Clinical Study Protocol Amendment	
Amendment Number	3
Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00004
Date	[redacted]
Protocol Dated	[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:

AstraZeneca AB, S-151 85 Södertälje, Sweden

Centers affected by the Amendment:

This amendment affects all centers in the study.

The protocol for the study is to be amended as follows:

1. Update of the AstraZeneca Research and development site representative

2. Update of study timetable and end of study

3. Protocol D4280C00002 will be combined with the identically designed D4280C00004 protocol to form 1 cUTI study.

   – Update of the sample size for the combined protocols (D4280C00002 and D2480C00004) so that 964 patients will be enrolled in 1 cUTI study.

4. All data analyses for efficacy, safety, tolerability, pharmacokinetics, and exploratory variables, will be based on data from the combined study database only.

- All data analyses including statistical analyses will be performed only based on a single, combined study database.

- Patients from each study (D4280C00002 and D4280C00004) will be randomized to receive either CAZ-AVI or doripenem after informed consent is obtained and eligibility is confirmed.

- The sample size is updated to support adequate assessment of the safety and tolerability of CAZ-AVI compared with doripenem.

- The sample size is updated to support analyses of the primary efficacy and safety objectives.

- The sample size is updated to support analyses of the coprimary endpoints.

5. Update of visit structure, timing of visits and assessments.

   - Update of Table 1 including footnotes (study plan) to align with amended items in the protocol

   - Update of Figure 1 including footnotes (study flow chart) to align with amended items in the protocol.

   - Clarification of the timing of patient-reported symptomatic response assessment

   - Clarification of the recording of adverse events

   - Clarification of the ECG assessments required following completion of study drug.

   - Clarification of the timing of temperature assessments.

   - Clarification of the timing of plasma sample collection for pharmacokinetic assessments.

   - Clarification of the timing of collection of variables

   - Clarification of the safety and tolerability assessments

6. Clarification of analysis of isolates

7. Amendment of the exclusion criteria

8. Amendment of patient enrolment and random assignment to treatment

9. Amendment of treatment regimens, concomitant and poststudy treatment(s)

10. Clarification of the timing for follow-up if a patient discontinues investigational product or withdraws from the study

11. Administrative changes to include required typographical and grammatical updates, and update of references.

Changes made to the protocol are presented in bold text in the following sections:

1. UPDATE OF THE ASTRAZENECA RESEARCH AND DEVELOPMENT SITE REPRESENTATIVE

Section of the protocol affected:

Cover page

Previous text, Cover page:

[redacted]

Revised text, Cover page:

[redacted]

2. UPDATE OF STUDY TIMETABLE AND END OF STUDY

Section of protocol affected:

Protocol Synopsis, Section 9.5

Previous text, Synopsis study centers and number of patients planned:

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

Revised text, Synopsis study centers and number of patients planned:

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

Previous text, Section 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].

Revised text, Section 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 **second** quarter of [redacted].

Reason for the Amendment:

Updated to reflect a more recent estimate for the duration of the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3. PROTOCOL D4280C00002 WILL BE COMBINED WITH THE IDENTICALLY DESIGNED D4280C00004 PROTOCOL TO FORM 1 cUTI STUDY

Section of protocol affected:

Protocol synopsis

Previous text, Synopsis 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).

Revised text, Synopsis Study centers and number of patients planned:

This will be a multicenter study enrolling 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).

Another study will be conducted concurrently under an identical protocol (D4280C00004).

The data collected from a combined total of approximately 964 patients (482 patients per treatment group) enrolled and randomized under 2 identical protocols, D4280C00002 and D4280C00004, without a pre-specified number of patients from each individual study, will be combined into a single study database for all analyses.

Reason for Amendment:

Clarification that 2 identical protocols will be combined to form 1 cUTI study. As there will only be 1 combined cUTI study, the sample size requirement has been updated to ensure there are sufficient numbers to make an assessment of not only the primary efficacy, but also the safety and tolerability of CAZ-AVI.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Synopsis Study design:

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.

Revised text, Synopsis Study design:

The data collected from a combined total of approximately 964 **patients enrolled and randomized under the 2 identical protocols, D4280C00002 and D4280C00004, without a pre-specified number of patients from each individual study will be combined into a single study database.** Hospitalized patients (18 to 90 years of age, inclusive) who are suspected of having a cUTI due to a Gram-negative pathogen, 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 **and randomized into this study**. 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.

Reason for Amendment:

Clarification that 2 identical protocols will be combined to form 1 cUTI study; the data from these 2 identical protocols will be combined in a single study database.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

4. ALL DATA ANALYSES FOR EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EXPLORATORY VARIABLES, WILL BE BASED ON DATA FROM THE COMBINED STUDY DATABASE ONLY

Section of protocol affected:

Protocol Synopsis, Section 12, Section 12.1, Section 12.4

Previous text, Synopsis 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.

Revised text, Synopsis Target patient population:

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.

Reason for Amendment:

Clarification that 2 identical protocols will be combined to form 1 cUTI study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Synopsis 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

Revised text, Synopsis Statistical methods:

All analysis sets will be based on the single combined study database, which will include all data collected under the 2 identical protocols, D4280C00002 and D4280C00004. The statistical analyses for efficacy, safety and tolerability, pharmacokinetics, and exploratory variables will be performed for different analysis sets according to the purpose of analysis.

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

Reason for Amendment:

Clarification that data from 2 identical protocols will be combined in a single study database.

As there will only be 1 combined cUTI trial, the sample size requirement has been updated to ensure there are sufficient numbers to make an assessment of not only the primary efficacy, but also the safety and tolerability of CAZ-AVI.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Synopsis Statistical methods:

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.

Revised text, Synopsis Statistical methods:

As all statistical analyses for efficacy, safety and tolerability, pharmacokinetics, and exploratory variables will be performed only based on the single, combined study database, which will contain data collected under 2 identical protocols, D4280C00002 and D4280C00004; the statistical inference on noninferiority in the coprimary endpoints will be based on the single combined study database. To make the single, combined database a single statistically powered study for the coprimary endpoints the corresponding sample size will be calculated as follows:

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, the sample size of the combined study database will provide 90% power for a 10% noninferiority margin, required in some regions (therefore providing >95% power to assess noninferiority using a 12.5% margin).**

A combined total of approximately 964 patients will be enrolled and randomized under 2 identical trials, D4280C00002 and D4280C00004. 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).

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 study (**D4280C00002 or D4280C00004**) and **pre-specified** 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, **study,** type of infection, baseline pathogens, age, sex, race, and region.

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).

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 **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.

Reasons for Amendment:

Two identical protocols will be combined to form 1 cUTI study.

As there will only be 1 cUTI study, the sample size requirement has been updated to ensure there are sufficient numbers to make an assessment of the coprimary endpoints.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Addition of text, Section 12 Statistical methods and sample size determination:

All statistical analyses for efficacy, safety and tolerability, pharmacokinetics, and exploratory variables will be performed only based on the single combined study database.

Reason for Amendment:

Clarification that data from the 2 identical protocols will be combined in a single study database.

As there will only be 1 cUTI study, the sample size requirement has been updated to ensure there are sufficient numbers to make an assessment of not only the primary efficacy, but also the safety and tolerability of CAZ-AVI.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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.

Revised text, Section 12.1 Description of analysis sets:

All analysis sets will be defined based on all patients in the single combined study database, will include all data collected under 2 identical protocols, D4280C00002 and D4280C00004.

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.

Reason for Amendment:

Clarification that data from the 2 identical protocols will be combined in a single study database.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 12.2.2 Analysis of study population and patient characteristics, Primary efficacy variable:

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.

Revised text, Section 12.2.2 Analysis of study population and patient characteristics, Primary efficacy variable:

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 **study (D4280C00002 or D4280C00004) and** 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, **study**, type of infection, baseline pathogens, age (≥18 to 45, 46 to 64, 65 to 74, ≥75 to ≤90), sex, race, and region. **A subgroup analysis by study will be performed for the primary endpoint (cIAI)/coprimary endpoints (cUTI) only as part of the investigation of subgroups.** Forest plots will be used to present the point estimate and the CI for the difference in proportion for the subgroups.

Reason for Amendment:

Clarification that subgroup analysis by study will be performed.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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).

Revised text, Section 12.4 Determination of sample size:

As all statistical analyses for efficacy, safety and tolerability, pharmacokinetics, and exploratory variables will be performed only based on the single combined study database, which contains data collected from the 2 individual studies; the statistical inference on noninferiority in the coprimary endpoints will be based on the single combined study database. The sample size will be calculated to make the single combined database as a single statistically powered study for the coprimary endpoints. The corresponding details are provided as follows:

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).

A combined total of approximately 964 patients will be **enrolled and randomized under the 2 identical protocols, D4280C00002 and D4280C00004, without a pre-specified number of patients enrolled into each individual study**. 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).

Reason for Amendment:

Clarification that data from the 2 identical protocols will be combined in a single study database.

As there will only be 1 cUTI trial, the sample size requirement has been updated to ensure there are sufficient numbers to make an assessment of not only the primary efficacy, but also the safety, tolerability, pharmacokinetics and exploratory variables of CAZ-AVI.

The statistical inference on noninferiority in the coprimary endpoints will be based on the (single) combined study database.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

5. UPDATE OF VISIT STRUCTURE, TIMING OF VISITS AND ASSESSMENTS

Sections of protocol affected

Synopsis, Section 3.1, Section 6.2.2, Section 6.2.5, Section 6.2.6, Section 6.3.1, Section 6.4.3, Section 6.4.9, Section 6.4.10.2, Section 11, Section 12.3

Previous text, Synopsis and Section 3.1 Study periods table:

Study periods	
Eligibility/Screening Period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0[a]
Treatment Period	
Visit 2 (Baseline/randomization)	Day 1
Visits 3 to 15 (Days 2 to 14)[b]	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[c]
Visit 18 (LFU)	Day 45 visit[d]

[a] Study treatment should be started as soon as a patient's eligibility has been confirmed and the patient has been randomized. Consequently, Day −1 and Day 0 may be the same calendar day as Day 1.
[b] 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.
[c] 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.
[d] 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.

Revised text, Synopsis and Section 3.1 study periods table:

Study periods	
Eligibility/Screening Period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0[a]
Treatment Period	
Visit 2 (Baseline **and Day 1)**[b]	
Visits 3 to 15 (Days 2 to 14)[c]	While on IV therapy

Study periods	
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)	**21 calendar days from randomization**[d]
Visit 18 (LFU)	**45 calendar days from randomization**[e]

[a] Study treatment should be started as soon as a patient's eligibility has been confirmed and the patient has been randomized. Consequently, Day −1 and Day 0 may be the same calendar day as Day 1. **Subsequent study days are based on 24-hour periods from the time of the first infusion**.

[b] **Administration of the first dose of IV study therapy marks the beginning of study Day 1. Subsequent study days are based on 24-hour periods from the time of the first infusion.**

[c] 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.

[d] If it is not possible to perform the TOC visit **21 calendar days from randomization (eg, the patient is on holiday), the allowed visit window is 21 to 25 calendar days from randomization**.

[e] **If it is not possible to perform the LFU visit 45 calendar days from randomization** (eg, the patient is on holiday), the allowed visit window is **45 to 52 calendar days from randomization**.

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

Previous text, Synopsis:

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.

Revised text, Synopsis:

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 **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.

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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).

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.

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 programmatically assess the patient-reported symptomatic response via the algorithm for the primary endpoint presented in Section 11.1.

Revised text, Section 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. **Hospitalized** patients between the ages of 18 and 90 years of age, inclusive, who are suspected of having a cUTI due to Gram-negative pathogens, 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 **enrolled and randomized** 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.

A combined total of approximately 964 patients **(482 patients per treatment group)** will be **enrolled and randomized under the 2 identical protocols, D4280C00002 and D4280C00004, without a pre-specified number of patients enrolled into each study. In each study, the eligible** patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule **of each of the studies**. 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).

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 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.

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, **Visits 3-15**, at EOT, TOC, and LFU). The data collected from the questionnaires will be used to programmatically assess the patient-reported symptomatic response via the algorithm for the primary endpoint presented in Section 11.1.

Reason for Amendment:

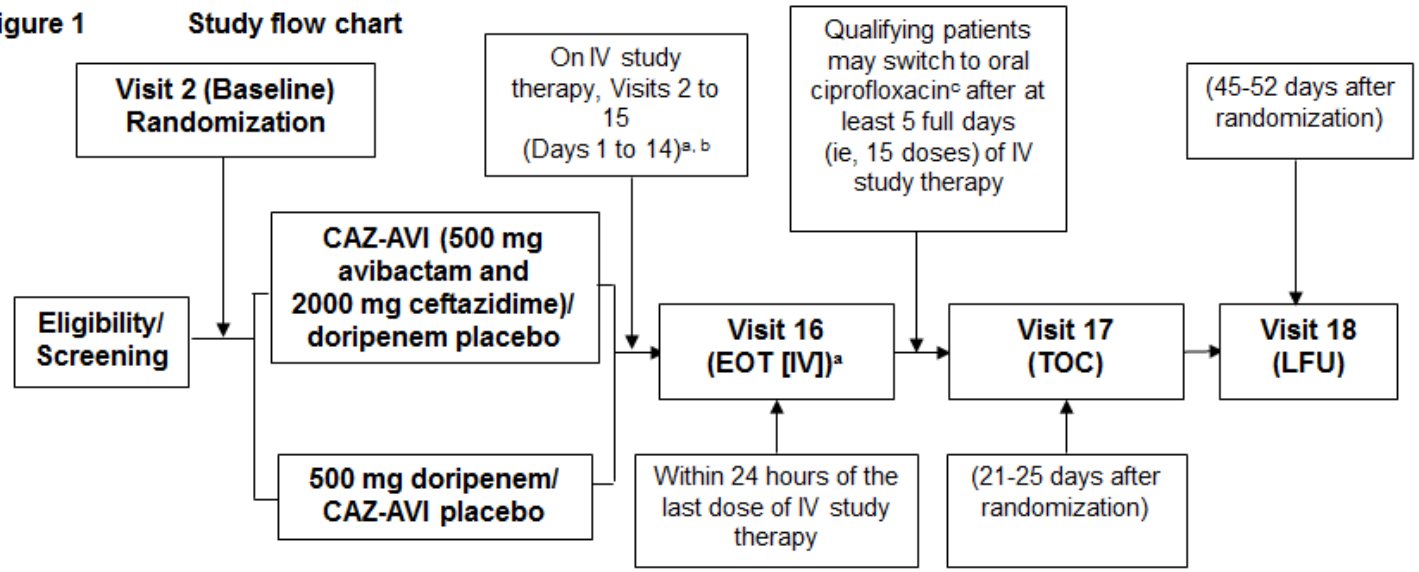
Clarification of visit structure and timing of visits and clarification of creatinine clearance values.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 3.1 Figure 1 Study flow chart:

Figure 1 Study flow chart



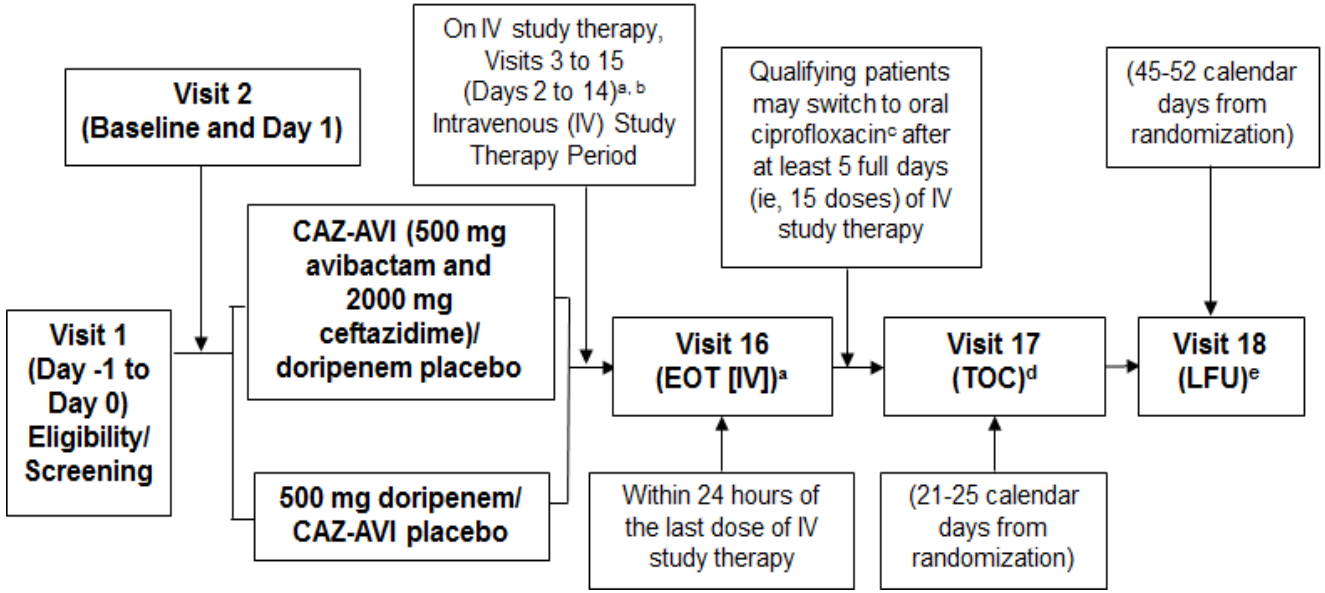
a Study treatment should be started as soon as a patient's eligibility has been confirmed and the patient has been randomized. Consequently, Day −1 and Day 0 may be the same calendar day as Day 1. The Treatment Period includes the Baseline visit (Day 1), Visits 2 to 15 (Days 2 to 14), and the EOT (IV) 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.

Revised text, Section 3.1 Figure 1 Study flow chart:

Figure 1 Study flow chart



a Study treatment should be started as soon as a patient's eligibility has been confirmed and the patient has been randomized. Consequently, Day −1 and Day 0 may be the same calendar day as Day 1. **Administration of the first dose of IV study therapy marks the beginning of study Day 1. Subsequent study days are based on 24-hour periods from the time of the first infusion.** The Treatment Period includes the Baseline visit (Day 1), Visits 3 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.

d **If it is not possible to perform the TOC visit 21 calendar days from randomization (eg, the patient is on holiday), the allowed visit window is 21 to 25 days from randomization.**

e **If it is not possible to perform the LFU visit 45 calendar days from randomization (eg, the patient is on holiday), the allowed visit window is 45 to 52 calendar days from randomization.**

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

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 3.1 Table 1 Study plan and footnotes:

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16[d]**	**Visit 17[d]**	**Visit 18[d]**
Procedures and Assessments	**Day –1 to 0[a]**	**Day 1 (Baseline)[b]**	**Days 2 to 14[c] (while on IV study therapy)**	**EOT (IV)[e] (within 24 hours after completion of last infusion of IV study therapy)**	**TOC (21-25 days after randomization)**	**LFU (45-52 days after randomization)**
Informed consent	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

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16[d]**	**Visit 17[d]**	**Visit 18[d]**
Procedures and Assessments	**Day –1 to 0[a]**	**Day 1 (Baseline)[b]**	**Days 2 to 14[c] (while on IV study therapy)**	**EOT (IV)[e] (within 24 hours after completion of last infusion of IV study therapy)**	**TOC (21-25 days after randomization)**	**LFU (45-52 days after randomization)**
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
Estimate creatinine clearance[k]	X	----------As clinically indicated----------				
Urinalysis[l]	X			X	X	X
Quantitative urine culture	X[m]	X[m]		X[n]	X	X
Blood cultures[o]	X	------If screening blood cultures results are positive, repeat at least every 3 days until negative. Blood cultures may also be obtained as clinically indicated------				

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16[d]**	**Visit 17[d]**	**Visit 18[d]**
Procedures and Assessments	**Day –1 to 0[a]**	**Day 1 (Baseline)[b]**	**Days 2 to 14[c] (while on IV study therapy)**	**EOT (IV)[e] (within 24 hours after completion of last infusion of IV study therapy)**	**TOC (21-25 days after randomization)**	**LFU (45-52 days after randomization)**
Serum β-hCG (women of childbearing potential)	X[p]					X
Blood for PK analysis[q]			X			
Randomization		X				
Monitor AEs[r]	X	X	Daily	X	X	X
Administer IV study therapy[s, t]		X	X			

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16[d]**	**Visit 17[d]**	**Visit 18[d]**
Procedures and Assessments	**Day –1 to 0[a]**	**Day 1 (Baseline)[b]**	**Days 2 to 14[c] (while on IV study therapy)**	**EOT (IV)[e] (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[u]	X	X
Investigator-determined clinical response evaluation				X[v]	X	X

[a] Study treatment should be started as soon as a patient's eligibility has been confirmed and the patient has been randomized. Consequently, Day −1 and Day 0 may be the same calendar day as Day 1.

[b] Repeat assessments are not required for visits that occur on the same calendar day as the eligibility/screening visit.

[c] 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.

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

[e] 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.

[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 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 doripenem/doripenem placebo infusion and one measurement at the end of the corresponding CAZ-AVI/CAZ-AVI placebo infusion. Each ECG measurement should be performed in triplicate. 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), and TOC if the local laboratory is equipped to do so; study centers unable to perform direct Coombs testing will not be required to perform this test. Abnormal safety laboratory results obtained throughout the study, including the LFU 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 If screening blood cultures results are positive, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. If repeat cultures have not been finalized negative by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit. When obtaining samples for blood cultures, 2 sets from 2 different sites must be collected (a total of 4 bottles; 2 aerobic and 2 anaerobic, each inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL of blood per collection). One set should be drawn through a venipuncture.

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.

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] 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.

[s] 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. The patient is to return to the study center for all remaining study visits following discharge from the hospital.

[t] 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.

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

[v] 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.

Revised text, Section 3.1 Table 1 Study plan and footnotes:

Table 1 Study plan

	Visit 1	Visit 2 [a]	Visits 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
	Eligibility/ Screening Assessments (Day –1 to 0)	**Baseline Assessments and Day 1 of study therapy[b]**	**On Therapy Assessments (Day 2 to Day 14)[b]**	**EOT Assessments (Within 24 hrs after completion of last dose of IV therapy)**	**TOC (21 calendar days from randomization)**	**LFU (45 calendar days from randomization)**
Informed consent	X					

Table 1 Study plan

	Visit 1	Visit 2 [a]	Visits 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
	Eligibility/ Screening Assessments (Day –1 to 0)	**Baseline Assessments and Day 1 of study therapy[b]**	**On Therapy Assessments (Day 2 to Day 14)[b]**	**EOT Assessments (Within 24 hrs after completion of last dose of IV therapy)**	**TOC (21 calendar days from randomization)**	**LFU (45 calendar days from randomization)**
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical and surgical history	X					
Prior and concomitant medications/**antibiotics**	X	X	Daily	X	X	X
Complete physical **examination**[e]	X			X	X	X
UTI-focused physical **examination**[f]	X	X	Daily	X	X	X
Vital **signs**[g]	X	X	Daily	X	X	X
Height/weight	**X**	**Repeat weight only to calculate CrCl when clinically indicated**				
12-lead **ECG**[h]		**X**	**Day 3 and as clinically indicated**	X		
Assess urinary device status		X	**Daily**	X	X	X

Table 1 Study plan

	Visit 1	Visit 2 [a]	Visits 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
	Eligibility/ Screening Assessments (Day –1 to 0)	**Baseline Assessments and Day 1 of study therapy[b]**	**On Therapy Assessments (Day 2 to Day 14)[b]**	**EOT Assessments (Within 24 hrs after completion of last dose of IV therapy)**	**TOC (21 calendar days from randomization)**	**LFU (45 calendar days from randomization)**
Serum **and urine** β-hCG[i]	X					X
Estimate creatinine **clearance**[j]	X	As clinically indicated**; use local serum creatinine measurements**				
Coombs test[k]		**X**		**X**	**X**	
Blood cultures	X	If blood cultures are positive, repeat at least every 3 days until negative. Blood cultures **should** also **be performed** as clinically indicated				
Quantitative urine culture[l,m]	**X**			X	X	X
Urinalysis[l,m]	X			X	X	X
Monitor AEs	X	X	Daily	X	X	X
Randomization		X				
Administer IV study **therapy**[n]		**X**[a,b]	**X**[o,p]			
Blood and urine for safety to central laboratory[q]	X		**Study Day 2 then every 3 days while on IV therapy**	X	X	X
Blood for PK to central laboratory[r]			**Day 3**			

Table 1 Study plan

	Visit 1	Visit 2 [a]	Visits 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
	Eligibility/ Screening Assessments (Day –1 to 0)	**Baseline Assessments and Day 1 of study therapy[b]**	**On Therapy Assessments (Day 2 to Day 14)[b]**	**EOT Assessments (Within 24 hrs after completion of last dose of IV therapy)**	**TOC (21 calendar days from randomization)**	**LFU (45 calendar days from randomization)**
Pre-morbid Patient Symptom Assessment Questionnaire		X				
Daily Patient Symptom Assessment Questionnaire		X	Daily	**X[s]**	X	X
Investigator-determined clinical response evaluation				**X[t]**	X	X

[a] **Visit 2 includes the baseline visit and the first 24 hours of therapy. All assessments during Visit 2 must occur prior to first dose of IV study therapy.**

[b] **Administration of the first dose of IV study therapy marks the beginning of study Day 1. Subsequent study days are based on 24-hour periods from the time of the first infusion.**

[c] **For example, if the patient is randomized on the first of the month, the TOC visit should occur on the 21st of the month. The FU visits are calculated from the date of randomization. If it is not possible to perform the TOC visit 21 calendar days from randomization, the allowed visit window is 21 to 25 calendar days from randomization.**

[d] **If it is not possible to perform the TOC visit 45 calendar days from randomization, the allowed visit window is 45 to 52 calendar days from randomization.**

[e] **See Section 6.4.8 for components of a complete physician examination.**

[f] **UTI-focused examination includes assessments of costovertebral angle and suprapubic tenderness.**

[g] **Assess heart rate** and blood pressure **after the patient has been** resting in a supine position for at least 10 minutes **(See Section 6.4.10).** If any medication with antipyretic properties has been taken by the patient, temperature readings should be taken at the end of the dosing interval **(See Section 6.4.10.2).**

[h] **At baseline and EOT, 12-lead ECGs should be performed in triplicate. On Day 3, triplicate ECGs must be performed twice: once after completion of meropenem/meropenem placebo infusion and once after completion of CAZ-AVI/CAZ-AVI placebo infusion. If QTcF prolongation is observed (QTcF** increase from baseline of **>30 ms or QTcF >460 ms), additional ECGs** must be performed (see Section 6.4.9).

[i] **Serum β-hCG must be performed as part of screening/eligibility. If serum β-hCG cannot be performed locally, it may be sent to the central laboratory. If the results of β-hCG are not expected prior to dosing of study therapy, a patient may begin therapy on the basis of a negative urine β-hCG, but a serum test must still be obtained.**

[j] Study center personnel will calculate the estimated CrCl **from the most recent local laboratory results. Appendix E provides details for the calculation of estimated CrCl.**

[k] **Coombs test is to be performed locally where possible.**

[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] 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 4-hour dosing window around the second dose).** If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose.

[o] 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.

[p] 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.

[q] **Safety labs should be collected at Screening, Baseline (every 3 days while on IV therapy [Day 2, Day 5, Day 8, etc]), EOT, TOC and LFU. See Section 6.4.6.**

[r] **Blood samples for pharmacokinetics will be collected on Day 3 following a dose administration that is convenient for the plasma sample collections at the following time points: anytime from 15 minutes prior to stopping until 15 minutes after stopping CAZ-AVI/CAZ-AVI placebo infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI/CAZ-AVI placebo infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI/CAZ-AVI placebo infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient. See Section 6.5.1.**

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

[v] 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; **hr, hour(s)**; 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.

Reason for Amendment:

Clarification of visit structure, timing of visits, and assessment requirements for each visit.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.2 section title:

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

Revised text, Section 6.2.2 section title:

6.2.2 Visit 2 **(**Baseline **and Day 1)** assessment procedures

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.5 section title:

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

Revised text, Section 6.2.5 section title:

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

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.6 section title:

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

Revised text, Section 6.2.6 section title:

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

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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 the baseline symptoms and changes in symptoms over time (ie, Baseline, daily while on IV therapy, at EOT [IV], TOC, and LFU).

Revised text, Section 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 the baseline symptoms and changes in symptoms over time (ie, Baseline, **Visits 3-15**, at EOT [IV], TOC, and LFU).

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.3 Recording of adverse events, 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.

Revised text, Section 6.4.3 Recording of adverse events, 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 **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.

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.9 Resting ECG:

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.

Revised text, text, Section 6.4.9 Resting ECG:

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 (prior to receiving any study drug). Assessments should be performed after the completion of study drug administration and be recorded as unscheduled assessments. **If at least 2 ECGs have been obtained after completion of study drug and the QTcF has not returned to baseline, ECGs may be discontinued if all of the following apply: the QTcF has not worsened over the previous 3 days, the investigator considers that the QTcF is not due to study therapy, and the investigator feels it is safe to discontinue daily ECGs. In the event that daily ECGs are discontinued under these circumstances, an ECG should be obtained at the TOC visit (and if still meeting significant QTcF criteria at TOC, at LFU as well).**

Reason for Amendment:

Clarification of visit structure, timing of visits, and assessments at each visit.

Clarification of the required ECG assessments following completion of study drug.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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.

Revised text, Section 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 **be evaluated at all visits. During therapy, temperature should** 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.

Reason for Amendment:

Clarification of the timing of temperature assessments.

Persons who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, 6.5.1 Collection of samples (Pharmacokinetics):

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 CAZ-AVI/CAZ-AVI placebo infusion

Revised text, 6.5.1 Collection of samples (Pharmacokinetics):

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 **from** 15 minutes prior to **stopping until 15 minutes** after stopping the CAZ-AVI infusion

Reason for Amendment:

Clarification of the timing of plasma samples for pharmacokinetic assessments.

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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).

Revised text, Section 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. **Randomization will occur at Visit 2 following the baseline assessments**.

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 12.3 Safety and tolerability:

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.

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.

Revised text, Section 12.3 Safety and tolerability:

Adverse events occurring from the first dose of IV study therapy up to the **EOT (IV) visits** will be summarized by preferred term and system organ class using MedDRA vocabulary (Version 12.0 or higher) by dose group for the primary hypothesis. Adverse events will also be summarized for events occurring from the first dose of IV study therapy up to the **LFU** 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.

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 **baseline** values in QT and QTcF values (≥30 ms, ≥60 ms) will also be presented. All other ECG variables will be listed.

Reason for Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6. CLARIFICATION OF ANALYSIS OF ISOLATES

Section of the protocol affected:

Section 3.1.1.3

Previous text, Section 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 sulfamethoxazole /trimethoprim to provide susceptibility results, as these are the options allowed for the switch to oral medication.

Revised text, Section 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 cut-off 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 **unless sites are unable to perform these tests**. 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 sulfamethoxazole/trimethoprim to provide susceptibility results, as these are the options allowed for the switch to oral medication.

Reason for Amendment:

Clarification that local susceptibility testing to CAZ-AVI is required unless sites are unable to perform these tests.

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7. AMENDMENT OF EXCLUSION CRITERIA

Section of protocol affected:

Synopsis, Section 4.2, Section 12.1.1.2, Section 12.1.2.5

Previous text, Synopsis Statistical methods 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 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 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 randomization
- Had 1 or at most 2 baseline pathogens susceptible to both IV study therapies

Revised text, Synopsis Statistical methods, 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
- **Received prior antibiotic before the initiation of study therapy for this infection except if the patient has received only one dose of an antibiotic regimen and is shown to have at least one of the following**
  - **Acute pyelonephritis**
  - **Arterial hypotension associated with this infection (SBP < 90 mm Hg or MAP < 70 mm Hg or an SBP decrease > 40 mm Hg)**
  - **Heart rate >100 bpm**
  - **Tachypnea >20 bpm**
  - **Creatinine > 2 mg/dL (176.8 mmol/L) or increase >0.5 mg/dL (44.2 mmol/L)**
  - **Leukocytosis (WBC count >15 000/mL) or leukopenia (WBC count <4000/mL)**

- 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 randomization

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

Reason for Amendment:

Clarification of the use of prior antibiotics before study entry

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Synopsis Statistical methods, 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 a study entry urine culture obtained ≤48 hours before randomization

Revised text, Synopsis Statistical methods, 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
- **Received prior antibiotic before the initiation of study therapy for this infection except if the patient has received only one dose of an antibiotic regimen and is shown to have at least one of the following**

  – Acute pyelonephritis

  – Arterial hypotension associated with this infection (SBP < 90 mm Hg or MAP < 70 mm Hg or an SBP decrease > 40 mm Hg)

  – Heart rate >100 bpm

  – Tachypnea >20 bpm

  – Creatinine > 2mg/dL (176.8 mmol/L) or increase >0.5 mg/dL (44.2 mmol/L)

– **Leukocytosis (WBC count >15000/mL) or leukopenia (WBC count <4000/mL)**

– Did not receive antibiotic therapy with potential activity against the baseline uropathogens 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 randomization

Reason for Amendment:
Clarification of the use of prior antibiotics before study entry

Persons who initiated the Amendment:
AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 4.2 Exclusion criteria #5:

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

Revised text, Section 4.2 Exclusion criteria #5

5**. Patient has received prior antibiotics before the initiation of study therapy for this infection except if the patient has received only one dose of an antibiotic regimen and is shown to have at least one of the following:**

(a) Acute pyelonephritis

(b) Arterial hypotension associated with this infection (SBP <90 mm Hg or MAP < 70 mm Hg or an SBP decrease >40 mm Hg)

(c) Heart rate >100 bpm

(d) Tachypnea >20 bpm

(e) Creatinine > 2 mg/dL (176.8 mmol/L) or increase >0.5 mg/dL (44.2 mmol/L)

(f) Leukocytosis (WBC count >15 000/mL) or leukopenia (WBC count <4000/mL)

Reason for Amendment:

Clarification of the use of prior antibiotics before study entry

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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 any of the baseline uropathogens 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 protocol-allowed oral options (ciprofloxacin or sulfamethoxazole/trimethoprim) or agents with narrow spectrum Gram-positive coverage (ie antibiotics without Gram-negative coverage, for example linezolid, vancomycin). 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 randomization
- Had 1 or at most 2 baseline pathogens susceptible to both IV study therapies

Revised text, Section 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
- **Received prior antibiotic before the initiation of study therapy for this infection except if the patient has received only one dose of an antibiotic regimen and is shown to have at least one of the following**
  - **Acute pyelonephritis**
  - **Arterial hypotension associated with this infection (SBP < 90 mm Hg or MAP < 70 mm Hg or an SBP decrease > 40 mm Hg)**
  - **Heart rate >100 bpm**
  - **Tachypnea >20 bpm**
  - **Creatinine > 2 mg/dL (176.8 mmol/L) or increase >0.5 mg/dL (44.2 mmol/L)**
  - **Leukocytosis (WBC count >15 000/mL) or leukopenia (WBC count <4000/mL)**
- Did not receive any antibiotic therapy with potential activity against the baseline uropathogens 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 protocol-allowed oral options (ciprofloxacin or sulfamethoxazole/trimethoprim) or agents with narrow spectrum Gram-positive coverage (ie, antibiotics without Gram-negative coverage, for

example linezolid, vancomycin). 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 randomization
- Had 1 or at most 2 baseline pathogens susceptible to both IV study therapies

Previous text, Section 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 any of the baseline uropathogens 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 protocol-allowed oral options (ciprofloxacin or sulfamethoxazole/trimethoprim) or agents with narrow spectrum Gram-positive coverage (ie antibiotics without Gram-negative coverage, for example linezolid, vancomycin). 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 randomization

Revised text, Section 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
- **Received prior antibiotic before the initiation of study therapy for this infection except if the patient has received only one dose of an antibiotic regimen and is shown to have at least one of the following**
  - **Acute pyelonephritis**
  - **Arterial hypotension associated with this infection (SBP < 90 mm Hg or MAP < 70 mm Hg or an SBP decrease > 40 mm Hg)**
  - **Heart rate >100 bpm**
  - **Tachypnea >20 bpm**
  - **Creatinine > 2mg/dL (176.8 mmol/L) or increase >0.5 mg/dL (44.2 mmol/L)**
  - **Leukocytosis (WBC count >15000/mL) or leukopenia (WBC count <4000/mL)**
- Did not receive antibiotic therapy with potential activity against the baseline uropathogens 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 protocol-allowed oral options (ciprofloxacin or sulfamethoxazole/ trimethoprim) or agents with narrow spectrum Gram-positive coverage (ie antibiotics without Gram-negative coverage, for example linezolid, vancomycin). 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 randomization

Reason for Amendment:
Clarification of the use of prior antibiotics before study entry

Persons who initiated the Amendment:
AstraZeneca CAZ-AVI Clinical Project Team

8. AMENDMENT OF PATIENT ENROLLMENT AND RANDOM ASSIGNMENT TO TREATMENT

Section of the protocol affected:

Section 5.2

Previous text, Section 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.

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.

Revised and reordered text, Section 5.2 Patient enrollment and random assignment to treatment:

Prior to enrollment and randomization, the investigator will:

1. Obtain signed informed consent from the potential patient.

2. Assign potential patient a unique enrollment number, beginning with "E0001001 (EXXXXYYY)" where XXXX reflects the center number and YYY will be allocated

sequentially to enrolled patients at each center. **The IVRS system will be used to assign an enrollment code to the patient after consenting, but before eligibility is confirmed.**

3. **Complete** patient eligibility (see Sections 4.1 and 4.2).

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

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

9. AMENDMENT OF TREATMENT REGIMENS, CONCOMITANT AND POSTSTUDY TREATMENT(S)

Section of the protocol affected:

Section 5.5.2, Section 5.6

Previous text, Section 5.5.2 Doses and treatment regimens:

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.

Revised text, text, Section 5.5.2 Dose and treatment regimens:

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.

Dosing adjustments for doripenem/doripenem placebo and CAZ-AVI/CAZ-AVI placebo in patients with renal insufficiency are described in Sections 5.5.2.2. The initial dose chosen should be based on the most recent estimate of CrCl obtained prior to dosing.

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.

Reason for Amendment:

Clarification of doses and treatment regimens.

Clarification that administration of concomitant antibiotics should not be withheld if it puts the patient at risk.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 5.6 Concomitant and poststudy treatment(s):

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 anti Gram-negative antibacterial treatments are permitted while receiving study therapy at any time up to the LFU visit. However, if a Gram-positive uropathogen is identified post-randomization, and the investigator considers it warrants treatment, then use of agents with narrow spectrum Gram-positive coverage (ie, antibiotics without Gram-negative coverage, for example, linezolid, vancomycin) is permitted.

Revised text, Section 5.6 Concomitant and poststudy treatment(s):

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 anti Gram-negative antibacterial treatments are permitted while receiving study therapy at any time up to the LFU visit. However, if a Gram-positive uropathogen is identified post-randomization, and the investigator considers it warrants treatment, then use of agents with narrow spectrum Gram-positive coverage (ie, antibiotics without Gram-negative coverage, for example, linezolid, vancomycin) is permitted. **In**

addition, if a new infection develops at a remote site (ie, outside of the urinary tract) between the date and time of randomization and the LFU visit and the investigator considers addition of nonstudy antibiotics essential to the safety and wellbeing of the patient, additional antibiotics may be added to the study therapy. If possible, the investigator should attempt to choose antibiotics that would not have antibacterial activity against the patient's baseline uropathogen(s) to avoid confounding the assessment of the effect of study therapy. It is anticipated that in instances of clinical failure, alternative "rescue" therapy to treat the cUTI would be instituted.

Reason for Amendment:

Clarification that administration of concomitant antibiotics should not be withheld if it puts the patient at risk.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

10. CLARIFICATION OF THE TIMING FOR FOLLOW-UP IF A PATIENT DISCONTINUES INVESTIGATIONAL PRODUCT

Sections of protocol affected:

Section 5.8

Previous text, Section 5.8 Discontinuation of investigational product:

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.

Revised text, **Section 5.8 Discontinuation of investigational product:**

Patients who discontinue IP early should be seen at the time they discontinue from IP and at the **TOC and** LFU visits 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.

Reason for Amendment:

Clarification of the timing for follow-up if a patient discontinues investigational product.

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 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.

Revised text, Section 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 **TOC and** LFU visits. 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.

Reason for Amendment:

Clarification of the timing for follow-up if a patient discontinues investigational product.

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

11. ADMINISTRATIVE CHANGES

Sections of the protocol affected:

Section 1.1.1, Section 1.1.3, Section 3.1.1.1

References updated:

Previous text, Section 1.1.1:

Go et al 2004
Go CH, Cunha BA. *Escherichia coli* infections. Last updated 2004 June 27. Available from: http://www.emedicine.com.

Revised text, Section 1.1.1:

Go **and Cunha 2004**
Go CH, Cunha BA. *Escherichia coli* infections. Last updated 2004 June 27. Available from: http://www.emedicine.com.

Previous text, Section 1.1.1:

Hirsch et al 2010
Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother. 2010;65(6):1119-25.

Revised text, Section 1.1.3

Hirsch **and Tam 2010**
Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother. 2010;65(6):1119-25.

Previous text, Section 3.1.1.1

Murray et al. 2007
Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, editors. Manual of clinical microbiology. Washington DC; American Society for Microbiology; 2007 (Available upon request).

Revised text, Section 3.1.1.1

Murray **and Nurminen 2007**
Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, editors. Manual of clinical Microbiology. Washington DC; American Society for Microbiology; 2007 (Available upon request).

Reason for the Amendment:

Update of references

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team