Clinical Study Protocol

Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00004
Edition Number	1
Date	[redacted]

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ-AVI, [redacted]) Versus Doripenem Followed by Appropriate Oral Therapy in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, With a Gram-Negative Pathogen in Hospitalized Adults

Sponsor:

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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.

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PROTOCOL SYNOPSIS

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ-AVI, [redacted]) Versus Doripenem Followed by Appropriate Oral Therapy in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, With a Gram-Negative Pathogen in Hospitalized Adults

International Co-coordinating Investigator

[redacted]

Study centers and number of patients planned

This will be a multicenter study enrolling approximately 964 hospitalized patients (18 to 90 years of age, inclusive) with a clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the investigator to be serious (requires intravenous [IV] therapy).

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 assess the noninferiority of ceftazidime-avibactam (CAZ-AVI, formerly CAZ104) compared with doripenem with respect to the following coprimary endpoints in the microbiological modified intent-to-treat (mMITT) analysis set:

- Symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) and resolution of, or improvement in, flank pain based on the patient-reported symptom assessment response at the Day 5 visit

- Both per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the Test of Cure (TOC) visit

Secondary Objectives

- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the per-patient microbiological response at the End of IV Therapy [EOT (IV)], TOC, and Late Follow-Up (LFU) visits in patients who are in the mMITT, microbiologically evaluable (ME), and extended ME analysis sets

- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on patient-reported symptom assessment response at the TOC and LFU visits in patients who are in the mMITT analysis set

- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the per-pathogen microbiological response at the EOT (IV), TOC, and LFU visits in patients who are in the mMITT, ME, and extended ME analysis sets

- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the investigator-determined clinical cure at the EOT (IV), TOC, and LFU visits in patients who are in the mMITT, ME, extended ME, and clinically evaluable (CE) analysis sets

- To evaluate the efficacy of CAZ-AVI versus doripenem in pathogens resistant to ceftazidime

- To compare the time to first defervescence of CAZ-AVI versus doripenem in patients who are on IV study therapy and who have fever at study entry in the mMITT, ME, extended ME, and CE analysis sets

- To evaluate the safety and tolerability profile of CAZ-AVI compared with doripenem in the treatment of patients with a cUTI in the safety analysis set

- To evaluate the pharmacokinetics of the individual components of CAZ-AVI (avibactam and ceftazidime)

- To evaluate CAZ-AVI exposure and the antimicrobial response relationship

Exploratory Objectives

- To explore the timing of the resolution of symptoms associated with a cUTI for patients receiving CAZ-AVI versus doripenem
- To explore the efficacy of CAZ-AVI compared with doripenem with respect to the per-patient and per-pathogen microbiological response using a cutoff of $<10^3$ colony-forming units (CFU)/mL at the EOT (IV), TOC, and LFU visits in patients who are in the mMITT, ME, and extended ME analysis sets
- To assess the consequence of first-line treatment failure in the treatment of patients with a cUTI as defined by the health utilization variables. The results of this analysis will not be included in the clinical study report (CSR) for this study.
- To collect blood samples for DNA extraction and storage for future possible exploratory research that may include response (ie, distribution, safety, tolerability, and efficacy) of CAZ-AVI and/or combination treatment compared with that of any comparators and/or susceptibility to bacterial infections. The results of any genetic research will not form part of the 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 form part of the CSR for this study.

Study design

This is a prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of CAZ-AVI versus doripenem in the treatment of adults with cUTIs, including acute pyelonephritis. Each patient is expected to complete the study, including follow-up, within approximately 8 weeks. The duration of antibiotic treatment with study therapy (IV plus optional oral therapy) will be 10 days unless the patient is bacteremic at study entry, in which case, the duration of antibiotic treatment with study therapy may be extended to a total of up to 14 days (IV plus optional oral therapy). Before being eligible to switch from IV to oral therapy, patients must have received at least 5 full days (ie, 15 doses for patients whose estimated creatinine clearance [CrCl] remains >50 mL/min) of treatment with IV study therapy administered in the hospital and meet clinical criteria outlined in Section 5.5.3.

Approximately 964 hospitalized patients (18 to 90 years of age, inclusive) who are suspected of having a cUTI due to a Gram-negative pathogen, have not received any prior antibiotic treatment for the cUTI or acute pyelonephritis, and are judged by the investigator to require IV therapy and to be treatable with 10 days of antibiotic therapy (IV plus optional oral therapy), which may be extended up to 14 days if the patient is bacteremic at study entry, will be enrolled. Complicated UTIs include acute pyelonephritis, UTIs in men with a documented history of chronic urinary retention, or UTIs associated with obstruction, foreign bodies,

recent urinary instrumentation, or urologic abnormalities. All patients will undergo a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study therapy.

After obtaining written informed consent and confirming eligibility, patients will be stratified based on the type of infection at Baseline (acute pyelonephritis or other cUTIs without pyelonephritis) and region (North America and Western Europe, Eastern Europe, and the rest of the world). Patients will be randomized to 1 of 2 of the following treatment groups in a 1:1 ratio according to the central randomization schedule:

- Doripenem placebo plus CAZ-AVI
- Doripenem plus CAZ-AVI placebo

If all of the protocol-specified criteria for clinical improvement are met, patients may be switched to 500 mg oral open-label ciprofloxacin after receiving a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy (note: each dose of IV study therapy consists of one 60-minute infusion followed immediately by one 120-minute infusion with a total of three 180-minute infusions in a 24-hour period administered 8 hours apart). Depending on the clinical response and duration of treatment received, patients may be discontinued from study drug at the EOT (IV) visit (ie, on Day 10 of therapy) or may be converted to oral therapy as allowed per the protocol (ie, after Day 5 up to Day 10 of therapy). Regardless of whether the patient will receive oral therapy, an investigator assessment of clinical cure and the collection of a urine specimen for culture must be performed within 24 hours after the last dose of IV study therapy. In the event a patient is converted to oral therapy, patients should complete the EOT (IV) visit assessments prior to switching from IV to oral therapy and such patients must have the assessment of clinical symptoms and the collection of a urine specimen for culture performed before the first dose of oral drug.

The EOT (IV) visit should include a patient-reported assessment of clinical symptoms (the Daily Patient Symptom Assessment Questionnaire), which need not be repeated if it was performed previously that same calendar day and symptoms have not changed. It is not necessary to wait for the culture result before changing to oral therapy. The choice of oral antimicrobials allowed per the protocol is limited to 1 preferred oral option and 1 alternative oral option to decrease confounding factors when analyzing the study efficacy data. Ciprofloxacin 500 mg taken orally twice daily is the oral option of choice. If the patient has a fluoroquinolone-resistant pathogen, the patient may receive oral sulfamethoxazole/trimethoprim 800 mg/160 mg twice daily as the alternative option. If there are reasons other than fluoroquinolone resistance that a patient cannot receive ciprofloxacin or there are reasons that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are valid choices, then the investigator will be required to discuss patient management with the medical monitor and provide additional documentation as per directives in the study center manual. The uropathogen(s) must be susceptible to the switched oral medication.

Switching to oral ciprofloxacin is not mandated; patients may continue receiving IV study therapy for the entire 10-day course (up to 14 days for patients who are bacteremic at study entry). Those patients who remain on IV study therapy after 5 full days will receive their IV study therapy from study center personnel while in the hospital or from a qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT (IV), TOC, and LFU visits following discharge from the hospital.

Study therapy and study periods are defined in the following tables.

Study therapy

Treatment group	IV study therapy	Optional oral therapy[a]
Ceftazidime-avibactam (CAZ-AVI)	Doripenem placebo followed by CAZ-AVI	Ciprofloxacin
Doripenem	Doripenem followed by CAZ-AVI placebo	Ciprofloxacin

[a] Before being switched from IV to oral therapy, patients must receive a minimum of 5 full days (ie, 15 doses for patients whose estimated creatinine clearance remains >50 mL/min) of IV study therapy, which must be administered in the hospital. All patients should have a repeat urine culture obtained within 24 hours after the end of IV therapy and before switching from IV to oral therapy. For patients with a fluoroquinolone-resistant pathogen, sulfamethoxazole/trimethoprim 800 mg/160 mg taken orally twice daily is an alternative option. If there is a valid reason that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are an appropriate choice, then the investigator will be required to discuss patient management with the medical monitor.

Abbreviation: IV, intravenous.

Study periods

Eligibility/Screening Period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0
Treatment Period	
Visit 2 (Baseline/randomization)	Day 1
Visits 3 to 15 (Days 2 to 14)[a]	While on IV therapy
Visit 16 (EOT [IV])	Within 24 hours after completion of the last infusion of IV study therapy and before the first dose for oral study therapy (if converted to oral therapy)
Follow-Up Period	
Visit 17 (TOC)	Day 21 visit[b]
Visit 18 (LFU)	Day 45 visit[c]

[a] The duration of treatment with study therapy (IV plus optional oral therapy) will be 10 days unless the patient is bacteremic at study entry, in which case the duration of treatment with study therapy may be up to 14 days.
[b] If it is not possible to perform the TOC visit on Day 21 (eg, the patient is on holiday), the allowed visit window is Day 21 to 25.
[c] If it is not possible to perform the LFU visit on Day 45 (eg, the patient is on holiday), the allowed visit window is Day 45 to 52.
Abbreviations: EOT, End of Therapy; IV, intravenous; LFU, Late Follow-Up; TOC, Test of Cure.

Target patient population

Approximately 964 (482 per treatment group) hospitalized patients (18 to 90 years of age, inclusive) with a clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the investigator to be serious (requires IV therapy) will be enrolled in the study.

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

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

Section 5.5.2.2). An appropriate flush with 0.9% sodium chloride infusion solution should be administered at the end of the infusion to ensure that the patient receives the entire dose. The flush should be administered according to local procedures and be appropriate for the infusion lines used by the clinical center.

Comparator (doripenem), dosage, and mode of administration

Patients randomized to receive the comparator will receive 500 mg doripenem administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes immediately followed by CAZ-AVI placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes. Treatments will be repeated every 8 hours (±30 minutes) in patients with normal renal function or mild renal impairment; for patients with moderately impaired renal function, dose regimen adjustments will be made (see Section 5.5.2.2). An appropriate flush with 0.9% sodium chloride infusion solution should be administered at the end of the infusion to ensure that the patient receives the entire dose. The flush should be administered according to local procedures and be appropriate for the infusion lines used by the clinical center.

Duration of treatment

The total number of days of combined treatment with study therapy (IV with optional oral therapy) will be 10 days unless the patient is bacteremic at study entry, in which case, the duration of antibiotic treatment with study therapy may be extended to a total of up to 14 days (IV with optional oral therapy). If all of the protocol-specified criteria for clinical improvement are met, patients may be switched to 500 mg oral open-label ciprofloxacin (or oral sulfamethoxazole/trimethoprim) after receiving a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy administered in the hospital.

Outcome variables:

- Primary efficacy variable

  The 2 coprimary efficacy outcome variables are the:

  - Proportion of patients with symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) with resolution of, or improvement in, flank pain based on the patient-reported symptom assessment response at the Day 5 visit in the mMITT analysis set

  - Proportion of patients with both a per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC visit in the mMITT analysis set

- Secondary efficacy variables

  Secondary efficacy outcome variables include the following:

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

  – Proportion of patients with symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC and LFU visits in the mMITT analysis set

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

  – Proportion of patients with an investigator-determined clinical cure at the EOT (IV), TOC, and LFU visits in the mMITT, ME, extended ME, and CE analysis sets

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

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

  – Proportion of patients with symptomatic resolution (as defined in the coprimary variables) at Day 5 and TOC for patients infected with a ceftazidime-resistant pathogen in the mMITT analysis set

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

- Safety and tolerability variables

  Safety and tolerability will be assessed by the incidence and severity of adverse events (AEs) and serious AEs (SAEs), mortality, reasons for discontinuation of study therapy and study, vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature), physical examination findings, 12-lead electrocardiogram parameters (QRS interval, heart rate, respiratory rate, heart rate, QT interval, corrected QT interval [Bazett and Fridericia formulas]), and clinically important changes in biochemistry, hematology, and urinalysis laboratory values.

- Pharmacokinetics

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

- Exploratory variables

  - Resolution of symptoms associated with cUTI at recorded time points

  - Proportion of patients with a favorable per-patient microbiological response using a cutoff of $<10^3$ CFU/mL at the EOT (IV), TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

  - Proportion of favorable per-pathogen microbiological response using a cutoff of $<10^3$ CFU/mL at the EOT (IV), TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

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

  - Length of hospital stay

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

  - Length of IV therapy

  - Mortality caused by cUTI (up to the LFU)

Statistical methods

The primary efficacy objective will be to assess the noninferiority of CAZ-AVI versus doripenem with respect to the coprimary efficacy outcome variables of the:

- Proportion of patients with symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) and there has been resolution of or improvement in flank pain based on the patient-reported symptom assessment response at the Day 5 visit in the mMITT analysis set

- Proportion of patients with per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC visit in the mMITT analysis set

The analysis of the primary efficacy outcome variables will be conducted in the mMITT analysis set. Additional analysis sets are defined for the secondary efficacy outcome variables and for the safety analysis.

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

  The mMITT analysis set includes all patients who:

  - Had clinical evidence of a cUTI and a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a Gram-negative pathogen
  - Had no more than 2 microorganisms identified in the study entry culture regardless of colony count. Any patient with a Gram-positive pathogen, or a bacterial species typically not expected to respond to both study drugs (eg, Acinetobacter, Stenotrophomonas) $\geq 10^5$ CFU/mL will be excluded.

- **Microbiologically evaluable analysis sets at the EOT (IV) and TOC visits**

  The ME analysis set at the EOT (IV) and TOC visits include all patients meeting the following criteria:

  - Were included in the mMITT analysis set
  - EITHER
    - Received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered64
    -

      OR

    - Received therapy <48 hours before discontinuing treatment due to an AE
  - Had no important protocol deviations that would affect the assessment of efficacy
  - Had a microbiological assessment at the EOT (IV) or TOC visits, respectively, with a microbiological response other than indeterminate, including a quantitative urine culture
  - Did not receive any prior antibiotics for the cUTI

- Did not receive any antibiotic therapy with potential activity against the baseline uropathogen collected at Screening between the time of the baseline culture and the EOT (IV) or TOC culture, respectively (other than protocol-defined study therapy). Study therapy is defined as blinded IV study drug and the allowed oral options (ciprofloxacin or sulfamethoxazole/trimethoprim). This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures

- Had a study entry urine culture obtained ≤48 hours before the start of treatment with IV study therapy

- Had 1 or at most 2 baseline pathogens susceptible to both IV study therapies

- **Microbiologically evaluable analysis set at the LFU visit**

  The ME analysis set at the LFU visit includes all patients meeting the following criteria:

  - Were included in the ME analysis set at the TOC visit

  - Had a microbiological assessment at the LFU visit, with a microbiological response other than indeterminate, including an interpretable quantitative urine culture

  - Had no confounding events since the TOC visit, defined as any events that could impact the assessment of the microbiologic responses. An example of confounding event is a deviation in study procedures

  - Did not receive any antibiotic therapy with potential activity against the baseline uropathogen since the TOC visit, except resuming oral antibiotic prophylaxis therapy after the TOC urine culture was obtained. This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures

- **Extended microbiological evaluable analysis set**

  The extended ME analysis set at the EOT (IV), TOC, and LFU visits includes patients meeting the criteria for the ME analysis set, with the exception that baseline pathogens need not be susceptible to either study therapy.

- **Clinically evaluable analysis set at the EOT (IV) and TOC visits**

  The CE analysis set at the EOT (IV) and TOC visits includes all patients meeting the following criteria:

  - Were included in the mMITT analysis set

- EITHER
  - Received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered

    OR

  - Received therapy <48 hours before discontinuing treatment due to an AE.
- Had no important protocol deviations that would affect the assessment of efficacy
- Had a clinical outcome assessment of clinical cure or failure (and not indeterminate) at the EOT (IV) or TOC visits, respectively
- Did not receive any prior antibiotics for the cUTI
- Did not receive antibiotic therapy with potential activity against the baseline uropathogen between the time of the baseline culture and the EOT (IV) or TOC culture, respectively (other than protocol-defined study therapy). Study therapy is defined as blinded IV study drug and the allowed oral options (or oral sulfamethoxazole/trimethoprim). This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures.
- Had the study entry urine culture obtained ≤48 hours before the start of treatment with IV study therapy

- **Clinically evaluable analysis set at the LFU visit**

  The CE analysis set at the LFU visit includes all patients meeting the following criteria:

  - Were included in the CE analysis set at the TOC visit
  - Had a clinical outcome assessment of clinical cure or failure (and not indeterminate) at the at the LFU visit
  - Had no important protocol deviations that would affect the assessment of efficacy
  - Did not receive any antibiotic therapy with potential activity against the baseline uropathogen since the TOC visit, except resuming oral antibiotic prophylaxis therapy after the TOC urine culture was obtained. This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures.

- **Safety analysis set**

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

- **Pharmacokinetic analysis set**

  The PK analysis set includes all patients who had at least 1 plasma concentration datum available for either ceftazidime or avibactam.

For each of the 2 coprimary outcome variables, a 2-sided 95% confidence interval (CI) for the observed difference in the proportion of patients with a favorable outcome between the CAZ-AVI and doripenem treatment groups will be calculated for the Day 5 and TOC visits using the unstratified method of Miettinen and Nurminen (Miettinen et al 1985).

The sponsor will conclude noninferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) is greater than –12.5% for both of these coprimary outcome variables; however, noninferiority may be assessed using a 10% margin in regions where this is a regulatory requirement. A sensitivity analysis stratified by prespecified stratification factors will also be performed for the 2 coprimary outcome variables for both the Day 5 and TOC visits and also separately for the components of the second coprimary variable, ie, per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) at TOC as part of the secondary efficacy variables assessment in the mMITT analysis set. The stratification factors are type of infection at Baseline (acute pyelonephritis or other cUTIs without pyelonephritis) and region (North America and Western Europe, Eastern Europe, and the rest of the world). The analysis for the 2 coprimary outcome variables and, as part of the secondary efficacy variable assessment, their components (as specified previously) will be performed and presented by subgroups. The subgroups to be analyzed will include, but not be limited to, type of infection, baseline pathogens, age, sex, race, and region.

Synthesis of historical trials has indicated that a 12.5% margin is appropriate for assessment of noninferiority in cUTI trials; however, there are regional variations in the regulatory requirements for noninferiority trials. In order to meet these requirements globally, this trial has been sized to provide 90% power for a 10% noninferiority margin, required in some regions (therefore providing >95% power to assess noninferiority using a 12.5% margin).

Approximately 964 patients will be recruited for this trial. This will provide 90% power for a 10% noninferiority margin using the lower limit of a 2-sided 95% CI for each of the 2 coprimary endpoints in the mMITT analysis set, assuming that the underlying true response rate is >73.5% for each coprimary endpoint and that 85% of patients will be included in the mMITT analysis set. The sample size was calculated using nQuery® version 7 (Statistical Solutions Ltd, Cork, Ireland) using the Newcombe-Wilson score method (uncorrected).

Secondary efficacy outcome variables considering proportions will be analyzed by determining 2-sided 95% CIs for the observed difference in the outcome proportion between

CAZ-AVI and doripenem (using the unstratified Miettinen and Nurminen method as described in the primary outcome variable). For time-to-event secondary outcome variables, treatment groups will be compared using a log-rank test. The median time to event will be calculated using a Kaplan-Meier method for each treatment group. Analyses of Day 1 (Baseline) characteristics, health utilization variables, and safety outcomes will be summarized using descriptive statistics or frequency counts in tables, listings, and figures as appropriate. Baseline value will be defined as the last nonmissing assessment prior to the start of IV study therapy. For microbiologic cultures (urine and/or blood culture), the initial culture will be defined as baseline.

The patient-reported symptom assessment response, investigator-determined clinical response of cure, per-patient microbiological response, and per-pathogen microbiological response will be presented by treatment group for patients infected with ceftazidime-resistant pathogens. The investigator-determined clinical response of cure, per-patient microbiological response, and per-pathogen microbiological response will be presented by MIC among pathogens considered to be causative in the CAZ-AVI treatment group. This will also be undertaken for the doripenem treatment group as a reference.

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 avibactam and ceftazidime for cUTI patients will be derived via a population modeling approach. The avibactam and ceftazidime concentration, patient demographics, and disease status data will be combined with the data from appropriate clinical studies for the population PK analysis. Individual compartmental PK parameters for patients with avibactam and ceftazidime plasma concentration data 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 avibactam and ceftazidime concentration time courses. All of the derived PK parameters will be descriptively summarized. The appropriate avibactam and ceftazidime exposure outcome variables predicted by the population PK modeling will be used for a PK/PD modeling for appropriate microbiological or clinical response 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 electrocardiogram parameters (QRS interval, RR interval, heart rate, QT interval, corrected QT interval using Bazett formula and Fridericia formulas), and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses. No inference will be made for safety analysis. Throughout the safety results sections, erroneously treated patients (eg, those randomized to CAZ-AVI treatment but who actually received doripenem) will be accounted for in the actual treatment received group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
β-hCG	β-human chorionic gonadotrophin
%T	Percentage of time above a threshold concentration
AmpC	A Class C β-lactamase (Amp = ampicillin)
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
CE	Clinically evaluable
CFU	Colony-forming units
CI	Confidence interval
CAZ-AVI	Ceftazidime-avibactam
cIAI	Complicated intra-abdominal infection
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 (IV)	End of Therapy (within 24 hours after completion of the last infusion of IV study therapy)
ESBL	Extended-spectrum β-lactamase
HHC	Home healthcare
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit

Abbreviation or special term	Explanation
IP	Investigational product
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KPC	*Klebsiella pneumoniae* carbapenemase
LFU	Late Follow-Up (45-52 days after randomization)
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
mMITT	Microbiological modified intent to treat
OAE	Other significant adverse event (see definition in Section 11.2.1)
PD	Pharmacodynamic
PGx	Pharmacogenetic
PK	Pharmacokinetic
[redacted]	[redacted]
PTA	Probability of target attainment
PVG	Pharmacovigilance
QTc	Corrected QT interval
QTcB	QTc interval corrected by Bazett
QTcF	QTc interval corrected by Fridericia
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TOC	Test of Cure (21-25 days after randomization)
ULN	Upper limit of normal
UTI	Urinary tract infection
WBC	White blood cell

1. INTRODUCTION

1.1 Background

1.1.1 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* spp. 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).

1.1.2 Multidrug resistance

The prevalence of multidrug-resistance (resistant 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 AmpC (a Class C β-lactamase [Amp = ampicillin]) enzymes have been reported from *Klebsiella* spp. and *E. coli*

isolates. Ampicillin, amoxicillin, first- and second-generation cephalosporins, and cephamycins are strong AmpC β-lactamase inducers. They are also rapidly inactivated by these β-lactamases; thus, resistance is readily documented in vitro (Fraser et al 2010).

1.1.3 Extended-spectrum β-lactamases

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

Extended-spectrum β-lactamases are capable of efficiently hydrolyzing penicillins, narrow-spectrum cephalosporins, many extended-spectrum cephalosporins, cephalosporins containing an oxyimino group (cefotaxime, ceftazidime), and monobactams (aztreonam). The majority of ESBL-producing organisms produce more than 1 β-lactamase, and strains producing multiple ESBLs are being reported. Different strains vary in the actual amount of each β-lactamase produced (Go 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. Like the third-generation cephalosporins, the minimum inhibitory concentration (MIC) of cefepime rises substantially when the inoculum of infecting organisms rises (Rodrigues et al 2004, Jacoby 1999, Rice et al 1996, Thauvin-Eliopoulos et al 1997).

Carbapenems are the drugs of choice for serious infections caused by ESBL-producing organisms. Carbapenems are the only reliable β-lactam drugs for the treatment of severe *Enterobacter* spp. infections. Resistance to carbapenems is rare but occurs in strains that produce serine-carbapenemases (*Klebsiella pneumoniae* carbapenemase [KPC] enzymes). Over the past decade, a group of serine-carbapenemases termed “KPC” has been increasingly reported from around the world (Hirsch et al 2010). As 1 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 slowly hydrolyzed by the

action of these β-lactamases. Widespread use of carbapenems may lead to the emergence of carbapenem-resistant *Acinetobacter baumannii*, *P. aeruginosa*, and *Stenotrophomonas maltophilia*, and vancomycin-resistant enterococci (Rodrigues et al 2004).

1.1.4 Ceftazidime-avibactam

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

Beta-lactamase inhibition by avibactam is effected through the formation of a stable covalent carbamoyl linkage to the enzyme complex. 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 clinically useful 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-avibactam combination against Enterobacteriaceae producing Class A, and importantly Class C, β-lactamases has been confirmed in vivo in murine pneumonia, septicemia, and pyelonephritis models.

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

1.1.5 Human experience – Phase I

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

- A Phase I double-blind, placebo-controlled, escalating single-dose study with and without ceftazidime in healthy adult male subjects (Study NXL104/1001)
- A Phase I double-blind, placebo-controlled, multiple-dose study over 5 or 10 days with and without ceftazidime, intravenous and oral formulations, in healthy adult male subjects (Study NXL104/1002)
- A Phase I open-label, single-dose study to assess the effect of renal impairment on pharmacokinetic (PK) parameters in patients with varying degrees of renal

insufficiency and in patients with end-stage renal failure on hemodialysis (Study NXL104/1003)

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

The Phase I studies completed to date have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly male and female subjects. The PK and tolerability of avibactam have also been determined in 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, [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 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 intravenous (IV) dose of CAZ-AVI (3000 mg ceftazidime plus 2000 mg avibactam) does not prolong the QTc (corrected QT interval) corrected by Fridericia (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. For several individual subjects, vital sign findings and liver function parameter values were noteworthy but did not result in the identification of a new safety concern. One subject, a healthy 41-year-old Japanese male (randomized to avibactam alone), had transaminase elevations that were classified as an other significant adverse event (OAE). 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). The transaminases 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. The increase in the transaminase values was considered mild in severity and related to the investigational product (IP).

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

1.1.6 Human experience – Phase II

A prospective, multicenter, double-blind, randomized, 2-arm, parallel-group (1:1) study in 203 patients aged between 18 and 88 years with complicated intra-abdominal infections (cIAI) has been completed (Study NXL104/2002). This study was designed to assess the 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 1 hour) versus meropenem (1000 mg IV every 8 hours over 30 minutes) in the treatment of cIAI. The primary objective of the study was to estimate the efficacy of CAZ-AVI plus metronidazole with respect to the clinical response in baseline microbiologically evaluable (ME) patients (ie, patients with at least 1 pathogen isolated that was susceptible to both study therapies) with cIAI at the Test-of-Cure (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 adverse events (AEs) reported (>7.5% incidence overall) were nausea, vomiting, pyrexia, ALT increased, AST increased, and alkaline phosphatase increased. 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) has been completed in patients with complicated urinary tract infections (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 plus 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 drug therapies). The primary objective of the study was to estimate the efficacy of CAZ-AVI with respect to microbiological response in ME patients with cUTI at the TOC visit, 5 to 9 days after treatment, compared with imipenem cilastatin. 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, 0 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 Research hypothesis

The following hypotheses will be assessed during this study:

- Intravenous CAZ-AVI administered every 8 hours will demonstrate clinical efficacy comparable with that of IV doripenem administered every 8 hours as treatment for patients with cUTIs
- The safety and tolerability profile of CAZ-AVI administered intravenously is acceptable

1.3 Rationale for conducting this study

Avibactam is a novel non–β-lactam, β-lactamase inhibitor with a spectrum of activity against Ambler Class A and Class C β-lactamases, including Class A carbapenemases such as KPC. Avibactam is being developed as an IV antibiotic formulation in combination with ceftazidime for the treatment of patients with serious Gram-negative bacterial infections. The strategy of using β-lactam, β-lactamase inhibitor combinations has been successful against Class A β-lactamases in a variety of bacterial infections. Gram-negative pathogens, including those producing ESBLs and AmpC β-lactamases, are important causes of cUTIs. The spectrum of activity of CAZ-AVI is well suited for the treatment of pathogens commonly responsible for cUTIs.

Doripenem has been selected as the comparator because it has demonstrated efficacy against Gram-negative pathogens isolated in cUTIs, including pyelonephritis. Doripenem is approved for and has been used widely for the treatment of cUTIs, and carbapenems are the drugs of choice against ESBL-producing Gram-negative pathogens, especially in serious infections.

This is a Phase III study of CAZ-AVI designed to evaluate the efficacy, safety, and tolerability compared with doripenem in the treatment of patients with a cUTI.

1.4 Benefit/risk and ethical assessment

Patients enrolled into this clinical study will have cUTIs that are of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to patients participating in this study is that they will receive effective antibiotic therapy for their infection. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for 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 cUTIs (ie, not as effective as the comparator treatment). 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. Other possible treatments include the marketed products doripenem, ciprofloxacin, and sulfamethoxazole/trimethoprim. As the risks for the marketed products are widely available in their respective prescribing information, such risks will not be discussed in this section.

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

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

- Hypersensitivity reactions. Though patients with hypersensitivity and serious allergic reactions to cephalosporins carbapenem or other β-lactam antibiotics are excluded from the trial, first-time episodes of such reactions could occur.
- Antibiotic-associated diarrhea, *Clostridium difficile* diarrhea, colitis, and pseudomembranous colitis
- Bacterial overgrowth with nonsusceptible organisms
- Distal necrosis as a result of inadvertent intra-arterial administration of ceftazidime
- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae, such as tremor, myoclonus, seizures, encephalopathy, and coma.

Potential risks for CAZ-AVI include the occurrence of events seen with ceftazidime alone but that go beyond the frequency and/or severity of those seen with ceftazidime. Local intolerance has been seen in the preclinical studies and has been monitored in the clinical program. In the Phase I studies, erythema and hematoma at the administration site were reported.

In the Phase II study (NXL104/2001) 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 42% 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 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 events 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 avibactam, ceftazidime, and 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 regard to hypersensitivity reactions, of those reported, there was 1 report in the CAZ-AVI clinical trials for which 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. Side effects for the avibactam part of CAZ-AVI include injection site redness and injection site bruising. The risks of the marketed antibiotics are considered acceptable. While it is anticipated that CAZ-AVI will have similar efficacy for the treatment of cUTIs, it is possible that efficacy will not be demonstrated. For each patient in the trial, appropriate treatment of the 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 the study is to assess the noninferiority of CAZ-AVI compared with doripenem with respect to the following coprimary endpoints in the microbiological modified intent-to-treat (mMITT) analysis set:

- Symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) and resolution of or improvement in flank pain based on the patient-reported symptom assessment response at the Day 5 visit

- Both per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC visit

2.2 Secondary objectives

Secondary efficacy objectives include the following evaluations of treatment with CAZ-AVI as compared with doripenem:

- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the per-patient microbiological response at the End of IV Therapy [EOT (IV)], TOC, and Late Follow-Up (LFU) visits in patients who are in the mMITT, ME, and extended ME analysis sets
- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC and LFU visits in patients who are in the mMITT analysis set
- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the per-pathogen microbiological response at the EOT (IV), TOC, and LFU visits in patients who are in the mMITT, ME, and extended ME analysis sets
- To determine the efficacy of CAZ-AVI compared with doripenem with respect to the investigator-determined clinical cure at the EOT (IV), TOC, and LFU visits in patients who are in the mMITT, ME, extended ME, and clinically evaluable (CE) analysis sets
- To evaluate the efficacy of CAZ-AVI versus doripenem in pathogens resistant to ceftazidime
- To compare the time to first defervescence of CAZ-AVI versus doripenem in patients who are on IV study therapy and who have fever at study entry in the mMITT, ME, extended ME, and CE analysis sets
- To evaluate the safety and tolerability profile of CAZ-AVI compared with doripenem in the treatment of patients with a cUTI in the safety analysis set
- To evaluate the pharmacokinetics of the individual components of CAZ-AVI (ceftazidime and avibactam)
- To evaluate CAZ-AVI exposure and the antimicrobial response relationship

2.3 Exploratory objectives

Exploratory efficacy objectives include the following evaluations of treatment with CAZ-AVI as compared with doripenem:

- To explore the timing of the resolution of symptoms associated with a cUTI for patients receiving CAZ-AVI versus doripenem

- To explore the efficacy of CAZ-AVI compared with doripenem with respect to the per-patient and per-pathogen microbiological response using a cutoff of $<10^3$ colony-forming units (CFU)/mL at the EOT (IV), TOC, and LFU visit in patients who are in the mMITT, ME, and extended ME analysis sets

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

- To collect blood samples for DNA extraction and storage for future possible exploratory research that may include response (ie, distribution, safety, tolerability, and efficacy) of CAZ-AVI and/or combination treatment compared with that of any comparators and/or susceptibility to bacterial infections. The results of any genetic research will not form part of the 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.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a Phase III, prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of CAZ-AVI versus doripenem in the treatment of hospitalized patients with cUTIs. Complicated UTI includes acute pyelonephritis, UTIs in men with a documented history of chronic urinary retention, or UTI associated with obstruction, foreign bodies, recent urinary instrumentation, or urologic abnormalities. Patients between the ages of 18 and 90 years of age, inclusive, who are suspected of having a cUTI due to Gram-negative pathogens, have not received any prior antibiotic treatment for the cUTI or acute pyelonephritis, and are judged by the investigator to require IV therapy and to be treatable with 10 days of antibiotic therapy (IV with optional oral therapy), which may be extended up to 14 days if the patient is bacteremic at study entry, will be recruited into the study.

Patients who have an indwelling bladder catheter that has been in place for >24 hours prior to Screening should have it removed or replaced prior to collection of the screening urinalysis and urine culture, unless removal or replacement is considered unsafe or is contraindicated due to a recent procedure or urological condition. Patients should only be enrolled in the study if it is expected that all catheters will be discontinued during study treatment. Section 3.1.1.1 describes acceptable methods of collecting urine cultures.

Approximately 964 patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule (approximately 482 patients per treatment group). Patients will be stratified based on the type of infection at Baseline (acute pyelonephritis or other cUTIs without pyelonephritis) and region (North America and Western Europe, Eastern Europe, and the rest of the world). After obtaining written informed consent and confirming eligibility, patients will be randomized to receive either doripenem placebo IV over 60 minutes and CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) IV over 120 minutes or 500 mg doripenem IV over 60 minutes and CAZ-AVI placebo IV over 120 minutes. Treatments will be repeated every 8 hours (±30 minutes) in patients with normal renal function or mild renal impairment; for patients with moderately impaired renal function, dose regimen adjustments will be made (see Section 5.5.2.2).

At the investigator's discretion, patients may be discharged from the hospital after the patient has received a minimum of 5 full days (ie, 15 doses) of treatment with IV study therapy (note: each dose of IV study therapy consists of one 60-minute infusion followed immediately by one 120-minute infusion, with a total of three 180-minute infusions in a 24-hour period administered 8 hours apart). Patients will be evaluated daily while on IV study therapy. Dosing may be adjusted based on changes in the patient's renal function (see Section 5.5.2).

Patients may be switched to 500 mg oral open-label ciprofloxacin twice daily after receiving a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy if all of the protocol-specified criteria for clinical improvement (see Section 5.5.3) are met. An investigator assessment of clinical cure and collection of a urine specimen for culture must be performed within 24 hours after the completion of the last infusion of IV study therapy. The EOT (IV) visit should include a patient-reported assessment of clinical symptoms (the Daily Patient Symptom Assessment Questionnaire), which need not be repeated if it was performed previously that same calendar day and symptoms have not changed. Patients converting to oral therapy must have the assessment of clinical symptoms and the collection of a urine specimen for culture performed before the first dose of oral drug. It is not necessary to wait for the culture result before changing to oral therapy.

The choice of oral antimicrobials allowed per protocol is limited to 1 preferred oral option and 1 alternative oral option to decrease confounding factors when analyzing the study efficacy data. Ciprofloxacin 500 mg taken orally twice daily is the oral option of choice. If the patient had a fluoroquinolone-resistant pathogen, the patient may receive oral sulfamethoxazole/trimethoprim 800 mg/160 mg taken twice daily as the alternative option. If there is a valid reason that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are an appropriate choice, then the investigator will be required to discuss patient management with the medical monitor and provide additional documentation as per directives in the study center manual. The uropathogen(s) must be susceptible to the switched chosen oral medication.

Switching to oral therapy is not mandated; patients may continue receiving IV study therapy for the entire 10-day course (up to 14 days if the patient is bacteremic at study entry). Those patients who remain on IV study therapy after 5 full days (ie, 15 doses) will receive their IV study therapy from study center personnel while in the hospital or from a qualified healthcare

provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT (IV), TOC, and LFU visits following discharge from the hospital. Study therapy is presented in the following table:

Study therapy

Treatment group	IV study therapy	Optional oral therapy[a]
Ceftazidime-avibactam (CAZ-AVI)	Doripenem placebo followed by CAZ-AVI	Ciprofloxacin
Doripenem	Doripenem followed by CAZ-AVI placebo	Ciprofloxacin

[a] Before being switched from IV to oral therapy, patients must receive a minimum of 5 full days (ie, 15 doses for patients whose estimated creatine clearance remains >50 mL/min) of IV study therapy, which must be administered in the hospital. All patients should have a repeat urine culture obtained before switching from IV to oral therapy. For those patients with a fluoroquinolone-resistant pathogen, sulfamethoxazole/trimethoprim 800 mg/160 mg taken orally twice daily is an alternative option. If there is a valid reason that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are an appropriate choice, then the investigator will be required to discuss patient management with the medical monitor.

Abbreviation: IV, intravenous.

At Screening (within 48 hours prior to administration of study therapy), patients will provide a urine sample for culture testing. Patients may be enrolled in the study before the urine culture results are available if they meet the criteria for a cUTI (see Section 4.1) and if it is likely (based on urinalysis results and clinical findings) that the urine culture results will be positive. **However, a urine Gram stain must be performed and demonstrate the presence of Gram-negative bacilli before study entry if a culture result is not available**. If more than 1 urine sample is collected within the 48 hours before administration of study therapy, then the results from the urine sample collected closest to randomization should be used.

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 (see Section 6.5.1).

The investigator will be responsible for determining the appropriate duration of treatment with IV study therapy (and subsequent treatment with oral ciprofloxacin or oral sulfamethoxazole/trimethoprim to complete the 10-day course if IV study therapy duration is less than 10 days), assessing the patient's clinical response to treatment and the relationship of AEs to study therapy. For purposes of this study, flank pain, frequency, urgency, dysuria, and suprapubic pain are considered cUTI-specific symptoms. Chills, warmth, rigors, nausea, vomiting, costovertebral angle tenderness, and suprapubic tenderness are signs and symptoms of interest but are not included in the primary outcome assessment.

During study conduct, patients will be required to report their cUTI symptoms on a series of formal questionnaires which will be administered by trained study center staff as detailed in Section 9.2. The Premorbid Patient Symptom Assessment Questionnaire will be administered once at Baseline to determine whether a patient normally experiences UTI symptoms (ie, in

the absence of a UTI) that may be attributable to other disease processes (eg, benign prostatic hyperplasia). To capture changes in symptoms over time, patients will be administered the Daily Patient Symptom Assessment Questionnaire at all visits starting at Baseline (ie, Baseline, daily while on IV therapy, at EOT, TOC, and LFU). The data collected from the questionnaires will be used to programatically assess the patient-reported symptomatic response via the algorithm for the primary endpoint presented in Section 11.1.

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. If analgesic medication is required for pain, the use of analgesics without antipyretic properties is preferred.

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

The total duration of patient participation in the study will be approximately 8 weeks including the Screening Period, Treatment Period, and the Follow-Up Period, which includes the TOC and LFU visits. Patients are to receive a total of 10 days of antibiotic therapy (IV plus optional oral therapy), which may be extended up to 14 days if the patient is bacteremic at study entry.

Study periods are defined in the following table:

Study periods	
Eligibility/Screening Period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0
Treatment Period	
Visit 2 (Baseline/randomization)	Day 1
Visits 3 to 15 (Days 2 to 14)[a]	While on IV therapy
Visit 16 (EOT [IV])	Within 24 hours after completion of the last infusion of IV study therapy and before the first dose for oral study therapy (if converted to oral therapy)
Follow-Up Period	
Visit 17 (TOC)	Day 21 visit[b]
Visit 18 (LFU)	Day 45 visit[c]

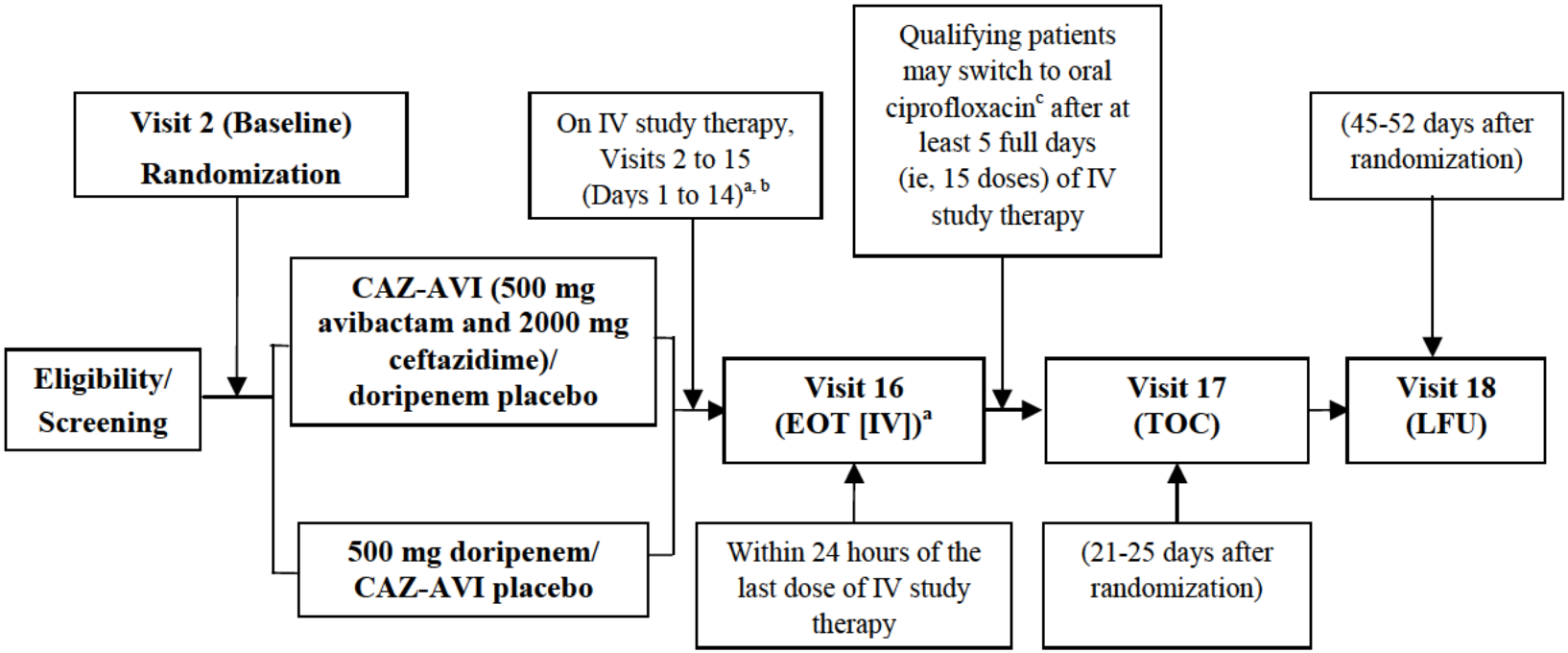
[a] The duration of treatment with study therapy (IV plus optional oral therapy) will be 10 days unless the patient is bacteremic at study entry, in which case the duration of treatment with study therapy may be up to 14 days.
[b] If it is not possible to perform the TOC visit on Day 21 (eg, the patient is on holiday), the allowed visit window is Day 21 to 25.
[c] If it is not possible to perform the LFU visit on Day 45 (eg, the patient is on holiday), the allowed visit window is Day 45 to 52.
Abbreviations: EOT, End of Therapy; IV, intravenous; LFU, Late Follow-Up; TOC, Test of Cure.

Patients must be withdrawn from IV study therapy under certain circumstances that are described in detail in Section 5.8. For patients who were randomized to treatment based on a urine Gram stain documenting Gram-negative bacilli and if the entry urine culture does not contain 1 or 2 recognized Gram-negative uropathogens $\geq 10^5$ CFU/mL (ie, does not conform to the defined baseline cultured pathogen entry criterion), the patient may be discontinued from study therapy at the discretion of the investigator. These patients should continue to be followed for safety assessments. Patients withdrawn from the IV study therapy for any reason should receive therapy deemed appropriate by the investigator. In all cases, the reason for withdrawal from study or discontinuation of study therapy must be recorded in the electronic case report form (eCRF) and in the patient's medical records. If the patient is withdrawn from IV study therapy due to an AE, the AE must be reported in accordance with the procedures in Section 6.4.3. All patients should be followed, whenever possible, until the LFU visit for the final outcome assessment and safety. If withdrawal from 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 0) up to and including the LFU visit.

The study flow chart is presented in Figure 1; definitions of study periods and details of the study plan can be found in Table 1.

Figure 1 Study flow chart



[a] The Treatment Period includes the Baseline visit (Day 1),Visits 2 to 15 (Days 2 to 14), and the EOT (IV) visit. Visit 16 (EOT [IV]) must occur and urine specimen for culture must be obtained before the patient starts oral therapy.

[b] The duration of treatment with study therapy (IV plus optional oral therapy) will be 10 days. If the patient is bacteremic at study entry, then the duration of treatment is 14 days.

[c] If the patient has a fluoroquinolone-resistant pathogen, sulfamethoxazole/trimethoprim is an alternative oral option.

Abbreviations: EOT, End of Therapy; IV, intravenous; LFU, Late Follow-Up; TOC, Test of Cure.

Table 1 Study plan

Procedures and Assessments	Eligibility/ Screening Visit 1 Day –1 to 0	Visit 2 Day 1 (Baseline)[a]	Treatment Period Visits 3 to 15 Days 2 to 14[b] (while on IV study therapy)	Visit 16[c] EOT (IV)[d] (within 24 hours after completion of last infusion of IV study therapy)	Follow-Up Period Visit 17[c] TOC (21-25 days after randomization)	Visit 18[c] LFU (45-52 days after randomization)
Informed consent[e]	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical and surgical history	X					
Review prior and/or concomitant medications	X	X	Daily	X	X	X
Complete physical examination[f]	X			X	X	X
UTI-focused physical examination[g]	X	X	Daily	X	X	X
Vital sign measurements[h]	X	X	Daily	X	X	X
12-lead digital electrocardiogram		X[i]	X[i]	X		
Assess urinary device status (as appropriate)		X	X	X	X	X
Blood for safety analysis[j]	X	X	Every 3 days[j]	X	X	X

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16[c]**	**Visit 17[c]**	**Visit 18[c]**
Procedures and Assessments	**Day –1 to 0**	**Day 1 (Baseline)[a]**	**Days 2 to 14[b] (while on IV study therapy)**	**EOT (IV)[d] (within 24 hours after completion of last infusion of IV study therapy)**	**TOC (21-25 days after randomization)**	**LFU (45-52 days after randomization)**
Estimate creatinine clearance[k]	X	----------As clinically indicated----------				
Urinalysis[l]	X			X	X	X
Quantitative urine culture	X[m]			X[n]	X	X
Blood cultures[o]	X	----------As clinically indicated----------				
Serum β-hCG (women of childbearing potential)	X[p]					X
Blood for PK analysis[q]			X			
Pharmacogenetic blood sample[r]		X				
Biomarker samples[s]		X	X	X		
Randomization		X				
Monitor AEs[t]	X	X	Daily	X	X	X
Administer IV study therapy[u,v]		X	X			

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16[c]	Visit 17[c]	Visit 18[c]
Procedures and Assessments	**Day –1 to 0**	**Day 1 (Baseline)[a]**	**Days 2 to 14[b] (while on IV study therapy)**	**EOT (IV)[d] (within 24 hours after completion of last infusion of IV study therapy)**	**TOC (21-25 days after randomization)**	**LFU (45-52 days after randomization)**
Premorbid Patient Symptom Assessment Questionnaire		X				
Daily Patient Symptom Assessment Questionnaire		X	Daily	X[w]	X	X
Investigator-determined clinical response evaluation				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] Visits 3 to 15 assessments are required while the patient is on IV study therapy. Patients are to receive 10 days of total antibiotic treatment (IV plus optional oral therapy). Patients who are bacteremic at study entry may have their treatment with study therapy extended to up to 14 days.

[c] Patients are to return to the study center for their scheduled visits (EOT [IV], TOC, and LFU) following discharge from the hospital.

[d] The EOT (IV) visit can be as follows: 1) the last day of treatment with IV study therapy because the patient completed the entire course of therapy with IV or the patient has met the criteria to switch to oral treatment, 2) the day of premature withdrawal from IV study therapy, or 3) the day of failure on IV study therapy. If the patient is converted to oral therapy to complete the protocol-defined length of treatment, then this visit should occur before the patient starts oral therapy.

[e] Separate informed consents should be obtained for both the pharmacogenetic and biomarker assessments prior to these assessments being conducted. Declining participation in the pharmacogenetic and biomarker portion of the study will not exclude the patient from participating in the main study.

[f] A complete physical examination will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, abdominal, musculoskeletal, and neurological systems. Physical examination should include assessments such as suprapubic pain and/or costovertebral angle tenderness. Height will be measured at Screening only. Weight will be measured as necessary to calculate the patient's estimated CrCl.

[g] The daily UTI-focused physical examination should include assessments of suprapubic pain and costovertebral angle tenderness.

[h] 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. 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.

[i] A digital ECG must be performed prior to dosing on Day 1 (Baseline). The ECG measurement should be performed in triplicate. Two mandatory digital ECG measurements must be performed on Day 3: one measurement at the end of a CAZ-AVI/CAZ-AVI placebo infusion and 1 measurement at the end of the corresponding doripenem/doripenem placebo infusion. Each ECG measurement should be performed in triplicate. If indicated, additional ECG assessments can be made at the discretion of the investigator; these assessments should be entered as an unscheduled assessment. If any significant increase of QTcF (ie, increase from Baseline of ≥30 ms or QTcF >460 ms) is observed, then additional ECG assessments must be performed (see Section 6.4.9).

[j] Laboratory specimens (see Table 11) will be obtained prior to dosing and sent to the central reference laboratory. A direct Coombs test should be performed at the study center at Baseline, EOT (IV), TOC, and LFU if the local laboratory is equipped to do so; study centers unable to perform direct Coombs testing will not be required to perform this test. Abnormal safety laboratory results obtained throughout the study, including the LFU visit, should be followed up as clinically indicated (see also Appendix F). Local laboratory test results will be used to qualify patients for random assignment to treatment.

[k] Study center personnel will calculate the estimated CrCl at Screening (and when clinically indicated) using serum creatinine results from the local laboratory. Appendix E provides details for the calculation of estimated CrCl.

[l] If a patient has an indwelling bladder catheter in place for >24 hours prior to Screening, it should be removed or replaced prior to the collection of the Screening urinalysis and urine culture, unless removal or replacement is considered unsafe or is contraindicated due to a recent procedure or urological condition.

[m] If a patient meets the entry criteria for complicated UTI, except for positive urine culture, the patient may be enrolled before urine culture results are available if the results are likely (based on urinalysis results and clinical findings) to be positive and study drugs are considered appropriate empiric therapy. However, a urine Gram stain must be performed and demonstrate the presence of Gram-negative bacilli before study entry if a culture result is not available.

[n] All patients should have a repeat urine culture obtained prior to switching from IV to oral therapy. When antibacterial therapy for the disease under study is changed, an appropriate specimen for urine culture must be obtained. The sample should be collected after stopping the IV study therapy but before the new alternative antibiotic is administered.

[o] Blood cultures are mandatory at Screening and should be repeated as clinically indicated or if previous blood cultures were positive. If the blood culture is positive at Baseline, daily samples must be collected until testing is negative. When obtaining samples for blood cultures, 2 sets from 2 different sites must be collected (a total of 4 tubes; 2 aerobic and 2 anaerobic, each inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL of blood per collection). One set must be drawn through a venipuncture.

[p] 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 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.

[q] Blood samples for PK 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 the CAZ-AVI/CAZ-AVI placebo infusion, anytime between 30 and 90 minutes after stopping the CAZ-AVI/CAZ-AVI placebo infusion, and anytime between 300 (5 hours) and 360 minutes (6 hours) after stopping the CAZ-AVI/CAZ-AVI placebo infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient.

[r] The pharmacogenetic sample should be taken from consented patients prior to commencement of study therapy. If this sample is not taken prior to the initiation of study therapy, it may be taken at Visit 3.

[s] Biomarker samples should be taken from consented patients. Biomarker sampling should be taken at Baseline and at the following times: 8 hours after the beginning of IV study therapy infusion, 24 hours after the beginning of IV study therapy infusion, and at the EOT (IV) visit.

[t] Patients will be monitored for nonserious AEs and serious AEs from the time when informed consent is obtained at Screening up to and including the LFU. Should a patient experience significant diarrhea during or after study therapy, the investigator should consider obtaining a stool sample and test for *Clostridium difficile* toxin.

[u] If necessary, a 1-time dose-interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule 8 hours apart (±30 minutes). The dosing interval adjustment must be made 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-interval adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. Before being eligible to switch from IV to oral therapy, patients must receive at least 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV therapy, which must be administered in the hospital. Patients may be switched to oral ciprofloxacin (or oral sulfamethoxazole/trimethoprim if the patient has a fluoroquinolone-resistant pathogen) if all criteria in the protocol are met (see Section 5.5.3). Those patients who remain on IV study therapy after 5 full days (ie, 15 doses) will receive IV study therapy from study center personnel while in the hospital or from a qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for scheduled visits (EOT [IV], TOC, and LFU) following discharge from the hospital.

[v] For patients switching to oral therapy after 5 days, a subset of Visits 6 to 15 may be missing. For patients without bacteremia, Visits 12 through 15 will be missing.

[w] If already performed on the same calendar day and symptoms have not changed, do not repeat.

[x] Perform prior to starting oral therapy.

Abbreviations: AE, adverse event; β-hCG, β-human chorionic gonadotropin; CAZ-AVI, ceftazidime-avibactam; CrCl, creatinine clearance; ECG, electrocardiogram; EOT, End of Therapy; IV, intravenous; LFU, Late Follow-Up; PK, pharmacokinetic; QTc, corrected QT interval; QTcF, QTc interval corrected by Fridericia; TOC, Test of Cure; UTI, urinary tract infection.

3.1.1 Microbiological assessments

Microbiological assessments will be initiated at the local laboratory for specimen collection, analysis of isolates, and shipment to the central laboratory according to the following sections and as outlined in more detail in the study center manual. All microbiological pathogens from blood and all Gram-negative uropathogens at $\geq 10^5$ CFU/mL from urine must be shipped to the central laboratory for confirmation of microbiological assessments.

3.1.1.1 Specimen collection

An adequate urine specimen for microbiologic evaluation must be obtained from all 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. Blood and urine culture specimens should be taken prior to enrollment (at Screening). All cultured pathogens from blood, isolates of Gram-negative uropathogens at $\geq 10^5$ CFU/mL from the study entry urine culture, and isolates of Gram-negative uropathogens at $\geq 10^3$ CFU/mL from subsequent (ie, follow-up) urine cultures 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 cultures: For any patients who have an indwelling bladder catheter in place for >24 hours prior to Screening, it must be removed or replaced prior to collection of the screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or is contraindicated due to a recent procedure or urological condition, so that the urine culture results are an accurate representation of the pathogen(s) present. For urine specimens, 1 positive pretreatment urine culture, defined as $\geq 10^5$ CFU/mL for the causative pathogen, is required. Urine samples should not be obtained from urinary catheter bags. Acceptable methods of collection of urine for culture include:

- Midstream clean catch (straight catheterization using sterile technique is preferred for female patients)
- Straight catheterization using sterile technique
- Suprapubic specimen collection using sterile technique
- Whenever possible, urine specimens should not be obtained from indwelling bladder 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 Gram stain should be performed on the urine specimen and the sample should be plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, these tests may be performed within 24 hours of collection if the specimen is stored at 2°C to 8°C before processing. The baseline specimen for microscopic

evaluation (eg, Gram stain) and culture should be collected before administration of antimicrobial therapy. For an organism to be considered a pathogen at study entry, it must be a Gram-negative organism normally associated with a UTI (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.

Blood cultures: Specimens will be obtained for all patients at Screening and as appropriate throughout the study. Two sets of blood cultures should be collected (ie, 4 tubes) from 2 different sites for aerobic and anaerobic incubation. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. At least 1 set of blood cultures must be obtained through a venipuncture. Organisms isolated in the blood at study entry will be assigned a microbiologic response similar to those given for uropathogens isolated from urine cultures as noted in Table 8 except that specifications for quantity will not apply for blood isolates. Details concerning the collection of blood cultures are provided in the laboratory manual.

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

3.1.1.2 Shipment of isolates

The central laboratory will supply the local laboratory with media containing transport vials and instructions for shipment of isolates to the central laboratory and will also supply susceptibility testing discs for CAZ-AVI, ceftazidime, and doripenem. All isolated Gram-negative uropathogens determined to be $\geq 10^5$ CFU/mL along with any Gram stain of the urine specimen should be sent to the central laboratory. The central laboratory will monitor and verify resistant isolates and Gram stains reported by the local laboratory. All shipment documentation for isolates sent to the central laboratory should be maintained and available for review by the [redacted] representative. Blood isolates should also be sent to the central laboratory.

3.1.1.3 Analysis of isolates

All bacterial pathogens from blood samples, all Gram-negative uropathogens meeting the criteria of $\geq 10^5$ CFU/mL from study entry urine specimens, and all Gram-negative uropathogens meeting the criteria of $\geq 10^3$ CFU/mL from subsequent (ie, follow-up) urine cultures must be identified to the genus and species level using confirmatory, not presumptive, identification methods. (Criterion for microbiologic eradication is a urine culture demonstrating $<10^4$ CFU/mL, but a cutoff of $<10^3$ CFU/mL will be used in exploratory analyses.) The disk diffusion method should be used for CAZ-AVI, the comparator doripenem, and ceftazidime with results reported in the eCRF. The laboratory manual will

provide details on how to report susceptibility results of CAZ-AVI to the principal investigator. The laboratory can perform any additional testing on doripenem (eg, MIC) and any additional agents as they normally do to provide susceptibility results of isolated microorganisms. Disk zone size determinations for interpretation of susceptibility for all isolated microorganisms will be according to Clinical Laboratory Standards Institute criteria for comparator agents. Characterization of β-lactamases associated with the bacterial pathogens and molecular profiling (eg, pulse-field gel electrophoresis) will be performed by [redacted]. Susceptibility tests (either broth microdilution or disk diffusion as per study center standard practice) must also be performed with ciprofloxacin and trimethoprim/sulfamethoxazole to provide susceptibility results, as these are the options allowed for the switch to oral medication.

Note: all anaerobic bacterial pathogens isolated from blood must be identified to at least the genus level. If the local laboratory cultures and performs susceptibility testing on anaerobic organisms, it should follow Clinical Laboratory Standards Institute methodologies by either broth microdilution (*Bacteroides fragilis* group) or agar dilution MIC testing only on doripenem. However, all anaerobic isolates should be sent to the central reference laboratory for confirmation of identification and susceptibility.

The central reference laboratory will confirm pathogen identifications and susceptibility test results on all clinical isolates reported and shipped by the local laboratory. If discrepancies occur between the results obtained at the central reference laboratory and those obtained at the study center 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 results and the central laboratory will provide the definitive result for pathogen identification and susceptibility test results. 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 or is not recoverable for a second sample from the local laboratory.

3.2 Rationale for study design, doses, and control groups

This study is a randomized, double-blind, double-dummy, comparative design implemented to minimize potential bias in the investigator's assessment of clinical response and safety events. Given the risk to patients and severity of disease, a placebo-controlled trial would not be ethically appropriate. This study will be conducted in patients suspected of having a cUTI due to Gram-negative pathogens. For purposes of this study, flank pain, frequency, urgency, dysuria, and suprapubic pain are considered cUTI-specific symptoms. Chills, warmth, rigors, nausea, vomiting, costovertebral angle tenderness, and suprapubic tenderness are signs and symptoms of interest but are not included in the primary outcome assessment.

The dose of ceftazidime approved for the treatment of serious Gram-negative infections for patients with a CrCl of >50 mL/min is 2000 mg for 30 minutes intravenously every 8 hours, and for patients with a CrCl of ≥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.

The active comparator chosen for this study is IV doripenem. Doripenem has efficacy against Gram-negative pathogens and is approved for and has been used widely for the treatment of cUTIs, and carbapenems are the drugs of choice against ESBL producing Gram-negative pathogens. Patients participating in this study and randomized to doripenem will receive 500 mg doripenem intravenously every 8 hours.

Complicated UTIs are frequently managed initially with IV antibacterial therapy with subsequent conversion to oral antibacterial therapy after improvement in clinical symptoms. In clinical practice, the oral agent chosen is dependent upon the results of culture and susceptibility testing. The oral step-down antimicrobial of choice is described in Section 5.5.3.

3.2.1 Dose rationale

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

3.2.1.1 Method of dose selection

Nonclinical data from in vitro susceptibility testing and PD hollow-fiber experiments support the concept that a critical threshold concentration (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 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 both ceftazidime and avibactam and covariate information collected in healthy volunteers, patients with renal impairment, and patients with cIAI (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 a 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 dosing regimen in Phase III compared with Phase II

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 dose 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 include those with bacteremia and pyelonephritis. 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 and 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 and 500 mg avibactam given every 8 hours and infused over 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 IV study therapy. There can be no exceptions to this rule.

Where patients who do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the [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 that all such contacts are appropriately documented.

4.1 Inclusion criteria

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

1. Patient must provide a signed written informed consent prior to any study-specific procedures. However if a patient is unable, the patient's legally acceptable representative may provide written consent, as approved by the institutional specific guidelines. Those patients who are unconscious or considered by the investigator to

be clinically unable to consent at Screening and who are entered into the study by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

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

3. Patient has a clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the investigator to be serious (requires patient to be hospitalized for treatment with IV therapy).

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

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

OR

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

- Has had normal menstrual periods for the 3 months prior to study entry, and
- Has a negative serum pregnancy test (serum 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 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 dose of IV study therapy, to practice highly effective methods of birth control, such as intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), and medroxyprogesterone injections (Depo-Provera®), or remain sexually abstinent. Oral contraceptives should not be used as the sole method of birth control because the effect of CAZ-AVI on the efficacy of oral contraceptives has not yet been established. Barrier methods (such as male condom or diaphragm with spermicide) can be used if another method of acceptable contraception (not oral contraceptives) is also used.

5. Patient has pyuria 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.

6. Patient has a positive urine culture: 1 midstream clean catch or catheterized urine specimen within 48 hours of enrollment containing ≥10^5 CFU/mL of a recognized uropathogen known to be susceptible to the IV study therapy (CAZ-AVI and doripenem).

Note: If patients meet all of entry criteria except for positive urine culture as outlined in entry criterion 6, the patients may be enrolled before urine culture results are available if the results are likely (based on urinalysis and clinical findings) to be positive and study drugs are considered appropriate empiric therapy. However, a urine Gram stain must be performed and demonstrate the presence of Gram-negative bacilli before study entry if a culture result is not available.

7. Demonstrates either acute pyelonephritis or complicated lower UTI without pyelonephritis as defined by the following criteria:

(a) Acute pyelonephritis is indicated by flank pain (must have onset or worsening within 7 days of enrolment) 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

(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 must have onset or have worsened within 7 days of enrollment and include dysuria, urgency, frequency, and 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 chronic urinary retention (male patients)
  - Obstructive uropathy that is scheduled to be medically or surgically relieved during IV 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 >48 hours prior to the diagnosis of cUTI (indwelling bladder catheters that have been in place for >24 hours prior to Screening must be

removed or replaced prior to collection of the screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or is contraindicated due to a recent procedure or urological condition)

- Urogenital procedure (eg, cystoscopy or urogenital surgery) within the 7 days prior to study entry.

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

8. 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 protocol, so long as he or she provides a signed written informed consent to participate in the main study.

4.2 Exclusion criteria

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

1. A Gram stain or urine culture (if urine culture results are available) demonstrates that a Gram-positive organism is present at $\geq 10^5$ CFU/mL.

2. Where a urine culture result is available, at least 1 Gram-negative uropathogen is resistant to CAZ-AVI or doripenem.

3. Where a urine culture result is available, patient's urine culture at study entry isolates more than 2 microorganisms regardless of the colony count.

4. Where a urine culture result is available, patient has a confirmed fungal UTI with colony count $>10^3$/mL.

5. Patient has received any prior antibiotic before the initiation of study therapy for this infection.

6. Patient is receiving prophylactic antibiotics, unless the prophylactic antibiotics are stopped at study entry.

7. Patient needs effective concomitant systemic antibacterials (ie, oral, intramuscular, and/or IV) in addition to those designated in the 2 treatment groups.

8. Patient has complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, prostatitis, or history of any illness that, in the opinion of the investigator, may confound the results of the study or pose additional risk in administering the study therapy to the patient.

9. Patient has UTI symptoms potentially attributable to another process (eg, sexually transmitted disease, prostatitis).

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

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

12. Patient has any of the following laboratory values:

(a) Creatinine clearance ≤30 mL/min by Cockcroft-Gault formula (Cockcroft et al 1976). Refer to Appendix E for the formula for calculating CrCl.

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

(c) Absolute neutrophil count <500/mm^3

(d) Platelet count <50000/mm^3

(e) Bilirubin >3.0 × the upper limit of normal (ULN), unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease

(f) ALT or AST >3.0 × ULN values used by the laboratory performing the test. Patients with values >3.0 × ULN and <5.0 times ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

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

13. Patient is considered unlikely to survive the 6- to 8-week study period or have a rapidly progressive or terminal illness.

14. Patient is unlikely to respond to 10 days of therapy for the treatment of cUTI without bacteremia or up to 14 days of therapy for treatment of cUTI with bacteremia.

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

16. Patient is receiving hemodialysis or peritoneal dialysis.

17. Patient had a renal transplant.

18. Patient has acute hepatitis, chronic hepatitis, cirrhosis (Child-Pugh Class B or C), acute hepatic failure, or acute decompensation of chronic hepatic failure.

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

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

21. Patient has any urinary catheter or device that will not be removed during the study treatment period, including indwelling bladder catheter, urinary catheter, nephrostomy tubes, or stent.

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

(a) Human immunodeficiency virus infection, with either a current AIDS-defining condition (eg, Kaposi sarcoma, Pneumocystis carinii pneumonia) or a CD4 plus T-lymphocyte count <200/mm3 at the time of study entry

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

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

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

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

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

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

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

27. Patient had a nonleukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

28. Patient had a previous allogenic bone marrow transplant.

See Section 5.3 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 IV study therapy. Such recommendations may address the need for a second method of contraception until the hormonal method becomes fully effective.

5.2 Patient enrollment and random assignment to treatment

For patient enrollment and randomization, the investigator will perform the following:

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

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

3. Complete patient eligibility.

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

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

6. After written informed consent has been obtained and eligibility established, the study center's unblinded pharmacist or 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 Randomisation 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 study center.

Eligible patients will be randomized to treatment in a 1:1 ratio to CAZ-AVI plus doripenem placebo or CAZ-AVI placebo plus doripenem.

Patient randomization will be stratified based on the type of infection at Baseline (acute pyelonephritis or other cUTIs without pyelonephritis) and region (North America and Western Europe, Eastern Europe, and the rest of the world). Randomization codes will be assigned strictly sequentially to eligible patients (within each stratum).

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

5.3 Procedures for handling patients incorrectly enrolled or randomized

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

Where patients who do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the [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

5.4.1 Methods for ensuring blinding

This study will be double-blinded with regard to IV therapy (CAZ-AVI or doripenem). After written informed consent has been obtained and eligibility established, using the IVRS/IWRS, the study center's unblinded pharmacist or designee will obtain the randomization code. The IVRS/IWRS will also confirm the IV study therapy assignment including the unique identification numbers of the kits to be prepared for the patient's IV therapy. The unblinded pharmacist or designee will be responsible for maintaining accountability and preparing the blinded IV study therapy according to the handling instructions. Study center personnel, with the exception of the unblinded pharmacist or designee, will remain blinded to the identity of the IV study therapy until the database has been locked and the study has been unblinded. In

the case of a medical emergency requiring the investigator to know the identity of the IV study therapy, the investigator will follow the procedures outlined in Section 5.4.2.

5.4.2 Methods for unblinding the study

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

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

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

5.5 Treatments

5.5.1 Identity of investigational products

CAZ-AVI contains both 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, doripenem, ciprofloxacin, or sulfamethoxazole/trimethoprim) dosage, form, and strength is provided in Table 2. Investigational product (CAZ-AVI and doripenem) will be supplied by AstraZeneca. Normal saline solution (0.9%) for placebo CAZ-AVI and placebo doripenem will be supplied by the study centers, unless local regulations require sourcing from the sponsor as detailed in the pharmacy manual. Oral ciprofloxacin and sulfamethoxazole/trimethoprim will be supplied by AstraZeneca.

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 and 500 mg avibactam for solution for infusion
Doripenem	Sterile powder, 500 mg
Ciprofloxacin	Oblong, nearly white to slightly yellowish film-coated tablet, containing 500 mg ciprofloxacin
Sulfamethoxazole/trimethoprim (Septrin Forte)	White, elongated tablet, coded GX02C, biconvex, scored along the shorter axis containing 800 mg sulfamethoxazole and 160 mg trimethoprim
Sodium Chloride Injection	0.9% Sodium Chloride Injection, 100 mL

Abbreviation: CAZ-AVI, ceftazidime-avibactam.

5.5.2 Doses and treatment regimens

Each patient will receive a 1-hour infusion followed by a 2-hour infusion, 3 times a day.

Patients randomized to receive CAZ-AVI will receive doripenem placebo (0.9% saline) intravenously immediately followed by CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) intravenously. Patients randomized to receive the comparator, doripenem, will receive 500 mg doripenem intravenously immediately followed by CAZ-AVI placebo (0.9% saline).

Doripenem/doripenem placebo will be given at a constant IV rate over 60 minutes, and CAZ-AVI/CAZ-AVI placebo will be given at a constant IV rate over 120 minutes. Patients will receive study therapy every 8 hours (±30 minutes). Before being switched to optional oral therapy, patients must receive a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy while in the hospital.

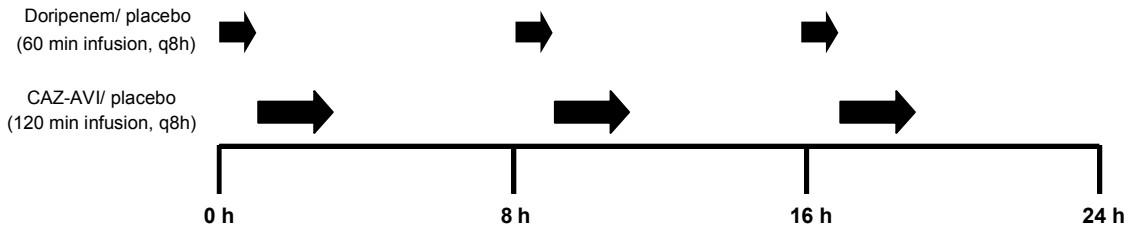
An appropriate flush with 0.9% sodium chloride infusion solution should be administered at the end of the infusion to ensure that the patient receives the entire dose. The flush should be administered according to local procedures and be appropriate for the infusion lines used by the clinical center.

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion, the investigator may continue the patient in the study at his or her own discretion. However, since dosing recommendations for the study drugs vary depending on the patient's renal function, the investigator should consider whether the change in CrCl warrants a change in IV study drug dosage or frequency. 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.

5.5.2.1 Dosing intervals in patients with normal renal function or mild renal impairment (estimated creatinine clearance value >50 mL/min)

Treatments will be repeated every 8 hours (±30 minutes) as described in Figure 2.

Figure 2 Schematic of dosing intervals for patients with normal renal function/mild renal impairment (for an arbitrary 24-hour period)



Abbreviations: CAZ-AVI, ceftazidime-avibactam; h, hour; min, minute; q8h, every 8 hours.

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

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

5.5.2.2 Dose regimen adjustments for patients with moderate and severe renal impairment (estimated creatinine clearance value ≤50 mL/min)

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

If subsequent to study entry and while still on IV study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (ie, estimated CrCl is ≤30 mL/min), retesting should be performed promptly. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl is <31 mL/min, the investigator should use his or her discretion in determining whether an immediate dose change, a short period of continued observation, or discontinuation of therapy is warranted. Once a dose change is decided upon, the investigator should inform the dispensing pharmacist immediately. The pharmacist should then provide the appropriate dose adjustments, as outlined in Table 4, to allow the patient to continue receiving blinded study therapy.

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

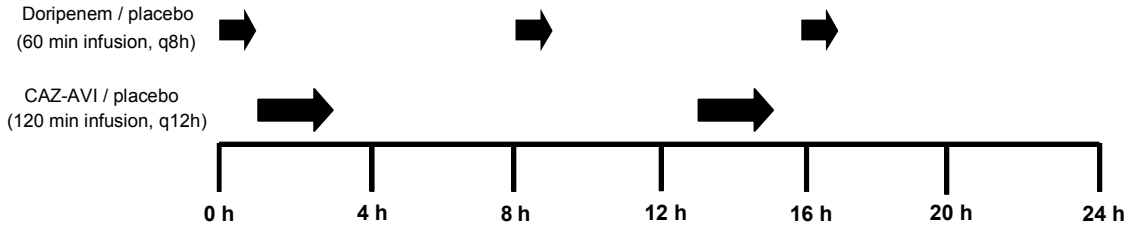
Dose adjustments for CAZ-AVI or doripenem for patients with an estimated CrCl between 50 and 31 mL/minute (moderate renal impairment) are outlined in Table 3. A schematic of the dosing intervals for patients with moderate renal impairment is displayed in Figure 3.

Table 3 Dose regimens and infusion times for patients whose estimated creatinine clearance is 50 to 31 mL/min while on IV study therapy

Estimated CrCl (mL/min)[a]	Dose regimen and infusion time			
	0 h	8 h	13 h	16 h
50 – 31	Doripenem 250 mg/placebo CAZ-AVI (1000 mg ceftazidime and 250 mg avibactam)/ placebo	Doripenem 250 mg/placebo	CAZ-AVI (1000 mg ceftazidime and 250 mg avibactam)/ placebo	Doripenem 250 mg/ placebo

[a] Estimated CrCl using Cockcroft-Gault formula (Appendix E).
Abbreviations: CAZ-AVI, ceftazidime-avibactam; CrCl, creatinine clearance; h, hour; IV, intravenous.

Figure 3 **Schematic of dosing intervals for patients with moderate renal impairment – estimated creatinine clearance value 31 to 50 mL/min (for an arbitrary 24-hour period)**



Abbreviations: CAZ-AVI, ceftazidime-avibactam; h, hour; min, minute; q8h, every 8 hours; q12h, every 12 hours.

The dose regimens and infusion times for patients with severe renal impairment are presented in Table 4.

Table 4 **Dose regimens and infusion times for patients whose estimated creatinine clearance is <31 mL/min while on IV study therapy**

Estimated CrCl (mL/min) [a]	**Dose regimen and infusion time**	
	0 h	12 h
30 – 16	Doripenem 250 mg/placebo CAZ-AVI (1000 mg ceftazidime and 250 mg avibactam)/placebo	Doripenem 250 mg/placebo
15 – 10	Doripenem 250 mg/placebo CAZ-AVI (500 mg ceftazidime and 125 mg avibactam)/placebo	Doripenem 250 mg/placebo

[a] Estimated CrCl using Cockcroft-Gault formula (Appendix E).
Abbreviations: CAZ-AVI, ceftazidime-avibactam; CrCl, creatinine clearance; h, hour; IV, intravenous.

5.5.3 Additional study drug step-down treatment

Patients are to receive 10 days of antibiotic therapy (IV plus optional oral therapy). The duration may be extended up to 14 days if the patient is bacteremic at study entry. If all of the following criteria for clinical improvement are met, patients may be switched to oral ciprofloxacin (or oral sulfamethoxazole/trimethoprim) after receiving a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy administered in the hospital.

1. The patient has been afebrile (<37.8°C) for at least 24 hours; without the influence of medication with antipyretic effects (eg, medications containing paracetamol, anti-inflammatory drugs, or aspirin). If antipyretic medication has been taken by the patient, it is recommended that body temperature readings 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. Use of antipyretic medication and timing of dosing relative to temperature recordings should be recorded.

2. The patient is able to tolerate oral medication and improvement has been noted in most of the following signs and symptoms: chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, and suprapubic pain, as documented on the Daily Patient Symptom Assessment Questionnaire (see Appendix G).

All patients must have the investigator-determined clinical response evaluation, and the collection of a urine specimen for culture performed before switching from IV to oral therapy. The Daily Patient Symptom Assessment Questionnaire should also be performed unless previously assessed on the same calendar day and symptoms have not changed. The investigator should complete the eCRF page documenting that the patient met the criteria to switch to oral therapy.

The choice of oral antimicrobials allowed per protocol is limited to 1 preferred oral option and 1 alternative oral option to decrease confounding factors when analyzing the study efficacy data. The oral option of choice is 500 mg ciprofloxacin taken orally twice daily. If the patient has a fluoroquinolone-resistant pathogen, the patient may receive oral sulfamethoxazole/trimethoprim (800 mg/160 mg) taken twice daily as the alternative option. If there is a valid reason that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are an appropriate choice (eg, patient is hypersensitive to either ciprofloxacin or sulfamethoxazole/trimethoprim), the investigator will be required to discuss patient management with the medical monitor and provide additional documentation as per directives in the study center manual. The uropathogen(s) must be susceptible to the switched oral medication.

Switching to oral therapy is not mandated; patients may continue receiving IV study therapy for the entire 10-day course (up to 14 days of therapy for those patients who are bacteremic at

study entry). Patients who are switched to oral ciprofloxacin (or oral sulfamethoxazole/trimethoprim) should receive the first dose of oral therapy approximately 8 hours after the last dose of IV study therapy and then twice daily (approximately every 12 hours). Ciprofloxacin and sulfamethoxazole/trimethoprim will be dispensed as open-label study therapy.

5.5.4 Labeling

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

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

5.5.5 Storage

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

5.6 Concomitant and poststudy treatments

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

Patients who meet protocol-specific criteria may be switched to oral ciprofloxacin after a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy. For those patients with a fluoroquinolone-resistant pathogen, oral sulfamethoxazole/trimethoprim is an alternative option (Section 5.5.3). No other oral, intramuscular, or IV concomitant antibacterial treatments are permitted while receiving study therapy at any time up to the LFU visit. A patient requiring such antibacterial treatments other than the allowed study therapy for the treatment of the cUTI will be considered a treatment failure.

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 medications without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after being randomized to IV study therapy, the investigator should contact the AstraZeneca physician or [redacted] medical monitor (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 was to continue in the study. Patients who have completed study therapy and are in the Follow-up Period should remain in the study, as they are not actively on study therapy but are being followed for outcomes.

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

5.6.1 Surgical procedures

Any patient planning to undergo surgical treatment not compatible with the aims of the study must not be enrolled. For patients who need to undergo an unplanned surgical procedure during the study, the reason for the surgery must be documented as an AE in the eCRF.

5.6.2 Management of indwelling bladder catheters

For those patients entering the trial with the complicating factor of having an indwelling bladder catheter, it must have been present for >48 hours prior to the diagnosis of cUTI. In addition, those indwelling bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of the screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or is contraindicated due to a recent procedure or urological condition, so that the urine culture results are an accurate representation of the pathogen(s) present.

Patients should only be enrolled if the indwelling bladder catheter is expected to be permanently discontinued during the study treatment period (IV plus oral). For patients with indwelling bladder catheters during the conduct of the study, these should be managed according to the following catheter management guidelines to ensure standardization during the conduct of this trial.

Indwelling bladder catheters should be maintained as a sterile, closed drainage system and the junction of the catheter and drainage tube should not be disconnected.

Besides permanent catheter discontinuation, other indications for indwelling bladder catheter change include the following:

- Malfunction or leakage
- Obstruction
- Contamination of the system (breakage between the catheter and drainage tube)

5.7 Treatment compliance

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

The qualified study center personnel at the investigative study center will administer IV study therapy and treatment compliance will be assured. For those patients who are discharged from the hospital but continue on IV therapy, IV study therapy will be administered by a qualified healthcare provider (eg, home health agency). The dose, date, and exact start and stop time of

administration of the IV study therapy will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

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

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

- All study staff trained and authorized by the investigator to prepare or administer IV study therapy are listed on the Delegation of Authority Log, OR
- The nurse manager(s)/supervisor(s) and study pharmacists authorized by the investigator are listed on the Delegation of Authority Log as the person(s) responsible for ensuring that the pharmacy and nursing staff are appropriately trained on IV 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 personnel in IV study therapy preparation and administration 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 which 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 performed 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 that the Delegation of Authority Log remains current and training of local HHC staff is provided and documented prior to HHC staff administering study therapy.

Records of IV study therapy usage should include the identification of the person to whom the IV study therapy was administered, the quantity and date of administration, and a record of unused IV study therapy. The investigator and pharmacist are responsible for maintaining accurate IV study therapy accountability records throughout the study on the relevant forms

provided by AstraZeneca/[redacted]. Each administration of IV study therapy will be documented in the eCRF.

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

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

The unblinded [redacted] representative performs complete IV study therapy accountability during each monitoring visit, including verifying documentation of receipt, dispensing, return, and destruction of IV study therapy and consistency of this documentation with physical inventory and IVRS/IWRS.

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

5.8 Discontinuation of investigational product

Patients may be discontinued prematurely from IP (CAZ-AVI plus optional oral ciprofloxacin or doripenem plus optional oral ciprofloxacin) (ie, prior to cure) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE (eg, risk to patients, as judged by the investigator and/or safety review committee, [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 hepatic/liver criteria are met (see also Appendix F):

  - 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.

The EOT (IV) visit assessments should be completed prior to starting the patient on other therapy including the study approved oral therapy.

For patients who discontinue IP early, their follow-up 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 (IV) visit within 24 hours after IV study therapy discontinuation.

Patients who discontinue IP early should be seen at the time they discontinue from IP and at the LFU visit and assessed by the investigator. Discontinuation from IV study therapy and oral study therapy will be recorded separately in the eCRF. It is understood that some patients may need to discontinue IV study therapy earlier than planned secondary to treatment failure or for other reasons. Anytime the antibacterial therapy for the disease under study is changed, an appropriate specimen for urine culture must be obtained. The sample should be collected after stopping the IV study therapy but before the new alternative antibiotic is administered.

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 IP and at the LFU visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and 6.4.5) and all study drugs (eg, ciprofloxacin) should be returned by the patient.

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 LFU visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and 6.4.4) and all study therapy (eg, ciprofloxacin, sulfamethoxazole/trimethoprim) should be returned by the patient.

For patients who were randomized to treatment based on a urine Gram stain documenting Gram-negative bacilli, if the entry urine culture does not contain 1 or 2 recognized Gram-negative uropathogens at $>10^5$ CFU/mL (ie, does not conform to the defined baseline cultured pathogen entry criterion), the patient may be withdrawn from the study at the discretion of the investigator. These patients should continue to be followed for safety assessments.

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

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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

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

6.1.1 Electronic data capture

Data will be collected electronically for each patient by an EDC data management and work flow 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 6.2.6.

6.2.1 Visit 1 eligibility/screening (Day –1 to Day 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 IV study therapy. Screening assessments will consist of:

1. Obtaining informed consent
2. Reviewing inclusion and exclusion criteria with the patient
3. Collecting demographics
4. Collecting medical and surgical history
5. Reviewing prior and concomitant medications (including prior antibiotic therapy)
6. Performing a 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.
7. Performing a UTI-focused physical examination (suprapubic pain and costovertebral angle tenderness)
8. Measuring vital signs including supine blood pressure (BP), heart rate, respiratory rate, and body temperature as defined in Section 6.4.10
9. Obtaining blood sample for clinical chemistry, hematology, and coagulation assessments
10. Estimating CrCl using the serum creatinine results from the local laboratory and the patient's actual body weight (see Appendix E)
11. Obtaining a urine sample for routine urinalysis (central laboratory)
12. Obtaining a urine specimen for quantitative urine culture and susceptibility. Culture results must have Gram-negative bacilli isolated or Gram-negative bacilli must be seen on urine Gram stain prior to entry.
13. Obtaining a blood sample for blood culture

14. 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 IP, a patient may be enrolled on the basis of a negative urine pregnancy test obtained locally, though serum β-hCG must still be obtained. If either test is positive, the patient must be excluded. If a study center can not do serum β-hCG testing, a urine β-hCG test must be obtained.

15. Monitoring for AEs

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

The following assessment will be performed at Visit 2 before administering the first dose of study therapy. Repeat assessments are not required for visits that occur on the same calendar day (ie, if screening and randomization occur on the same day). Local laboratory test results will be used to qualify patients for randomization, although samples will also be sent to the central laboratory for testing. Baseline assessments will consist of:

1. Reviewing the inclusion and exclusion criteria with the patient

2. Administering Premorbid Patient Symptom Assessment Questionnaire

3. Administering Daily Patient Symptom Assessment Questionnaire

4. Reviewing concomitant medications

5. Performing a UTI-focused physical examination (suprapubic pain and costovertebral angle tenderness)

6. Measuring vital signs including supine BP, heart rate, respiratory rate, and body 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. Assessing urinary device status (as appropriate)

9. Obtaining blood sample for clinical chemistry, hematology, and coagulation assessments (central laboratory). Coombs test performed locally and results recorded in the eCRF. Abnormal safety laboratory results obtained throughout the study should be followed up as clinically indicated (see Appendix F).

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

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

12. Collecting blood sample for pharmacogenetic (PGx) research analysis (from patients who signed the separate PGx informed consent and will receive study therapy) (can be obtained at Visit 3 if not collected before the first dose of IP)

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

14. Randomizing eligible patient to treatment group through the IVRS/IWRS

15. Monitoring for AEs

16. Administering IV study therapy

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

The duration of antibiotic treatment with study therapy (IV plus optional oral therapy) will be 10 days unless the patient is bacteremic at study entry, in which case, the duration of antibiotic treatment with study therapy may be extended to a total of up to 14 days (IV plus optional oral therapy). Those patients who remain on IV study therapy after 5 full days (ie, 15 doses) will receive their IV study therapy from study center personnel while in the hospital or from a qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT, TOC, and LFU visits following discharge from the hospital. Samples for clinical laboratory assessments should be collected prior to dosing.

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

Daily

1. Administering Daily Patient Symptom Assessment Questionnaire

2. Reviewing concomitant medications (daily while on IV therapy)

3. Performing a UTI-focused physical examination (suprapubic pain and costovertebral angle tenderness)

4. Measuring vital signs including supine BP, heart rate, respiratory rate, and body temperature as defined in Section 6.4.10 (daily while on IV therapy)

5. Monitoring for AEs daily while on IV therapy. Should a patient experience significant diarrhea during or after study therapy, the investigator should consider obtaining a stool sample and test for *C. difficile* toxin.

6. Assessing urinary device status as appropriate

Day 3

7. Two ECG measurements: 1 measurement at the end of a CAZ-AVI/CAZ-AVI placebo infusion and 1 measurement at the end of the corresponding doripenem/doripenem placebo infusion. Each ECG measurement should be performed in triplicate.

8. Obtaining blood sample for PK analysis (see Section 6.5.1 for sample collection times)

Other than daily

9. Obtaining blood sample for clinical chemistry, hematology, and coagulation assessments (central laboratory; every 3 days). Abnormal safety laboratory results obtained throughout the study should be followed up as clinically indicated (see Appendix F).

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

11. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated (repeat daily if initial culture is positive or as clinically indicated)

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

13. Administering study therapy (the investigator may switch the patient from IV to oral therapy after the patient has received at least 5 full days [ie, 15 doses for patients whose estimated CrCl remains >50 mL/min] of treatment with IV study therapy while hospitalized and met protocol-specified criteria for clinical improvement)

6.2.4 Visit 16 EOT (IV) assessment procedures

The EOT (IV) visit should occur prior to the patient starting oral therapy and within 24 hours after the last IV dose. The following assessment procedures will be performed:

1. Administering Daily Patient Symptom Assessment Questionnaire (unless performed previously on the same calendar day and symptoms have not changed)

2. Reviewing concomitant medications

3. Conducting investigator-determined clinical response assessment prior to switching from IV to oral therapy

4. Performing a complete physical examination as defined in Section 6.4.8

5. Performing a UTI-focused physical examination (suprapubic pain and costovertebral angle tenderness)

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

7. 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.

8. Assessing urinary device status as appropriate

9. Obtaining blood sample for clinical chemistry, hematology, and coagulation assessments. Coombs test performed locally and results recorded in the eCRF. Abnormal safety laboratory results obtained throughout the study should be followed up as clinically indicated (see Appendix F).

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

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

12. Obtaining a urine specimen for quantitative urine culture and susceptibility prior to switching from IV to oral therapy

13. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated

14. Obtaining a blood sample for biomarker analysis (consenting patients only)

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

6.2.5 Visit 17 Test of Cure (TOC) (21-25 days after randomization) assessment procedures

The following assessment procedures will be performed:

1. Administering Daily Patient Symptom Assessment Questionnaire

2. Reviewing concomitant medication

3. Conducting investigator-determined clinical response assessment

4. Performing a complete physical examination as defined in Section 6.4.8

5. Performing a UTI-focused physical examination (suprapubic pain and costovertebral angle tenderness)

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

7. Assessing urinary device status (as appropriate)

8. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments. Coombs test performed locally and results recorded in the eCRF. Abnormal safety laboratory results obtained throughout the study, including the LFU, should be followed up as clinically indicated (see Appendix F).

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

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

11. Obtaining a urine specimen for quantitative urine culture and susceptibility

12. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated

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

6.2.6 Visit 18 Late Follow-Up (LFU) (45-52 days after randomization) assessment procedures

The following assessment procedures will be performed:

1. Administering Daily Patient Symptom Assessment Questionnaire

2. Reviewing concomitant medications

3. Conducting investigator-determined clinical response evaluation

4. Performing a complete physical examination as defined in Section 6.4.8

5. Performing a UTI-focused physical examination (suprapubic pain and costovertebral angle tenderness)

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

7. Assessing urinary device status (as appropriate)

8. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (as clinically indicated). Coombs test performed locally and results recorded in the eCRF. Abnormal laboratory test results should be followed-up as clinically indicated.

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

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

11. Obtaining a urine specimen for quantitative urine culture and susceptibility

12. Obtaining a blood sample for blood culture if the previous blood culture was positive and also as clinically indicated

13. Obtaining a serum β-hCG sample for females of childbearing potential

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

6.3 Efficacy

6.3.1 Patient-reported symptomatic response assessment

During study conduct, patients will be required to report their cUTI symptoms on a series of formal questionnaires that will be administered by trained study center staff as detailed in Section 9.2 The Premorbid Patient Symptom Assessment Questionnaire will be administered once at Baseline to determine whether a patient normally experiences UTI symptoms (ie, in the absence of a UTI) that may be attributable to other disease processes (eg, BHP). The patients will be administered the Daily Patient Symptom Assessment Questionnaire at all visits starting at Visit 2 to capture changes in symptoms over time (ie, Baseline, daily while on IV therapy, at EOT [IV], TOC, and LFU).

Patients should be reminded to report any health problems directly to the investigator. The investigator will assess AEs as in Section 6.4. Patient-reported outcomes are not to be used as a vehicle for AE reporting.

The data collected from the questionnaires will be used to programatically assess the patient-reported symptom assessment response via the algorithm presented in Section 11.1. The patient-reported symptomatic resolution is defined in Table 5 and Table 6.

Table 5 Definition of resolution of patient-reported symptomatic response at Day 5

Symptomatic response	Definition
Symptomatic resolution	All of the following baseline cUTI-specific symptoms have resolved or returned to premorbid state (frequency, urgency, dysuria, and suprapubic pain) and there has been resolution of or improvement in flank pain
Symptom persistence	Does not meet symptomatic resolution criteria immediately above
Indeterminate	Relevant Patient Symptom Assessment Questionnaire(s) were not administered

Abbreviation: cUTI, complicated urinary tract infection.

Table 6 Definition of resolution of patient-reported symptomatic response at the TOC and LFU visits

Symptomatic response	Definition
Symptomatic resolution	All baseline cUTI-specific symptoms (ie, flank pain, frequency, urgency, dysuria, and suprapubic pain) have resolved or returned to premorbid state
Symptom persistence	Does not meet symptomatic resolution criteria immediately above
Indeterminate	Relevant Patient Symptom Assessment Questionnaire(s) were not administered

Abbreviations: cUTI, complicated urinary tract infection; LFU, Late Follow-Up; TOC, Test of Cure.

6.3.2 Investigator-determined clinical response evaluation

The investigator should consider the entirety of the patient's clinical course and current status, including an evaluation of signs and symptoms (eg, fever, dysuria, and costovertebral angle tenderness) and physical examination in order to classify the patient's clinical response at the EOT (IV), TOC, and LFU visits according to the definitions listed in Table 7.

Table 7 Definition of investigator-determined clinical response at the EOT (IV), TOC, and LFU visits

Clinical response	Definition
Clinical cure	All or most pretherapy signs and symptoms of the index infection have improved or resolved such that no additional antibiotics[a] are required
Clinical failure	Patients who meet any one of the criteria below will be considered as failure: • Death related to cUTI • No apparent response to treatment; persistence or progression of most or all pretherapy signs and symptoms or use of additional antibiotics[a] for the current infection • Patient previously met criteria for failure (not applicable for the EOT [IV] visit)
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 at either the EOT (IV), TOC, or LFU visit • Death where cUTI is clearly noncontributory • Circumstances that preclude classification as a cure or failure

[a] Additional antibiotics do not include the protocol-allowed oral study therapy options (ciprofloxacin or sulfamethoxazole/trimethoprim).

Abbreviations: cUTI, complicated urinary tract infection; EOT, End of Therapy; IV, intravenous; LFU, Late Follow-Up; TOC, Test of Cure.

A patient will be said to have clinical relapse at the LFU visit if their clinical response was clinical cure at the TOC visit and is clinical failure at the LFU visit. Similarly, a patient will be said to have sustained clinical cure at the LFU visit if their clinical response was clinical cure at the TOC visit and is clinical cure at the LFU visit.

6.3.3 Microbiological response assessment

The microbiologic response of eradication at the TOC visit in the mMITT analysis set is one of the components of the primary outcome. The per-patient and per-pathogen microbiologic response of CAZ-AVI compared with doripenem in the mMITT, ME, and extended ME analysis sets for patients with cUTIs at the EOT (IV), TOC, and LFU visits are secondary outcomes.

Microbiological response will be assessed per-pathogen and per-patient according to the definitions listed in Sections 6.3.3.1 and 6.3.3.2, respectively. Microbiological outcome per-patient is assessed in a blinded manner. It is based on outcome per-pathogen isolated at the initial visit (considered as causative) and on the isolation of pathogens during the course of treatment or the posttreatment period.

Each baseline (initial/prestudy) pathogen will be categorized according to the definitions in Table 8 (Gram-negative organism normally associated with a UTI or nonfermentative Gram-negative pathogens).

Table 8 Microbiological response categories for each pathogen identified at initial/prestudy culture, EOT, TOC, and LFU

Microbiological response	Definition
Eradication	A urine culture taken within 48 hours prior to randomization and compared with the culture from the EOT (IV) visit or compared with the culture from the TOC or LFU visit shows that the urine culture obtained at the relevant visit demonstrates $<10^4$ CFU/mL of the original uropathogen, and the patient was not bacteremic (if the patient was bacteremic at Screening, the bacteremia has resolved).
Persistence	• A uropathogen present at Screening grew at $\geq 10^4$ CFU/mL at EOT (IV) or TOC • Death related to cUTI
Persistence with increasing MIC	A urine culture taken after at least 2 full days of treatment grows $\geq 10^4$ CFU/mL of an original uropathogen species that was susceptible or intermediately susceptible to study therapy pretreatment and displays ≥4-fold higher MIC to study therapy after treatment with IV study therapy.
Indeterminate	Study data are not available for evaluation of efficacy, for any reason including: • Patient is lost to follow-up or an assessment is not undertaken such that no urine culture was obtained (or culture results could not be interpreted for any reason) at either the EOT (IV), the TOC, or the LFU visit • Death where cUTI is clearly noncontributory • Circumstances that preclude classification as an eradication, persistence, or persistence with increasing MIC • Patient has no baseline culture

Abbreviations: CFU, colony-forming units; cUTI, complicated urinary tract infection; EOT, End of Therapy; IV, intravenous; LFU, Late Follow-Up; MIC, minimum inhibitory concentration; TOC, Test of Cure.

Microbiologic response with a cutoff of $<10^3$ CFU/mL using the same definition presented in Table 8 will be evaluated for the exploratory analyses.

A patient will be said to have recurrence or recurrence with increasing MIC at the LFU visit if his or her microbiological response was eradication at the TOC visit and is either persistence or persistence with increasing MIC at the LFU visit. Similarly, a patient will be said to have sustained eradication at the LFU visit if his or her microbiological response was eradication at the TOC visit and is eradication at the LFU visit.

For blood pathogens, similar microbiological response assessments will be performed. However, if no blood cultures are performed for the EOT (IV), TOC, or LFU visits and the patient's clinical response is "clinical cure" for the corresponding visit, a microbiologic response of "presumed eradication" will be assigned. If, while on treatment with study therapy, a patient is discontinued due to clinical failure and the persistence of the study entry pathogen is not confirmed by culture results or the patient is considered a clinical failure and no valid culture is obtained, the pathogen is presumed to persist.

6.3.3.1 Per-pathogen microbiological assessments after completion of all follow-up visit

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 6. Microbiological responses other than "indeterminate" will be classified as "favorable" or "unfavorable." Favorable microbiological response assessments include "eradication." Unfavorable microbiological response assessments include "persistence," and "persistence with increasing MIC." Patients with a microbiological response assessment of "indeterminate" will be considered to be nonevaluable for the ME and extended ME analysis set. "Superinfection" and "new infection" will be considered separately.

6.3.3.2 Per-patient (overall) microbiological response assessments

Per-patient (overall) microbiological response will also be assessed as "favorable" or "unfavorable" for each patient.

For a favorable microbiological response, pathogens isolated at entry into the study with $\geq 10^5$ CFU/mL must at follow-up (EOT [IV] or TOC) be $<10^4$ CFU/mL to meet CFU criteria for eradication from urine. If the patient was bacteremic, the blood pathogen must be assessed as eradicated or presumed eradicated. If the microbiologic response is assessed as unfavorable for either urine or blood, the overall microbiologic response will be unfavorable.

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 2 baseline pathogens were isolated, the overall microbiological response assessment will be "favorable" only if the microbiological response assessment for each of the baseline pathogens isolated is "favorable."

6.3.3.3 MIC among pathogens

The favorable per-pathogen microbiological response at the EOT (IV), TOC, and LFU visits will be evaluated for MIC categories. The MIC categories that will 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.

6.3.3.4 Emergent infections

Pathogens first appearing after Screening are categorized in Table 9 and will be summarized separately.

Table 9 Emergent infections

Emergent infections	Definition
Superinfection	A urine culture grew $\geq 10^5$ CFU/mL of a uropathogen other than a baseline pathogen during the course of active treatment with study therapy along with worsening signs and symptoms of infection or the emergence during treatment with study therapy of a new pathogen.
New infection	A pathogen other than an original uropathogen found at Screening at a level of ≥105 CFU/mL anytime after treatment has finished. If any pathogen was isolated from a site distant to the primary infection after treatment with study therapy had been completed, this will also be designated as a new infection.

Abbreviation: CFU, colony-forming units.

Bacteria first encountered after the study entry culture (superinfection or new infection) are evaluated separately.

6.3.4 Primary efficacy outcome variable

The 2 coprimary efficacy outcome variables are the:

- Proportion of patients with symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) with resolution of or improvement in flank pain based on the patient-reported symptom assessment response at the Day 5 visit in the mMITT analysis set.

- Proportion of patients with both a per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC visit in the mMITT analysis set.

6.3.5 Secondary efficacy outcome variables

Secondary efficacy outcome variables include the following:

- Proportion of patients with a favorable per-patient microbiological response at the EOT (IV), TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC and LFU visits in the mMITT analysis set
- Proportion of favorable per-pathogen microbiological response at the EOT (IV) TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with an investigator-determined clinical cure at the EOT (IV), TOC, and LFU visits in the mMITT, ME, extended ME, and CE analysis sets
- Favorable per-pathogen microbiologic response at the EOT (IV), TOC, and LFU visits by categories of MIC in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with favorable investigator clinical response assessment and, separately, favorable per-patient microbiological response at the TOC visit for patients infected with a ceftazidime-resistant pathogen in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with symptomatic resolution (as defined in the coprimary variables) at Day 5 and TOC for patients infected with a ceftazidime-resistant pathogen in the mMITT analysis set
- Time to first defervescence while on IV study therapy in patients in the mMITT, ME, extended ME, and CE analysis sets who have fever at study entry

6.3.6 Exploratory variables

Exploratory variables include the following:

- Resolution of symptoms associated with cUTI at recorded time points
- Proportion of patients with a favorable per-patient microbiological response using a cutoff of $<10^3$ CFU/mL at the EOT (IV), TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with a favorable per-pathogen microbiological response using a cutoff of $<10^3$ CFU/mL at the EOT (IV), TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets

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

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

6.3.7 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 (BP and heart rate), physical examination findings, 12-lead ECG parameters (QRS interval, RR interval, heart rate, QT interval, QTc interval corrected by Bazett [QTcB], and QTcF), and clinically important changes in clinical chemistry, hematology, and urinalysis laboratory values.

6.3.8 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 and listing of ceftazidime and avibactam plasma concentrations at specified sampling windows will be reported in the CSR.

6.3.9 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 of the Treatment Period (Day 1, Baseline), it may be taken at any point until the patient leaves the study. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

6.3.10 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 IV 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 or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above, including suspected transmission via the IV study therapy of an infectious agent

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 F).

6.4.3 Recording of adverse events

Time period for collection of adverse events

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

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment will be followed up by the investigator until the event is resolved or stabilized. AstraZeneca/[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 collect for each AE:

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

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

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

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

  – Date of death

  – Autopsy performed

  – Primary/secondary cause of death

(b) Life threatening

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

- Date of hospitalization
- Date of discharge

(d) Congenital abnormality or birth defect

(e) Important medical event

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

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

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

Causality collection

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

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

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study center personnel: "Have you had any health problems since the previous visit or when you were last asked?" and "Have you had any new symptoms?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are

not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

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

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible, the reporting investigator will use 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 AE collection

6.4.4.1 Lack of effect

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

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

6.4.4.2 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which CAZ-AVI is being studied. It may be an increase in the severity of the disease under study and 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 IV study therapy actively contributed to the progression of the disease (ie, not by

way of insufficient therapeutic effect). Events that are unequivocally due to disease progression should not be reported as an AE during the study.

6.4.5 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the IV study therapy or to the study procedures. 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 follow-up 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 investigators 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 report 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 10 presents the safety laboratory variables that will be measured.

Table 10 Laboratory variables

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

Note: Local laboratory test results will be used to qualify patients for randomization.
Abbreviation: β-hCG, β-human chorionic gonadotropin.

Section 7.1 provides details on blood volume that will be drawn.

6.4.7 Actions required in cases of increases in liver chemistry values

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

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 the ALT and/or AST elevations. Additional testing for liver laboratory test results must be done every 48 hours until the peak value has been reached, as documented by a decline in the values and/or until the patient is feeling better. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or study drug has been discontinued and the patient is asymptomatic. The patient should be followed until resolution (including laboratory testing).

6.4.8 Physical examination

The timing of individual examinations is indicated in Table 1.

A complete physical examination will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, abdominal, musculoskeletal, and neurological systems. Physical examination should include assessments such as suprapubic pain and costovertebral angle tenderness. Height and weight will be measured at Screening only.

A UTI-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 obtained at the screening visit only. 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 interval, 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) are observed then additional ECG assessments must be performed. Electrocardiograms should be performed after the next dose of study drug then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to Baseline (Day 1 prior to receiving any study drug). Assessments should be performed after the completion of study drug administration and be recorded as unscheduled assessments.

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

All ECGs will be sent to the central reader who will judge the overall interpretation as normal or abnormal. If abnormal, the central reader will decide whether or not the abnormality is clinically significant and the reason for the abnormality will be recorded. The date, time, and central reader's interpretation (normal, abnormal clinically significant, 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 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 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 the CAZ-AVI/CAZ-AVI placebo infusion
- Anytime between 30 and 90 minutes after stopping the CAZ-AVI/CAZ-AVI placebo infusion
- Anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping the CAZ-AVI/CAZ-AVI placebo infusion

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

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

Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual. The date and time of sample collection will be recorded as well as the date and time of the immediately preceding dose of IV study therapy. Stop time is considered as the time at which the contents of the IV bag have been administered completely and before lines are flushed. Stop time must always be recorded by the study center on the patient's source documents.

Section 7.1 provides details on blood volume that will be drawn.

6.5.2 Determination of drug concentration

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

6.6 Pharmacodynamics

6.6.1 Collection of pharmacodynamic markers

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

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

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

Section 7.1 provides details of blood volume that will be drawn.

6.7 Pharmacogenetics

Appendix D provides details of PGx sampling.

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 in 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 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 11.

Table 11 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	6	30
	Hematology	3	6	18
	Coagulation	4.5	5	22.5
Pharmacokinetic sample		4	3	12
Biomarker sample		10	4	40
Blood culture		10 – 15	4[a]	40 – 60
Pharmacogenetic sample		10	1	10
Total				172.5 – 192.5

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

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

7.2 Handling, storage, and destruction of biological samples

Section 3.1.1 provides information on handling, storage, and destruction of microbiological samples. 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, [redacted] 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

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

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 will keep 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 that the laboratory/laboratories 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/laboratories holding the samples is/are informed about the withdrawn consent immediately, and that samples are disposed of or destroyed, the action documented, and the documentation 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, 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] before 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 study 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 will be approved by the relevant EC and, if applicable, the national regulatory authority before implementation. Local requirements will be followed for revised protocols.

AstraZeneca/[redacted] will distribute any subsequent amendments and new versions of the protocol to each investigator. Section 8.3 provides details of distribution to EC.

If a protocol amendment requires a change to a study 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 and to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH E6(R1), 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 a [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 that will be used.

The investigator will ensure that the appropriate training relevant to the study is given to all of the study center personnel (including home healthcare staff, as applicable), and that any new information relevant to the performance of this study is forwarded to the study center personnel involved. Information and instructions on administration of the Patient Symptom Assessment Questionnaire will be provided to investigators and study center personnel at the investigator's meetings. Personnel responsible for administering the questionnaires will undergo a computer-based training program certifying them to administer the Patient Symptom Assessment Questionnaires to patients.

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 being 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 for the use of the patient's biological samples is reported and biological samples are identified and disposed of or 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 Unblinded monitoring

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

9.3.2 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the CSA, the terms of the clinical study protocol shall prevail with respect to the conduct of the study and the treatment of patients; 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 take place or patients are randomized to IV study therapy.

9.4.1 Archiving of study documents

The investigator will follow the principles outlined in the CSA.

9.5 Study timetable and end of study

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

The study is expected to start in the second quarter of [redacted] and to end by fourth quarter of [redacted].

The study may be terminated at individual centers if the study procedures are not being performed according to ICH E6(R1) 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 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 from 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, Baseline will be defined as the last nonmissing assessment before the start of IV study therapy. For microbiologic cultures (urine and/or blood culture), the initial culture will be defined as baseline. Refer to Section 3.1 for the definitions of EOT (IV), TOC, and LFU visits. Study randomization is defined as Day 1 (Baseline).

11.1 Calculation or derivation of efficacy variables

The primary efficacy variable will be determined based on 2 assessments, per-patient microbiologic response and patient-reported symptomatic response.

The patient-reported symptomatic response will be categorized into symptomatic resolution or symptom persistence and will be programmatically derived from the data obtained from the patient questionnaires at Day 5 and the TOC and LFU visit, in addition to the Premorbid Patient Symptom Assessment Questionnaire. It is recognized that some patients enrolled into the trial will have underlying, chronic symptomatology that overlaps with the disease under study. As such, if symptoms are present at any follow-up visit, it will be necessary to establish whether the patient suffered from these symptoms premorbidly and, if so, to determine whether residual symptoms are consistent with their normal, premorbid condition as reported on the Premorbid Patient Symptom Assessment Questionnaire.

For the Day 5 visit, if the cUTI-specific symptoms (frequency, urgency, dysuria, and suprapubic pain) are absent and flank pain is either absent or improved compared with Baseline, the symptomatic response will be classified as symptomatic resolution. If the symptoms of frequency, urgency, dysuria, and suprapubic pain are present, or flank pain is the same severity as Baseline, then the severity of each symptom will be compared with the severity of the symptom reported on the Premorbid Patient Symptom Assessment Questionnaire. If any symptom is more severe than that reported on the Premorbid Patient Symptom Assessment Questionnaire, the patient will be classified as having symptomatic persistence. However, if all symptoms are of the same severity or better compared with the severity reported on the Premorbid Symptom Assessment Questionnaire, the patient will have symptomatic resolution. If any symptom is worse than symptoms reported at Baseline (as per the baseline Daily Patient Symptom Assessment Questionnaire), regardless of premorbid symptomatology, the patient will be classified as having symptomatic persistence.

For the TOC and LFU visits, if all cUTI-specific symptoms (frequency, urgency, dysuria, suprapubic pain, and flank pain) are absent, the response will be symptomatic resolution. If any symptom is present, then the severity of each symptom must be compared with the severity of the symptom reported on the Premorbid Patient Symptom Assessment Questionnaire. If any symptom is more severe than that reported on the Premorbid Patient Symptom Assessment Questionnaire, the patient will be classified has having symptomatic persistence. However, if all symptoms are of the same severity or better compared with the severity reported on the Premorbid Questionnaire, the patient will have symptomatic resolution. If any symptom is worse than the symptoms reported at Baseline (as per the

baseline Daily Patient Symptom Assessment Questionnaire), regardless of premorbid symptomatology, the patient will be classified as having symptomatic persistence.

The combined efficacy variable will be assessed based on Table 12.

Table 12 Combined primary variable response at TOC

Patient-reported symptomatic response	Per-patient microbiological response		
	Eradicated	**Persistence or persistence with increasing MIC**	**Indeterminate**
Symptomatic resolution	Favorable	Unfavorable	Indeterminate
Symptom persistence	Unfavorable	Unfavorable	Unfavorable
Indeterminate	Indeterminate	Unfavorable	Indeterminate

Abbreviations: MIC, minimum inhibitory concentration; TOC, Test of Cure.

The 2 coprimary efficacy outcome variables are the:

- Proportion of patients with symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) and there has been resolution of or improvement in flank pain based on the patient-reported symptom assessment response at the Day 5 visit in the mMITT analysis set

- Proportion of patients with both a per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC visit in the mMITT analysis set

The primary efficacy variable will be based on the definitions in Section 6.3.1, Section 6.3.3, and Table 12.

The proportion of patients with favorable combined response is defined as the number of patients with a favorable combined response at the Day 5 and TOC visits divided by the number of patients in the mMITT analysis set.

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

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 (CE and mMITT).

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

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

11.2 Calculation or derivation of safety variables

No statistical inference will be made for safety analysis. Throughout the safety results sections, erroneously treated patients (eg, those randomized to CAZ-AVI treatment but who actually received doripenem) will be accounted for in the actual treatment received group.

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

The baseline values will be defined as the last available value before the start of IV study therapy (either CAZ-AVI or doripenem). 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, BP, heart rate, respiratory rate, and body temperature
- ECG test results such as heart rate, respiratory rate, QRS interval, QT interval, QTcF, and QTcB

11.2.1 Other significant adverse events

During the evaluation of the AE data, [redacted] or AstraZeneca medically qualified experts 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's or [redacted] medical monitor's (as an AstraZeneca delegate) judgement, significant AEs of particular clinical importance may, after consultation with the AstraZeneca physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of other data from laboratory test results, vital sign

measurements, ECG findings, and other safety assessments will be performed for identification of OAEs.

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

11.3 Calculation or derivation of pharmacokinetic variables

The collected ceftazidime and avibactam concentrations will be listed and summarized by descriptive statistics and descriptively summarized at specified sampling windows in the CSR. The compartmental pharmacokinetics of avibactam and ceftazidime will be evaluated by population modeling. The actual dosing and plasma sampling times will be used in the population PK modeling.

The avibactam and ceftazidime concentration, patient demographics, disease status data will be combined with the data from appropriate previous clinical studies for the population PK modeling analysis. Individual compartmental PK parameters for patients with available avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, maximum concentration, minimum concentration, area under the plasma concentration-time curve at steady state, and elimination half-life, will be derived from the predicted avibactam and ceftazidime concentration-time courses. All the derived PK parameters will be descriptively summarized. The appropriate avibactam and ceftazidime exposure outcome variables predicted by the population PK modeling will be used for a 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 outcome variables and the ceftazidime exposure, such as %T >MIC, and relevant covariates will be conducted and reported as a separate population PK and PK/PD analysis.

11.4.2 Population analysis of pharmacokinetic/pharmacodynamic variables

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

11.5 Calculation or derivation of pharmacogenetic variables

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

11.6 Calculation or derivation of exploratory variables

The favorable per-patient and per-pathogen microbiologic response for the exploratory analysis will use the same definitions as in Section 11.1.

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

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 the validity of data for each of the analysis sets will be based on a blinded review of data and will be undertaken 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 analysis will be based on 1 or more of the analysis sets defined in Sections 12.1.1.1 through 12.1.1.5. Patients in the ME, extended ME, and CE analysis sets will be analyzed according to the treatment they received, while patients in the mMITT set will be analyzed according to the randomly assigned treatment.

12.1.1.1 Microbiological modified intent-to-treat analysis set

The mMITT analysis set includes all patients who:

- Had clinical evidence of a cUTI and a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a Gram-negative pathogen
- Had no more than 2 microorganisms identified in the study entry urine culture, regardless of colony count. Any patient with a Gram-positive pathogen, or a bacterial species typically not expected to respond to both study drugs (eg, Acinetobacter, Stenotrophomonas) $\geq 10^5$ CFU/mL will be excluded.

12.1.1.2 Microbiologically evaluable analysis sets at the EOT (IV) and TOC visits

The ME analysis set at the EOT (IV) and TOC visits includes all patients meeting the following criteria:

- Were included in the mMITT analysis set
- EITHER
  - Received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered

  OR
  - Received therapy <48 hours before discontinuing treatment due to an AE
- Had no important protocol deviations that would affect the assessment of efficacy
- Had a microbiological assessment at the EOT (IV) or TOC visits, respectively, with a microbiological response other than indeterminate, including a quantitative urine culture
- Did not receive any prior antibiotics for the cUTI
- Did not receive any antibiotic therapy with potential activity against the baseline uropathogen collected at Screening between the time of the baseline culture and the EOT (IV) or TOC culture (other than protocol-defined study therapy). Study therapy is defined as blinded IV study drug and the allowed oral options (ciprofloxacin or sulfamethoxazole/trimethoprim). This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures.
- Had a study entry urine culture obtained ≤48 hours before the start of treatment with IV study therapy
- Had 1 or at most 2 baseline pathogens susceptible to both IV study therapies

12.1.1.3 Microbiologically evaluable analysis set at the LFU visit

The ME analysis set at the LFU visit includes all patients meeting the following criteria:

- Were included in the ME analysis set at the TOC visit
- Had a microbiological assessment at the LFU visit with a microbiological response other than indeterminate, including an interpretable quantitative urine culture
- Had no confounding events since the TOC visit, defined as any events that could impact the assessment of the microbiologic responses. An example of a confounding event is a deviation in study procedures.

- Did not receive any antibiotic therapy with potential activity against the baseline uropathogen since the TOC visit, except resuming oral antibiotic prophylaxis therapy after the TOC urine culture was obtained. This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures.

12.1.1.4 Extended microbiological evaluable analysis set

The extended ME analysis set at the EOT (IV), TOC, and LFU visits includes patients meeting the criteria for the ME analysis set, with the exception that baseline pathogens need not be susceptible to either study therapy.

12.1.1.5 Clinically evaluable analysis set at the EOT (IV) and TOC visits

The CE analysis set at the EOT (IV) and TOC visits includes all patients meeting the following criteria:

- Were included in the mMITT analysis set
- EITHER
  - Received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered

  OR

  - Received therapy <48 hours before discontinuing treatment due to an AE
- Had no important protocol deviations that would affect the assessment of efficacy
- Had a clinical outcome assessment of clinical cure or failure (and not indeterminate) at the EOT (IV) or TOC visits, respectively
- Did not receive any prior antibiotics for the cUTI
- Did not receive antibiotic therapy with potential activity against the baseline uropathogen collected at Screening between the time of baseline culture and the EOT (IV) or TOC culture, respectively (other than protocol-defined study therapy). Study therapy is defined as blinded IV study drug and the allowed oral options (ciprofloxacin or sulfamethoxazole/trimethoprim). This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures.
- Had the study entry urine culture obtained ≤48 hours before the start of treatment with IV study therapy

12.1.1.6 Clinically evaluable analysis set at the LFU visit

The CE analysis set at the LFU visit includes all patients meeting the following criteria:

- Were included in the CE analysis set at the TOC visit
- Had a clinical outcome assessment of clinical cure or failure (and not indeterminate) at the LFU visit
- Had no important protocol deviations that would affect the assessment of efficacy
- Did not receive any antibiotic therapy with potential activity against the baseline uropathogen collected at Screening since the TOC visit, except resuming oral antibiotic prophylaxis therapy after the TOC urine culture was obtained. This does not include antibiotic therapy taken for the treatment of cUTIs by patients who were considered failures.

12.1.2 Safety analysis set

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

12.1.3 Pharmacokinetic analysis set

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

12.2 Methods of statistical analyses

12.2.1 General considerations

Statistical analyses as specified for each variable will be conducted and all comparisons will be between CAZ-AVI and doripenem. The 2-sided 95% confidence intervals (CIs) will be produced for all primary and secondary efficacy analyses. Descriptive statistics, including number, mean, SD, median, minimum and maximum for continuous variables, and number and percentage 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 than the source data, SD will be presented to 2 more decimal precision than source data, 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 10 for handling of missing data for efficacy variables.

Further details on the methods of statistical analysis will be provided via a comprehensive statistical analysis plan to be issued before unblinding the data.

As a consequence of differing regulatory requirements for the choice of primary endpoint and statistical analyses of this study, 2 separate regional analysis plans will be produced.

12.2.2 Analysis of study population and patient characteristics

The number of patients randomized to treatment, important protocol deviations, and the number of patients completing and discontinuing from study therapy as well as from the study, along with reasons for withdrawal, will be tabulated by treatment group. 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 and by treatment group.

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

Efficacy

General considerations: Refer to Section 12.2.1 for descriptions of treatment comparisons and summarizations. The analysis of the proportion of patients with coprimary efficacy outcome variables (see Section 12.2.1) in the mMITT analysis set is the primary analysis.

Primary alternative hypothesis: CAZ-AVI will demonstrate clinical efficacy comparable to that of doripenem as treatment for patients with cUTIs. The clinical efficacy will be assessed by the coprimary efficacy outcome variables.

This hypothesis will assess that the treatment effect measured by the primary efficacy variable of CAZ-AVI will be noninferior to doripenem. The sponsor will conclude noninferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) is greater than –12.5% for both EOT (IV) and TOC visits in the mMITT analysis set and symptomatic resolution for the Day 5 visit; however, noninferiority may be assessed using a 10% margin in regions where this is a regulatory requirement.

Primary efficacy variable: The primary efficacy objective will be to assess the noninferiority of CAZ-AVI versus doripenem with respect to the coprimary efficacy outcome variables of the:

- Proportion of patients with symptomatic resolution (or return to premorbid state) of UTI-specific symptoms except flank pain (frequency/urgency/dysuria/suprapubic pain) and with resolution of or improvement in flank pain based on patient-reported symptomatic response at the Day 5 visit.

- Proportion of patients with both a per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on the patient-reported symptom assessment response at the TOC visit.

The primary efficacy will be conducted in the mMITT analysis set.

For derivation of the coprimary efficacy outcome variables refer to Section 11. The numbers and percentage in each treatment group will be tabulated. Indeterminates will be included in the denominator for calculating the percentages for the mMITT set, but they will be excluded from the denominator for the ME, extended ME, and CE analysis sets. A 2-sided 95% CI for the observed difference in the proportion of patients with a favorable coprimary efficacy outcome variables between CAZ-AVI and doripenem will be computed using the unstratified method of Miettinen and Nurminen (Miettinen et al 1985). A sensitivity analysis stratified by prespecified stratification factors will also be performed for the 2 coprimary outcome variables for both the Day 5 and TOC visits and also separately for the components of the second coprimary variable, ie, per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) at TOC as part of the secondary efficacy variables assessment in the mMITT analysis set. The stratification factors are type of infection at Baseline (acute pyelonephritis or other cUTIs without pyelonephritis) and region (North America and Western Europe, Eastern Europe, and the rest of the world).

The analysis for the 2 coprimary outcome variables and, as part of the secondary efficacy variable assessment, their components (as specified previously) will be performed and presented by subgroups. The subgroups to be analyzed will include, but not be limited to, type of infection, baseline pathogens, age, sex, race, and region. The subgroups to be analyzed will include, but not be limited to, type of infection, baseline pathogens, age (≥18 to 45, 46 to 64, 65 to 74, ≥75 to ≤90), sex, race, and region. Forest plots will be used to present the point estimate and the CI for the difference in proportion for the subgroups.

Secondary efficacy variables: The numbers and percentages in each treatment group for clinical response recorded as cure, failure, and indeterminate as defined in Section 6.3 will be tabulated. Secondary efficacy outcomes variables considering proportions will be analyzed by determining 2-sided 95% CIs for the observed difference in the outcome proportion between CAZ-AVI and doripenem (using the unstratified Miettinen and Nurminen method as described for the primary outcome variable).

The secondary variables assessing the outcomes are:

- Proportion of patients with a favorable per-patient microbiological response at the EOT (IV), TOC, and LFU visits in the mMITT, ME and extended ME analysis sets
- Proportion of patients with symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms (frequency/urgency/dysuria/suprapubic pain/flank pain) based on patient-reported symptomatic response at the TOC and LFU visits in the mMITT analysis set
- Proportion of favorable per-pathogen microbiological response at the EOT (IV), TOC, and LFU visits in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with an investigator-determined clinical cure at the EOT (IV), TOC, and LFU visits in the mMITT, ME, extended ME, and CE analysis sets
- Proportion of patients with symptomatic resolution (as defined in the coprimary variables) at day 5 and TOC for patients infected with a ceftazidime-resistant pathogen in the mMITT analysis set

The definitions for the outcomes are presented in Section 6.3.

The analysis of time-to-event secondary variables is as follows:

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

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

The analysis of other secondary variables is as follows:

- Favorable per pathogen microbiologic response at the EOT (IV), TOC, and LFU visits by categories of MIC in the mMITT, ME, and extended ME analysis sets
- Proportion of patients with favorable investigator clinical response assessment and, separately, favorable per-patient microbiological response at the TOC visit for patients infected with a ceftazidime resistant pathogen in the mMITT, ME, and extended ME analysis sets

The patient-reported symptom assessment response, investigator-determined clinical response of cure, per-patient microbiological response, and per-pathogen microbiological response will be presented by treatment group for patients infected with ceftazidime-resistant pathogens. The investigator-determined clinical response of cure, per-patient microbiological response, and per-pathogen microbiological response will be presented by MIC among pathogens

considered to be causative in the CAZ-AVI treatment groups. This will also be undertaken for the doripenem treatment group as a reference.

In each treatment group of the study, MIC frequencies for each infecting species for which the number is 10 or more will be reported. Further MIC statistics will be reported for each infecting species as MIC range and the MIC to inhibit the growth of 50% of organisms. Additionally, for infecting species for which the number is 10 or higher, the MIC to inhibit the growth of 90% of organisms will be reported.

To understand the relationship between the pathogens in the study and the same species in general circulation, the frequency distributions of MIC of study therapy will be graphed for the following groups (where the numbers are sufficiently large): Enterobacteriaceae; *P. aeruginosa*; and other nonfermenting aerobes.

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 after dosing.

Exploratory variables

Proportion of patients with resolution of symptoms associated with cUTI at recorded time points will be presented in the mMITT analysis sets

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

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

The exploratory variables of microbiological response with the cutoff of $<10^3$ CFU/mL will be analyzed using the same methods as that of the microbiologic response with a cutoff of $<10^4$ CFU/mL.

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

12.3 Safety and tolerability

General considerations: In addition to earlier description of the methods of summarization under Section 12.2.1, graphical presentations will be used as appropriate. Examples may include line graphs showing individual or mean development over time, and shift plots showing pretreatment values on horizontal axis and posttreatment values on vertical axis.

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

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

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

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

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

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

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

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

For clinical laboratory tests, listings of values for each patient will be presented with abnormal or out-of-range values flagged. Clinically significant changes in the laboratory test will be

summarized and listed by treatment groups. Clinical laboratory data will be reported in Système International units in the CSR.

For ECG variables, the QT correction factor will be based on the Bazett and Fridericia 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.

12.3.1 Interim analyses

Not applicable.

12.4 Determination of sample size

Synthesis of historical trials has indicated that a 12.5% margin is appropriate for assessment of noninferiority in cUTI trials; however, there are regional variations in the regulatory requirements for noninferiority trials. In order to meet these requirements globally, this trial has been sized to provide 90% power for a 10% noninferiority margin, required in some regions (therefore providing >95% power to assess noninferiority using a 12.5% margin).

Approximately 964 patients will be recruited for this trial. This will provide 90% power for a 10% noninferiority margin using the lower limit of a 2-sided 95% CI for each of the 2 coprimary endpoints in the mMITT analysis set, assuming that the underlying true response rate is >73.5% for each coprimary endpoint and that 85% of patients will be included in the mMITT analysis set. The sample size was calculated using nQuery® version 7 (Statistical Solutions Ltd, Cork, Ireland) using the Newcombe-Wilson (Newcombe 1998) score method (uncorrected).

12.5 Data monitoring committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in close consultation with the 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 (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]

Region	Role in the study	Address and telephone number
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 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 in the Overdose eCRF module.
- An overdose without associated symptoms is only reported in the Overdose eCRF module.

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

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

For overdoses associated with an SAE, standard reporting times 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 IV study therapy under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities, birth defects, and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

The designated AstraZeneca/[redacted] representative will work 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 drug until 3 months after the last dose of study drug must be reported to AstraZeneca within 5 days and documented as specified in Section 13.3.1.

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