Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00002
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. Removal of genetic and biomarker sampling from study design
2. Removal of home health care agency (HHC)
3. Refinement of entry criteria with respect to female contraception and pregnancy testing, septic shock, removal of unconscious patients, and definition of acute pyelonephritis
4. Addition of detail on presentation of PK results
5. Revised definitions of emergent infections

6. Concomitant medications: use of agents with narrow gram-positive coverage

7. Clarifications: use of clinical information obtained as part of standard care before the informed consent is signed; collection of blood for Coombs test; randomization and enrollment into the study; UTI-focused physical examination; ECG measurements, order of assessments; purpose and use of the PREGREP and PREGOUT modules; revised blood volume collection per amended items: handling/disposition of pharmacokinetic and pharmacodynamic samples; simplify text describing visits to study center after discharge from the hospital; clarify when study urine culture is obtained; clarify the difference between withdrawal of consent and discontinuation of IP; remove the central reader assessment for abnormal ECGs

8. Revision of instructions for the Pre-morbid Patient Symptom Assessment (Appendix G)

9. Correction of Study Plan (Table 1) to align with amended items in the protocol

10. Additional administrative changes that include updating the List of Abbreviations

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

1. REMOVAL OF GENETIC AND BIOMARKER SAMPLING FROM STUDY DESIGN

Sections of protocol affected:

Synopsis; List of Appendices (Appendix D no longer applicable); Section 2.3; Section 4.1; Section 4.2; Section 6.2.2; Section 6.2.3; Section 6.2.4; Section 6.3.9; Section 6.3.10; Table 11; Section 6.7; Section 6.8; Section 7.2; Section 7.2.2; Section 7.5; Section 10; Section 11.5

Previous text, Synopsis and Section 2.3:

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

- To collect and store plasma and serum samples from patients for possible biomarker analysis. The results of any biomarker analysis research will not be included in the CSR for this study.

Revised text, Synopsis and Section 2.3:

Text deleted.

Previous text, List of Appendices:

Appendix A Signatures

Appendix B Additional Safety Information

Appendix C International Airline Transportation Association 6.2 Guidance document

Appendix D Pharmacogenetics Research

Revised text, List of Appendices:

Appendix A Signatures **– Not Applicable**

Appendix B Additional Safety Information

Appendix C International Airline Transportation Association 6.2 Guidance document

Appendix D Pharmacogenetics Research **(no longer applicable)**

Previous text, Section 4.1, Inclusion criterion 8:

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

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

Revised text, Section 4.1, Inclusion criterion 8:

No longer applicable.

Previous text, Section 4.2, Exclusion criteria 27 and 28:

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

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

28. Patient has previous allogenic bone marrow transplant.

Revised text, Section 4.2, Exclusion criteria 27 and 28:

No longer applicable.

Previous text, Section 6.2.2, Item 12:

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

Revised text, Section 6.2.2, Item 12:

Item deleted.

Previous text, Section 6.2.2, Item 13:

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

Revised text, Section 6.2.2, Item 13:

Item deleted.

Previous text, Section 6.2.3, Item 12:

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

Revised text, Section 6.2.3, Item 12:

Item deleted.

Previous text, Section 6.2.4, Item 14:

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

Revised text, Section 6.2.4, Item 14:

Item deleted.

Previous text, Section 6.3.9:

6.3.9 Pharmacogenetic outcome variables

Patients will be offered the possibility to participate in optional genetic exploratory research. After signing a separate consent for optional genetic research, a blood sample will be collected as per the inclusion criteria and Table 1. Genotype is a stable parameter; therefore, if for any reason the blood sample is not drawn on the first day in the Treatment Period (Day 1, Baseline), it may be taken at any point until patients leave the study. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

Revised text, Section 6.3.9:

6.3.9 Pharmacogenetic outcome variables

No longer applicable.

Previous text, Section 6.3.10:

6.3.10 Biomarker outcome variables

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

Revised text, Section 6.3.10:

6.3.10 Biomarker outcome variables

No longer applicable.

Previous text, Table 11:

Biomarker samples (banked specimen)

Revised text, Table 11:

Item deleted from table.

Previous text, Section 6.7:

6.7 Pharmacogenetics

Appendix D provides details of PGx sampling.

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

Revised text, Section 6.7:

6.7 Pharmacogenetics

No longer applicable.

Previous text, Section 6.8:

6.8 Collection of samples for biomarker research

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

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

6.8.1 Sample processing and shipping

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

6.8.2 Summary of biomarker assessments and analysis

The purpose of the biomarker research is to enable the generation of data for possible use in future retrospective analysis. The results of the biomarker research will not form part of the CSR for this study. The results may be pooled with biomarker data from other studies on CAZ104 to generate hypotheses to be tested in future studies.

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

Revised text, Section 6.8:

6.8 Collection of samples for biomarker research

No longer applicable.

Previous text, Section 7.2:

Section 3.1.1 provides information on handling, storage, and destruction of microbiological samples. The samples will be used up or disposed of after analyses or retained for further use as described here.

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

Revised text, Section 7.2:

Section 3.1.1 provides information on handling, storage, and destruction of microbiological samples. The samples will be used up or disposed of after analyses or retained for further use as described here.

Previous text, Section 7.2.2:

7.2.2 Pharmacogenetic samples

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

Revised text, Section 7.2.2:

7.2.2 Pharmacogenetic samples

No longer applicable.

Previous text, Section 7.5:

7.5 Withdrawal of informed consent for donated biological samples

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

The investigator:

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

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

Revised text, Section 7.5:

7.5 Withdrawal of informed consent for donated biological samples

No longer applicable.

Previous text, Section 10:

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

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

Revised text, Section 10:

Text deleted from the Section.

Previous text, Section 11.5:

11.5 Calculation or derivation of pharmacogenetic variables

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

Revised text, Section 11.5:

11.5 Calculation or derivation of pharmacogenetic variables

No longer applicable.

<u>Reason for Amendment</u>:

To remove collection of samples for genetic and biomarker analysis from the study design, as AstraZeneca deemed it unnecessary to collect this information in the study trial.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

2. REMOVAL OF HOME HEALTH CARE AGENCY (HHC)

Sections of the protocol affected:

Synopsis; Section 3.1; Section 5.7; Section 5.7.1; Section 6.2.3; Section 9.2

Previous text, Synopsis:

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

Revised text, Synopsis:

Switching to oral ciprofloxacin is not mandated; patients may continue receiving IV study therapy for the entire 10-day course (up to 14 days for patients who are bacteremic at study entry). Those patients who remain on IV study therapy after 5 full days will receive their IV study therapy from study center personnel while in the hospital. The patient is to return to the study center for **all remaining study** visits following discharge from the hospital.

Previous text, Section 3.1:

Switching to oral therapy is not mandated; patients may continue receiving IV study therapy for the entire 10-day course (up to 14 days if the patient is bacteremic at study entry). Those patients who remain on IV study therapy after 5 full days (ie, 15 doses) will receive their IV study therapy from study center personnel while in the hospital or from a qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT (IV), TOC, and LFU visits following discharge from the hospital.

Revised text, Section 3.1:

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

Previous text, Section 5.7:

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

Revised text, Section 5.7:

The qualified study center personnel at the investigative study center will administer IV study therapy and treatment compliance will be assured. The dose, date, and exact start and stop time of administration of the IV study therapy will be recorded and checked by the monitor at monitoring visits.

Previous text, Section 5.7.1:

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

Revised text, Section 5.7.1:

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

Previous text, Section 6.2.3

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

Revised text, Section 6.2.3

The duration of antibiotic treatment with study therapy (IV plus optional oral therapy) will be 10 days unless the patient is bacteremic at study entry, in which case, the duration of antibiotic treatment with study therapy may be extended to a total of up to 14 days (IV plus optional oral therapy). Those patients who remain on IV study therapy after 5 full days (ie, 15 doses) will receive their IV study therapy from study center personnel while in the hospital. The patient is to return to the study center for **all remaining study** visits following discharge from the hospital. Samples for clinical laboratory assessments should be collected prior to dosing.

Previous text, Section 9.2

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

Revised text, Section 9.2

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

Reason for Amendment

To remove the requirement for home health care from the study design, as the 5 days of protocol-required IV therapy will occur in the hospital home health care is not needed.

In the US, where hospitalisations for cUTI are typically shorter than 5 days, home health care may be required in some instances. Therefore a US-specific protocol amendment will be made to incorporate the use of home health care for the US only.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3. REFINEMENT OF ENTRY CRITERIA

3.1 Female contraception and pregnancy testing

Sections of protocol affected:

Section 4.1, Inclusion criteria 4, 4a and 4b; Section 4.2, Exclusion criterion 20.

Previous text, Section 4.1, Inclusion criteria 4, 4(a) and 4(b):

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

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

OR

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

- Has had normal menstrual periods for the 3 months prior to study entry, and
- Has a negative serum pregnancy test (serum β-human chorionic gonadotropin [β-hCG]) within 1 day prior to study entry (if the results of the serum β-hCG cannot be obtained prior to dosing of IP, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained), and
- Must be willing, during treatment and for at least 28 days after last dose of IV study therapy, to practice highly effective methods of birth control, such as intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), and medroxyprogesterone injections (Depo-Provera®), or remain sexually abstinent. Oral contraceptives should not be used as the sole method of birth control because the effect of CAZ-AVI on the efficacy of oral contraceptives has not yet been established. Barrier methods (such as male condom or diaphragm with spermicide) can be used if another method of acceptable contraception (not oral contraceptives) is also used.

Revised text, Section 4.1, Inclusion criteria 4, 4(a), 4(b), 4(c), and 4(d):

4. Female patient is authorized to participate in this clinical study if **at least one of** the following criteria **are met**:

(a) Surgical sterilization, (eg, bilateral oophorectomy and/or bilateral salpingectomy, but excluding bilateral tubal occlusion)

(b) **Age ≥50 and post menopausal as defined by amenorrhea for 12 months or more following cessation** of all **exogenous hormonal treatments**

(c) **Age <50 and post menopausal as defined by documented LH and FSH levels in the post menopausal range PLUS amenorrhea for 12 months or more following cessation of all exogenous hormonal treatments (if LH and FSH are not available, the patient must meet criterion d)**

(d) **Both** of the following conditions are met:

- **Patient has** a negative serum pregnancy test (serum β-human chorionic gonadotropin [β- hCG]) within 1 day prior to study entry (if the results of the serum β-hCG cannot be obtained prior to dosing of IP, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained). **If either test is positive, the patient must be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant menstrual history and sexual history, including methods of contraception, should be considered.**

- **Patient agrees not to attempt pregnancy while receiving study drugs** and for **a period of 7** days after last dose of study therapy **(IV and oral) and agrees to the use of the following acceptable** methods of **contraception: Prior to and during the study, use of an** intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), **regular** medroxyprogesterone injections (Depo-Provera®), or **sexual intercourse with only vasectomised partners, or complete sexual abstinence for the recommended period.**

  Note: Oral contraceptives should not be used as the sole method of birth control because the effect of CAZ-AVI on the efficacy of oral contraceptives has not yet been established. Barrier methods (such as male condom or diaphragm with spermicide) can be used if another method of acceptable contraception (not oral contraceptives) is also used.

Reason for Amendment:

Clarified the entry criteria for female patients to participate in the study with regards to methods of ascertaining child-bearing potential, contraception, and confirmation the patient is not pregnant. The time period for avoiding pregnancy after study completion was changed from 28 to 7 days, so as not to be overly restrictive but still to ensure that at least 5 drug half-lives have passed prior to a possible conception.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 4.2, Exclusion criterion 20:

20. Patient is pregnant or breastfeeding. A serum β-hCG pregnancy test must be sent for women of childbearing potential at the screening visit. If the results of the serum β-hCG cannot be obtained prior to dosing of IP, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained.

If either test is positive, the patient must be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant sexual history, including methods of contraception, should be considered. Any patient whose sexual history suggests the possibility of early pregnancy must be excluded.

Revised text, Section 4.2, Exclusion criterion 20:

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

Reason for Amendment:

Clarified that menstrual history is to be considered when assessing a female patient's eligibility to enter the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.2 Septic shock

Section of protocol affected:

Section 4.2, Exclusion criterion 13

Previous text, Section 4.2, Exclusion criterion 13:

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

Revised text, Section 4.2, Exclusion criterion 13:

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

Reason for Amendment:

To clarify that septic shock associated with a high risk of mortality should be considered as part of this exclusion criteria.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.3 Removal of unconscious patients

Sections of protocol affected:

Section 4.1, Inclusion criterion 1 and Section 8.4

Previous text, Section 4.1, Inclusion criterion 1:

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

Revised text, Section 4.1, Inclusion criterion 1:

1. Patient must provide a signed written informed consent prior to any study-specific procedures.

Previous text, Section 8.4, Item 5:

8.4 Informed consent

The investigator(s) at each study center will:

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

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

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

Revised text, Section 8.4, Item 5

The investigator(s) at each study center will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study
- Ensure that each patient is notified that he or she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the investigator's study file
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

Reason for Amendment:

Removed unconscious patients from enrolling in the study, because they cannot complete the Pre-Morbid Patient Study Assessment (Appendix G).

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.4 Definition of acute pyelonephritis

Section of protocol affected:

Section 4.1, Inclusion criterion 7(a)

Previous text, Section 4.1, Exclusion criterion 7(a):

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

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

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

Revised text, Section 4.1, Exclusion criterion 7(a):

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

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

- Fever, defined as body temperature >38°C (with or without patient symptoms of rigor, chills, or warmth).
- Nausea and/or vomiting

Reason for Amendment

Removed the timeframe from the definition of fever associated with pyelonephritis, to be consistent with the definition of fever associated with complicated lower UTI, as these are stratification factors.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.5 Comprehension of the Pre-morbid Patient Study Assessment and Daily Symptom Assessment Questionnaire

Section of protocol affected:

Section 4.2, Exclusion criterion 25

Previous text, Section 4.2, Exclusion criterion 25

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

Revised text, Section 4.2, Exclusion criterion 25

25. Patient is unlikely to comply with protocol, eg, **inability to fully comprehend and clearly respond to questions on the pre-morbid assessment and daily symptom assessment questionnaire in a reliable manner,** uncooperative attitude, inability to return for follow-up visits, and unlikely to complete the study.

Reason for Amendment

Added text to require that patients can comprehend and clearly respond to the questions on the pre-morbid assessment and daily symptom assessment questionnaire. Accurate completion of the questionnaire is central to the determination of a primary efficacy variable of the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

4. PRESENTATION OF PHARMACOKINETIC RESULTS

Sections of protocol affected:

Synopsis; Section 11.3

Previous text, Synopsis:

The collected ceftazidime and avibactam concentrations will be listed and descriptively summarized at specified sampling windows in the CSR. Individual compartmental PK parameters of avibactam and ceftazidime for cUTI patients will be derived via a population modeling approach.

The avibactam and ceftazidime concentration, patient demographics, and disease status data will be combined with the data from appropriate clinical studies for the population PK analysis. Individual compartmental PK parameters for patients with avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters such as maximum concentration, minimum concentration, area under the plasma concentration-time curve at steady state, and elimination

half-life will be derived from the predicted avibactam and ceftazidime concentration time courses. All of the derived PK parameters will be descriptively summarized. The appropriate avibactam and ceftazidime exposure outcome variables predicted by the population PK modeling will be used for a PK/PD modeling for appropriate microbiological or clinical response outcome variables. A separate population PK and PK/PD modeling analysis plan will be prepared and the results will be reported separately.

Revised text, Synopsis:

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

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

Previous text, Section 11.3:

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

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

microbiological or clinical cure outcome variables. A separate population PK and PK/PD modeling analysis plan will be prepared, and the results will be reported separately.

Revised text, Section 11.3:

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

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

Reason for Amendment:

To explain that only individual plasma concentrations collected from this trial will be included in the CSR and that further population PK analysis and investigation of potential PK/PD relationships will be reported in a separate report outside the CSR.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

5. DEFINITION OF SUPERINFECTION

Section of protocol affected:

Section 6.3.3.4, Table 10

Previous text, Table 10:

Table 10 Emergent infections

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

Revised text, Table 10:

Table 10 Emergent infections

Emergent infection	Definition
Superinfection	**Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen(s) from a urine culture which is accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy during the period up to and including EOT**
New infection	**Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen(s)) from a urine culture which is accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy in the time period after EOT**

Reason for Amendment:

To clarify the definition of emergent infection.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6. CONCOMITANT MEDICATIONS: USE OF AGENTS WITH NARROW GRAM-POSITIVE COVERAGE

Sections of protocol affected:

Section 5.6; Section 6.3.2, Table 8; Section 12.1.1.2, 6th bullet; Section 12.1.1.3, 4th bullet; Section 12.1.1.5, 6th bullet

Previous text, Secton 5.6, 2nd paragraph

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

Revised text, Section 5.6

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.**

Previous text, Section 6.3.2, Table 8, Footnote a

Table 8 Definition of investigator-determined clinical response at the EOT (IV), TOC, and LFU visits

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

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

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

Revised text, Section 6.3.2, Table 8, Footnote a

Table 8 Definition of investigator-determined clinical response at the EOT (IV), TOC, and LFU visits

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

[a] Additional antibiotics do not include the protocol-allowed oral study therapy options (ciprofloxacin or sulfamethoxazole/trimethoprim) **or agents with narrow spectrum Gram-positive coverage (ie, antibiotics without Gram-negative coverage, for example linezolid, vancomycin)**.

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

Previous text, Section 12.1.1.2, 6th bullet and Section 12.1.1.5, 6th bullet:

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

Revised text, Section 12.1.1.2, 6th bullet and Section 12.1.1.5, 6th bullet:

- 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.

Previous text, Section 12.1.1.3, 4th bullet:

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

Revised text, Section 12.1.1.3, 4th bullet:

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

Reason for Amendment:

Investigators feel it may become necessary to treat Gram-positive pathogens identified post-randomization in these patients. Therefore the protocol is revised to permit treatment using agents with a narrow spectrum Gram-positive coverage, that will not impact assessment of treatment with CAZ-AVI.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7. CLARIFICATIONS

7.1 Clinical information obtained before the informed consent is signed

Section of protocol affected:

Section 6.2

Previous text, Section 6.2:

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

Revised text, Section 6.2:

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

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

Reason for Amendment:

Clarification of enrollment requirements to specify that clinical information obtained as part of standard clinical care before the informed consent is signed may be used as part of the screening and evaluation process**.**

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.2 Collection of blood for Coombs test

Sections of protocol affected:

Section 6.2.2; Section 6.2.4; Section 6.2.5; Section 6.2.6

Previous text, Section 6.2.2, Item 9:

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

Revised text, Section 6.2.2, Item 9:

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

Previous text, Section 6.2.2, Item 11:

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

Revised text, Section 6.2.2, Item 11:

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

Previous text, Section 6.2.4, Item 9:

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

Revised text, Section 6.2.4, Item 9:

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

Previous text, Section 6.2.4, Item 11:

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

Revised text, Section 6.2.4, Item 11:

11. Obtaining a urine sample for routine urinalysis (central laboratory), **and direct Coombs test (to be performed locally).**

Previous text, Section 6.2.5, Item 8

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

Revised text, Section 6.2.5, Item 7 (previously Item 8)

7. Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments. Abnormal safety laboratory results obtained throughout the study, including the LFU, should be followed up as clinically indicated (see Appendix F).

Previous text, Section 6.2.5, Item 10

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

Revised text, Section 6.2.5, Item 9 (previously Item 10)

9. Obtaining a urine sample for routine urinalysis (central laboratory)**, and direct Coombs test (to be performed locally).**

Previous text, Section 6.2.6, Item 8

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

Revised text, Section 6.2.6, Item 7 (previously Item 8)

Obtaining a blood sample for clinical chemistry, hematology, and coagulation assessments (as clinically indicated). Abnormal laboratory test results should be followed-up as clinically indicated.

Reason for Amendment:

To clarify collection of Coombs test.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.3 Clarification of randomization and enrollment into the study

Sections of protocol affected:

Section 4.0; Section 4.1, Inclusion criterion 6

Previous text, Section 4.0:

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

Revised text, Section 4.0:

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

Reason for Amendment:

To clarify when enrollment and randomization are equivalent.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Sections of protocol affected:

Section 5.6

Previous text, Section 5.6:

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

Revised text, Section 5.6:

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

Reason fro Amendment:

Clarification of definitions.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.4 UTI-focused physical examination

Sections of protocol affected:

Section 6.2.1; Section 6.2.2, Section 6.2.3; Section 6.2.4; Section 6.2.5; Section 6.4.8

Previous text, Section 6.2.1, Item 6 and Item 7:

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

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

Revised text, Section 6.2.1, Item 6:

7. Performing a complete physical examination, **including a UTI-focused physical examination (suprapubic and costovertebral angle tenderness)**, as defined in Section 6.4.8. Height will be measured at Screening only. Weight will be measured as necessary to calculate the patient's estimated CrCl.

Previous text, Section 6.2.5, Item 4 and Item 5

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

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

Revised text, Section 6.2.5, Item 4

4. Performing a complete physical examination**, including a UTI-focused physical examination (suprapubic and costovertebral angle tenderness), as defined in Section 6.4.8.**

Reason for Amendment:

To clarify that a complete physical examination includes the UTI-focused physical examination. And to remove the word pain when describing suparpubic examination.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.2, Item 5, Section 6.2.3, Item 3, and Section 6.2.4 Item 5:

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

Revised text, Section 6.2.2, Item 5, Section 6.2.3, Item 3, and Section 6.2.4 Item 5:

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

Reason for Amendment:

To remove the word pain when describing suprapubic and costovertebral angle tenderness.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.8

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

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

Revised text, Section 6.4.8

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 and costovertebral angle tenderness. Height and weight will be measured at Screening only.

A UTI-focused physical examination will include an assessment for suprapubic and costovertebral angle tenderness.

Reason for Amendment:

To remove the word pain when describing suprapubic and costovertebral angle tenderness

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.5 Clarify electrocardiogram measurement text: order of assessments

Sections of protocol affected:

Section 6.2.3

Previous text, Section 6.2.3, Item 7:

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

Revised text, Section 6.2.3, Item 7:

7. Two ECG measurements: **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.

Reason for Amendment:

As doripenem/doripenem placebo is administered before CAZ-AVI/CAZ-AVI placebo, the revised text makes it clear that the ECG measurement taken at the end of the doripenem/doripenem placebo infusion will occur first.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.6 PREGREP and PREGOUT modules

Section of protocol affected:

Section 13.3.1

Previous text, Section 13.3.1:

The PREGREP module, provided to the study center personnel using a paper CRF, is used to report the pregnancy and the PREGOUT (also a paper CRF) is used to report the outcome of the pregnancy. These modules are not entered into the clinical database.

Revised text, Section 13.3.1:

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

Reason for Amendment:

To clarify the purpose and use of the PREGREP and PREGOUT modules; explains that PREGOUT will not be put onto the clinical database.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.7 Volume of blood

Section of protocol affected:

Section 7.1, Table 12

Previous text, Table 12:

Table 12 Volume of blood to be drawn from each patient

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

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

Revised text, Table 12:

Table 12 Volume of blood to be drawn from each patient

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

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

Reason for Amendment:

Revision of volume of blood to be drawn based on PK and blood culture sampling volume, and the removal of genetic and biomarker sampling.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.8 Pharmacokinetic and pharmacodynamic samples

Section of protocol affected:

Section 7.2.1

Previous text, Section 7.2.1:

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

Revised text, Section 7.2.1:

Samples will be disposed of **or anonymized by pooling** after the CSR has been finalized, unless retained for future analyses. **Pooled, anonymized samples may be used for analytical method development.**

Reason for Amendment:

To clarify the handling/disposition of pharmacokinetic and pharmacodynamic samples.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.9 Return to study center following discharge from the hospital

Section of protocol affected:

Synopsis, Section 3.1, Section 6.2.3

Previous text, Synopsis, Section 3.1, Section 6.2.3:

The patient is to return to the study center for the EOT (IV), TOC, and LFU visits following discharge from the hospital.

Revised text, Synopsis, Section 3.1, Section 6.2.3:

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

Reason for Amendment:

The text was simplified.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.10 Study entry urine culture

Section of protocol affected:

Synopsis; Section 12.1.1.2; Section 12.1.1.5

Previous text, Synopsis, Section 12.1.1.2, and Section 12.1.1.5:

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

Revised text, Synopsis, Section 12.1.1.2, and Section 12.1.1.5:

Had a study entry urine culture obtained ≤48 hours before **randomization**

Reason for Amendment:

To clarify when the study entry urine culture is to be obtained relative to randomization

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7.11 Difference between withdrawal of consent and discontinuation of IP

Section of protocol affected:

Section 5.9

Previous text, Section 5.9:

If possible, the patient will be seen and assessed by an investigator at the time of withdrawal and at the LFU visit.

Revised text, Section 5.9:

If possible, the patient will be seen and assessed by an investigator at the time of withdrawal.

Reason for Amendment:

To clarify the difference between withdrawal of consent and discontinuation of IP. Patients who withdraw consent are out of the study and should not undergo any additional visits.

Patients who discontinue IP but remain consented will undergo safety assessments per protocol. This modification does not change the template text.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Consequently, it is not deemed necessary to undertake a central readers interpretation of the ECG data in the event of an abnormal finding.

7.12 Remove central reader interpretation of abnormal ECGs

Section of protocol affected:

Section 6.4.9

Previous text, Section 6.4.9:

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

Revised text, Section 6.4.9:

All ECGs will be sent to the central reader who will judge the overall interpretation as normal or abnormal. **Specific procedures for use of the ECG recorder and transfer process will be provided in separate study documentation.**

Reason for Amendment:

A thorough QT study has completed which showed that a single intravenous dose of NXL104 2000 mg/ceftaroline fosamil 1500 mg did not prolong QTcF beyond 10 ms (the largest 90% upper bound for the placebo-corrected mean change from baseline was 5.5 ms). Consequently, it is not deemed necessary to undertake a central reader's interpretation of the ECG data in the event of an abnormal finding.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8. REVISION OF INSTRUCTIONS FOR THE PRE-MORBID PATIENT SYMPTOM ASSESSMENT (APPENDIX G)

Section of protocol affected:

Appendix G - Patient Symptom Assessment (Premorbid and Daily)

Previous text, Appendix G:

This questionnaire asks you about your symptoms in the 7 days prior to the onset of symptoms of your current Urinary Tract Infection (UTI).

Please respond whether you have had the following symptoms or problems in the 7 days prior to the onset of symptoms of your current Urinary Tract Infection (UTI) and how severe they were.

Answer each question by selecting only one response from the following: no symptom, mild, moderate, or severe.

Revised text, Appendix G:

This questionnaire asks about symptoms **you may or may not have had before the start of your current Urinary Tract Infection. Some symptoms we will ask about can be caused by health problems other than a Urinary Tract Infection. That's why we want to know what you experience when you may not have had Urinary Tract Infection symptoms over the previous 7 days.**

Please respond whether you have had any of the following symptoms in the 7 days before your current Urinary Tract Infection and how severe those symptoms were.

Answer each question by choosing only one response from the following **possible options: no symptoms, mild symptoms, moderate symptoms, or severe symptoms. Think about how you felt before the start of your current Urinary Tract Infection.**

Reason for Amendment:

The Introductory text for the pre-morbid assessment has been modified to provide clearer instructions for the patients.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

9. CORRECTION OF STUDY PLAN PER AMENDED ITEMS

Section of protocol affected:

Table 1

Previous text, Table 1:

	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[f]	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical and surgical history	X					
Review prior and/or concomitant medications	X	X	Daily	X	X	X
Complete physical examination[g]	X			X	X	X
UTI-focused physical examination[h]	X	X	Daily	X	X	X
Vital sign measurements[i]	X	X	Daily	X	X	X
12-lead digital electrocardiogram		X[j]	X[j]	X		
Assess urinary device status (as appropriate)		X	X	X	X	X
Blood for safety analysis[k]	X	X	Every 3 days[k]	X	X	X
Estimate creatinine clearance[l]	X	----------As clinically indicated----------				

	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)**
Urinalysis[m]	X			X	X	X
Quantitative urine culture	X[n]			X[o]	X	X
Blood cultures[p]	X	------If positive at Baseline, repeat at least every 3 days until negative. Blood cultures may also be obtained as clinically indicated------				
Serum β-hCG (women of childbearing potential)	X[q]					X
Blood for PK analysis[r]			X			
Pharmacogenetic blood sample[s]		X				
Biomarker samples[t]		X	X	X		
Randomization		X				
Monitor AEs[u]	X	X	Daily	X	X	X
Administer IV study therapy[v, w]		X	X			

	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[x]	X	X
Investigator-determined clinical response evaluation				X[y]	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] Separate informed consents should be obtained for both the pharmacogenetic and biomarker assessments prior to these assessments being conducted. Declining participation in the pharmacogenetic and biomarker portion of the study will not exclude the patient from participating in the main study.

[g] 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.

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

[i] Vital sign measurements include blood pressure, heart rate, respiratory rate, and body temperature. The patient should be resting in a supine position for at least 10 minutes before measuring blood pressure. 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.

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

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

l 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.

m 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.

n 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.

o 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.

p If the baseline blood culture is 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 mLs of blood per collection). One set should be drawn through a venipuncture.

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

r 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.

s The pharmacogenetic sample should be taken from consented patients prior to commencement of study therapy. If this sample is not taken prior to the initiation of study therapy, it may be taken at any visit until the last study visit.

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

[u] 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.

[v] If necessary, a 1-time dose-interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule 8 hours apart (±30 minutes). The dosing interval adjustment must be made such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose. If a 1-time dose-interval adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. Before being eligible to switch from IV to oral therapy, patients must receive at least 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV therapy, which must be administered in the hospital. Patients may be switched to oral ciprofloxacin (or oral sulfamethoxazole/trimethoprim if the patient has a fluoroquinolone-resistant pathogen) if all criteria in the protocol are met (see Section 5.5.3). Those patients who remain on IV study therapy after 5 full days (ie, 15 doses) will receive IV study therapy from study center personnel while in the hospital or from a qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for scheduled visits (EOT [IV], TOC, and LFU) following discharge from the hospital.

[w] 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.

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

[y] 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, Table 1:

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
Complete physical examination[f]	X			X	X	X
UTI-focused physical examination[g]	X	X	Daily	X	X	X
Vital sign measurements[h]	X	X	Daily	X	X	X
12-lead digital electrocardiogram		X[i]	X[i]	X		
Assess urinary device status (as appropriate)		X	X	X	X	X
Blood for safety analysis[j]	X	X	Every 3 days[j]	X	X	X

Table 1 Study plan

	Eligibility/ Screening	Treatment Period			Follow-Up Period	
	Visit 1	**Visit 2**	**Visits 3 to 15**	**Visit 16[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)**
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------				
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 culture**s 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 mLs 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.

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Reason for Amendment:

Revision of Table 1 to reflect changes to protocol (clarification of blood culture collection; removal of genetic and biomarker sampling; clarification of pregnancy testing; Coombs test; removal home health care; ECG measurements regarding order of assessments).

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

10. ADMINISTRATIVE CHANGES

- Edits to the List of Abbreviations for items added per amendment
- Editorial, formatting, and style corrections