of the efficacy outcome variable refer to Section 11. The number and percentage in each treatment

group and entry diagnosis will be tabulated. Indeterminates will be included in the denominator for calculating the percentages for only the MITT analysis set, but they will be excluded from the denominator for the extended ME analysis set. Two-sided 95% CIs for the proportion of clinical cure at TOC for CAZ-AVI and BAT will be computed using the Wilson method (Wilson 1927). Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Forest plots will be used to present the point estimate and the associated 2-sided 95% CI using Wilson's method for the clinical cure rate within each treatment group.

Secondary efficacy outcome variables:

The secondary variables assessing the outcomes are:

- Proportion of patients with clinical cure at the EOT, FU1, and FU2 visits in the MITT analysis set and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set
- Proportion of patients with clinical cure at the TOC visit by pathogen (eg, *E. coli*, *Klebsiella* spp., *P. aeruginosa*), by resistance mechanism (eg, KPC producer, ESBL producer), and by entry diagnosis (cIAI/cUTI) in the MITT and extended ME analysis sets
- Proportion of patients with clinical cure by previously failed treatment class (eg, quinolone, β-lactam/β-lactamase inhibitor, third- or fourth-generation cephalosporin, carbapenem), at the TOC visit in the MITT analysis set, and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set
- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits in the MITT and extended ME analysis sets
- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, FU1, and FU2 visits in the MITT and extended ME analysis sets
- Proportion of patients with a favorable microbiological response at the TOC visit by resistance mechanism (eg, KPC producer, ESBL producer) in the MITT and extended ME analysis sets
- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits, by MIC categories in the MITT 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 MITT and extended ME analysis sets. The microbiological response analyses will be presented for the MITT and extended ME analysis sets. Clinical response

rates per-pathogen will also be presented for the MITT and extended ME analysis sets. If a patient has more than 1 unique causative pathogen identified and has a response of clinical cure, then the patient's clinical response will be a clinical cure for all of the causative pathogens. Conversely, if the patient is a clinical failure, the patient's clinical response will be clinical failure for all of the causative pathogens.

The numbers and percentages in each treatment group, with corresponding 2-sided 95% Wilson CIs in each treatment group, will be presented for all the secondary efficacy variables listed above. The clinical and microbiological secondary efficacy variables will also be presented graphically as Forest plots.

The other secondary efficacy outcome variables are as follows:

- Reasons for treatment change and/or discontinuation in the MITT analysis set
- The 28-day mortality rate in the MITT and extended ME analysis sets

The numbers and percentages in each treatment group for corresponding time points and analysis sets will be presented for all the secondary efficacy variables listed above.

In each treatment group of the study, MIC frequencies for each infecting species isolated 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 as well as the MIC to inhibit the growth of 50% of the organisms. Additionally, for infecting species for which the number is 10 or more, the MIC to inhibit the growth of 90% of the organisms 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 species, *P. aeruginosa*, other nonfermenting aerobes, anaerobes, and facultative Gram-positive cocci.

Pharmacokinetic 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 post dosing.

Exploratory variables

The exploratory outcome variables are as follows:

- Change in symptoms from Baseline at recorded time points in the MITT and extended ME analysis sets
- Exploratory health utilization variables (to be reported outside the CSR) in the MITT analysis set and in the extended ME at TOC analysis set, include the following:

- Length of hospital stay
- Length of ICU stay and/or transfer to the ICU
- Length of study therapy
- Mortality caused by cIAIs and cUTIs (up to the TOC visit)

The change in symptoms from Baseline at recorded time points will be tabulated.

The health economics variables (which will be reported outside the CSR) such as length of hospital stay, length of ICU stay, percent of patients who transferred to the ICU, length of study therapy, and mortality for the duration from first dose of study therapy to the TOC visit will be tabulated for treatment cure versus treatment failure in the MITT analysis set and in the extended ME at TOC analysis set.

12.2.3 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 study therapy will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

No statistical inference will be made for safety analysis.

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 FU visits. 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 study therapy up to the FU visits will be summarized by preferred term and system organ class using MedDRA vocabulary (Version 12.0 or higher) by dose group. Adverse events will also be summarized for events occurring from the first dose of study therapy up to the FU visits. These summaries will also be presented by relationship to study therapy and severity. Adverse events leading to

discontinuation will be summarized. The same summarizations will also be presented for SAEs and other significant AEs.

Summaries and listings of death, SAEs, AEs, other significant AEs, 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 formulas. 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 Determination of sample size

Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal power calculations have been performed for this study; therefore, the sample size is based on practical considerations. Approximately 200 patients per treatment group will be recruited for this trial. This will provide sufficient data that the 95% CI for the cure rate within each treatment group will extend at most approximately 7% on either side of the observed proportion in the overall summary, or at most 17% on either side for each separate pathogen infecting at least 30 patients, or 13% on either side for pathogens infecting at least 60 patients.

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

12.4 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 Patient Safety Department. 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 [redacted] physician via the numbers listed below for the appropriate region.

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

Region	Role in the study	Address and telephone number
North America	Medical Monitor	[redacted]
	[redacted] Hotline 24-hour Service	[redacted]
Asia Pacific	Medical Monitor	[redacted]
	[redacted] Hotline 24-hour Service	[redacted]
Europe, Middle East, and Africa	Medical Monitor	[redacted]
	[redacted] Hotline 24-hour Service	[redacted]
Latin America	Medical Monitor	[redacted]
	[redacted] Hotline 24-hour Service	[redacted]

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's 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 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 [redacted].

13.3.1 Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the 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 [redacted] 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 [redacted] works with the investigator to ensure that all relevant information is provided to the AstraZeneca patient safety data entry site within 1 to 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 [redacted]. 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, provided to the study center personnel using a paper CRF, is used to report the pregnancy and the PREGOUT (also a paper CRF) is used to report the outcome of the pregnancy. These modules are 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 therapy until 3 months after the last infusion of study therapy must be reported to AstraZeneca within 5 days and documented as specified in Section 13.3.1.

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