Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00006
Date	[redacted]
Protocol Dated	[redacted]

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

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; expanded criterion for cIAI patients to include complete fascial closure; definition of acute pyelonephritis; mortality risk and inclusion of septic shock; update hepatic exclusion criteria; expand the exclusion criteria for UTI patients
4. Revisions to microbiological assessments: specimen collection and analysis of isolates
5. Revised definition of emergent infections

6. Clarifications: update to introduction; when study treatment should start; following patients discontinued prematurely; order of infusions for CAZ-AVI and metronidazole; 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; 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; anaerobic coverage for IAI patients; clarify the difference between withdrawal of consent and discontinuation of IP; remove the central reader assessment for abnormal ECGs; clarify when body temperature is to be measured during the study; possibly extend recruitment to meet study objectives; purpose and use of the PREGREP and PREGOUT modules

7. Clarify in definition of clinical response that per-protocol antibacterial therapy is allowed

8. Update safety laboratory variables

9. To modify the naming of the analysis population from modified intent-to-treat (MITT) to microbiological modified intent-to-treat (mMITT)

10. Correction of physiologic variables and reference ranges on the APACHE II Score Form in Appendix F

11. Correction of Figure 1 (Study flow chart): patients are to receive study therapy for a minimum of 5 days (15 doses).

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

13. 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 6.2.4; Section 6.3.8; Section 6.3.9; Table 7; 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 clinical study report (CSR) for this study. Blood samples for DNA extraction will not be collected in all countries (eg, China).

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

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 6:

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

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

Revised text, Section 4.1, Inclusion criterion 6:

6. **No longer applicable.**

Previous text, Section 4.2, Exclusion criteria 22 and 23:

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

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

23. Patient had previous allogenic bone marrow transplant.

Revised text, Section 4.2, Exclusion criteria 22 and 23:

22. No longer applicable.

23. No longer applicable.

Previous text, Section 6.2.2, Item 18:

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

Revised text, Section 6.2.2, Item 18:

Item deleted.

Previous text, Section 6.2.2, Item 19:

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

Revised text, Section 6.2.2, Item 19:

Item deleted.

Previous text, Section 6.2.4, Item 14:

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

Revised text, Section 6.2.4, Item 14:

Item deleted.

Previous text, Section 6.3.8:

6.3.8 Pharmacogenetic outcome variables

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

Revised text, Section 6.3.8:

6.3.8 Pharmacogenetic outcome variables

No longer applicable.

Previous text, Section 6.3.9:

6.3.9 Biomarker outcome variables

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

Revised text, Section 6.3.9:

6.3.9 Biomarker outcome variables

No longer applicable.

Previous text, Table 7:

Biomarker samples (banked specimen)

Revised text, Table 7:

Item deleted from table.

Previous text, Section 6.7:

6.7 Pharmacogenetics

For details of PGx sampling, see Appendix D.

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

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 study plan (Table 1). The samples will be processed to serum and plasma as directed in the laboratory manual.

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

6.8.1 Sample processing and shipping

Samples must be shipped frozen (–20°C or below) and transported to the relevant storage site, as indicated in the laboratory manual. Samples should be shipped in batches and coordinated with Covance 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 [redacted] 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:

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

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

Revised text, Section 7.2:

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

Previous text, Section 7.2.2:

7.2.2 Pharmacogenetic samples

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

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.

Revised 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.

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.

Reason for Amendment:

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

Previous text, Synopsis:

Those patients who remain on IV study therapy after 5 days (15 doses for those patients randomized to CAZ-AVI) 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, FU1 and FU2 visits following discharge from the hospital.

Revised text, Synopsis:

Those patients who remain on study therapy after 5 days (15 doses for those patients randomized to CAZ-AVI) will receive their study therapy by study center personnel while in the hospital. The patient is to return to the study center for **all remaining study visits** following discharge from the hospital.

Previous text, Section 3.1:

Those patients who remain on study therapy after 5 days (15 doses for those patients randomized to CAZ-AVI) will receive their study therapy by study center personnel while in the hospital or qualified healthcare provider (eg, home health agency) as an outpatient. The patient is to return to the study center for the EOT, TOC, FU1, and FU2 visits following discharge from the hospital. The assessments at the FU1 and FU2 visits would provide data from this study that could be put into context with data from other Phase III CAZ-AVI trials conducted in patients with cUTI and cIAI.

Revised text, Section 3.1:

Those patients who remain on study therapy after 5 days (15 doses for those patients randomized to CAZ-AVI) will receive their study therapy by study center personnel while in the hospital. 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 study therapy, 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 to the investigator or medically qualified personnel by the study center pharmacist. Intravenous study therapy will only be prepared and administered to patients by the study center pharmacists and medically qualified personnel who have been appropriately trained to prepare and administer study therapy. Written authorization of study personnel to administer IP must be documented for both hospital staff and, when applicable, home healthcare (HHC) staff, on the Delegation of Authority Log in 1 of 2 ways:

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

Revised text, Section 5.7.1:

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

Written documentation of training of study therapy administration and pharmacy study center personnel will be kept current throughout the study, and ongoing training will be provided by study center personnel as assigned by the investigator on the Delegation of Authority Log. It is the investigator's responsibility to ensure that all documentation remains current and complete throughout the study. The investigator will document how he or she will ensure that the staff are adequately trained before they perform the infusion, and he or she will ensure that there is a system in place that will guarantee supervision of the study therapy administration process and patient safety (eg, study therapy will only be administered to patients under supervision of an investigator). Source documentation should clearly indicate who administered the infusion.

Previous text, Section 6.2.3

The total number of days of combined treatment with study therapy will be a minimum of 5 and a maximum of 21 days. Those patients who remain on study therapy after 5 days (15 doses for patients randomized to the CAZ-AVI group with normal renal function or mild renal impairment) will receive their study therapy from study center personnel while in the hospital or from a qualified healthcare provider (eg, agency) as an outpatient. The patient is to return to the study center for their scheduled visits following discharge from the hospital.

Revised text, Section 6.2.3

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

Reason for Amendment:

To remove the requirement for home health care from the study design, as it has been determined that all protocol-required IV therapy will occur in the hospital.

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 3, 3(a) and 3(b); Section 4.2, Exclusion criterion 17.

Previous text, Section 4.1, Inclusion criteria 3, 3(a), and 3(b):

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

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

OR

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

- Has had normal menstrual periods for the 3 months prior to study entry, and
- Has a negative serum pregnancy test (serum 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 infusion of study therapy, to practice highly effective methods of birth control, such as

intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), 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 3, 3(a), 3(b), 3(c), and 3(d):

3. 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 postmenopausal as defined by amenorrhea for 12 months or more following cessation of all exogenous hormonal treatments**

(c) Age <50 and postmenopausal as defined by documented LH and FSH levels in the postmenopausal 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 infusion of study therapy **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 vasectomized 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 childbearing potential, contraception, and confirmation the patient is not pregnant. The time period for avoiding pregnancy after the last infusion of study therapy 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 17:

17. Patient is pregnant or breastfeeding. A serum β-hCG pregnancy test must be sent for women of childbearing potential at the screening visit. If the results of the serum β-hCG cannot be obtained prior to dosing of 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 17:

17. 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 Expanded criterion for cIAI patients to include complete fascial closure

Section of protocol affected:

Section 4.1, Inclusion criterion 7

Previous text, Section 4.1, Inclusion criterion 7:

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

Revised text, Section 4.1, Inclusion criterion 7:

7. Patient must have a ceftazidime-resistant Gram-negative pathogen isolated from an abdominal source during a surgical intervention. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. **Patients who undergo a surgical procedure with complete fascial closure are appropriate for the trial. The skin incision may be left open for purposes of wound management as long as complete fascial closure is accomplished.**

Reason for Amendment:

Expanded criterion to include complete fascial closure and clarify that an open skin incision is acceptable for purposes of wound management.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.3 Definition of acute pyelonephritis

Section of protocol affected:

Section 4.1, Inclusion criterion 12(a)

Previous text, Section 4.1, Inclusion criterion 12(a):

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

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

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

Revised text, Section 4.1, Inclusion criterion 12 (a):

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

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

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

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.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.4 Mortality risk and addition of septic shock

Section of protocol affected:

Section 4.2, Exclusion criterion 3

Previous text, Section 4.2, Exclusion criterion 3:

3. Patient has a rapidly progressive or terminal illness, including acute hepatic failure or respiratory failure with a high risk of mortality due to other cause

Revised text, Section 4.2, Exclusion criterion 3:

3. Patient has a rapidly progressive or terminal illness **with a high risk of mortality due to any cause**, including acute hepatic failure respiratory failure **or severe septic shock**

Reason for Amendment:

To clarify the timeframe of expected survival and 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

3.5 Update hepatic exclusion criteria

Section of the protocol affected:

Section 4.2, Exclusion criteria 10, 11, and 12

Previous text, Section 4.2, Exclusion criteria: 10, 11, and 12:

10. Presence of hepatic disease as indicated by ALT or AST >3 × upper limit of normal (ULN) at Screening. Patients with AST and/or ALT up to 5 × ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.

11. Patient has a bilirubin >3 × ULN, unless isolated hyperbilirubinemia is directly related the acute process

12. Patient has acute hepatic failure or acute decompensation of chronic hepatic failure

Revised text, Section 4.2, Exclusion criteria 10, 11, and 12:

10. **Acute hepatitis in the prior 6 months, cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure**

11. **For any individual, any of the following:**

(a) Bilirubin >3 × ULN, unless isolated hyperbilirubinemia is directly related to the acute **infection or due to known Gilbert's disease**

(b) **ALT or AST >3 × ULN values used by the laboratory performing the test. Patients with values >3 × ULN and <5 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented**

(c) **Alkaline phosphatase >3 × ULN. Patients with values >3 × ULN and <5 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented**

12. **No longer applicable**

Reason for Amendment:

To make criteria current and consistent with other Phase III protocols in the CAZ-AVI program.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.6 Expand exclusion criteria for UTI patients

Section of protocol affected:

Section 4.2, Exclusion criterion 32

Previous text, Section 4.2, Exclusion criterion 32:

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

Revised text, Section 4.2, Exclusion criterion 32:

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

Reason for Amendment:

To expand the exclusion criteria for UTI patients.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

4. REVISIONS TO MICROBIOLOGICAL ASSESSMENTS: SPECIMEN COLLECTION AND SHIPMENT AND ANALYSIS OF ISOLATES

Sections of protocol affected:

Section 3.1.2; Section 3.1.2.1; Section 3.1.2.2; Section 3.1.2.3; Section 3.1.2.4

Previous text, Section 3.1.2:

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

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

undergoing a surgical procedure on or after the date of the Baseline/Randomization visit. For an organism to be considered a pathogen on the study-qualifying culture, it must be a Gram-negative bacterial organism and be resistant to ceftazidime (eg, all Enterobacteriaceae including *E. coli*, *Klebsiella* spp., *Proteus* spp., *Providencia* spp., *Citrobacter* spp., and *Serratia* spp. as well as nonfermentative Gram-negative pathogens such as *P. aeruginosa*). Gram-negative organisms not considered to be pathogens are presumed to be contaminants and are not appropriate for study entry.

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

Revised text, Section 3.1.2:

It is important that the microbiology laboratory be instructed to retain all pathogens for at least 5 days from patients where a ceftazidime-resistant pathogen (the study-qualifying pathogen as described below) is isolated for possible inclusion in this trial. For this study, ceftazidime resistance is defined as those isolates whose susceptibility results are intermediate or resistant using CLSI methodology and isolates that are resistant using EUCAST methodology. All microbiological assessments will be initiated at the local laboratory according to study center standard of practice for specimen collection and analysis of isolates as outlined in the following sections and as presented in more detail in the **microbiology laboratory** manual. **Once the patient is randomized, the microbiology laboratory should be notified that all pathogens including the ceftazidime-resistant study-qualifying pathogen** must be shipped to the central **microbiology** laboratory for confirmation of microbiological assessments.

- **For cUTI, the** supplementary culture is required for all patients entering with a cUTI diagnosis.

- For cIAI, **the** supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the baseline/randomization visit.

For an organism to be considered a pathogen on the study-qualifying culture, it must be a Gram-negative bacterial organism and be resistant to ceftazidime (eg, all Enterobacteriaceae **such as** *E. coli*, *Klebsiella* spp., ***Enterobacter* spp.,** *Proteus* spp., *Providencia* spp., *Citrobacter* spp., and *Serratia* spp. as well as ***P. aeruginosa*).** Nonfermentative Gram-negative **organisms other than *P. aeruginosa,* (*Acinetobacter* spp., *Stenotrophomonas maltophilia*, etc.) are not expected to respond to CAZ-AVI and therefore should not be considered for this trial.** Gram-negative organisms not considered to be pathogens are presumed to be contaminants and are not appropriate for study entry.

Previous text, Section 3.1.2.1:

Abdominal culture for patients with cIAI

The ceftazidime-resistant Gram-negative bacterial isolate from the study-qualifying culture must be sent to the central microbiology vendor for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics. Any subsequent abdominal culture specimen should be sent to the local laboratory for culture, identification, and in vitro susceptibility testing and be processed according to recognized methods that culture for both aerobic and anaerobic bacterial organisms (Murray, et al.) following the standard operating procedures of the clinical microbiology laboratory at each study center. Blood culture specimens should be taken at Baseline and abdominal culture specimens should be obtained at the time of any surgical procedure. All Gram-negative cultured isolates that are resistant to ceftazidime should be kept by the local laboratory at –20°C or colder (preferably at –70°C) until the end of the study or when contacted by the central reference laboratory.

Urine culture for patients with cUTI

The ceftazidime-resistant Gram-negative bacterial isolate from the study-qualifying culture must be sent to the central microbiology vendor for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics. An adequate urine specimen for microbiological evaluation must be obtained from all cUTI patients and sent to the local laboratory for culture, identification, and in vitro antibacterial susceptibility testing. The specimens should be processed according to recognized methods (Murray et al 2007) and following the standard operating procedures of the clinical microbiology laboratory at each study center. Urine culture specimens should be taken at Baseline (the supplementary culture) and at the EOT, TOC, FU1, and FU2 visits. All cultured isolates of Gram-negative uropathogens at $\geq 10^5$ colony-forming units (CFU)/mL at Baseline (the supplementary culture) and at the EOT, TOC, FU1, and FU2 visits as well as any Gram-negative uropathogen isolated at Baseline regardless of quantification in urine that are resistant to ceftazidime should be kept by the local laboratory at –20°C or colder (preferably at –70°C) until the end of the study or when contacted by the central laboratory.

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

- Straight catheterization using sterile technique (preferred for female patients)
- Midstream clean catch
- Suprapubic specimen collection using sterile technique
- Whenever possible, urine specimens should not be obtained from indwelling catheters. When necessary, urine specimens in patients with indwelling bladder catheters should be obtained by sterile aspiration through the catheter port or by puncturing the catheter tubing with a needle and syringe if a port is not present.

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

Blood cultures for all patients (cIAI and cUTI)

If blood cultures had not been performed prior to study entry or if blood cultures were positive, but repeat cultures had not yet shown clearance of bacteremia, a blood culture must be obtained at Baseline/Randomization. Additional specimens for blood cultures will be collected as clinically indicated after randomization. Two sets of blood cultures should be collected from 2 different sites (ie, 4 tubes) for aerobic and anaerobic incubation. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. At least 1 set of blood cultures must be obtained through a venipuncture. Organisms isolated in the blood from a blood study-qualifying culture will be assigned a microbiological response similar to those given for pathogens isolated from abdominal cultures (cIAI) and to those given for uropathogens isolated from urine cultures as noted in Table 5, except that specification for quantity will not apply for blood isolates. The blood study-qualifying microbiological isolate will be utilized as the isolate to determine microbiological response. Details concerning the collection of blood cultures are provided in the laboratory manual.

Revised text, Section 3.1.2.1:

Blood cultures specimens for all patients (cIAI and cUTI)

When blood cultures are taken after consent, two sets of blood cultures should be collected from 2 different sites (ie, 4 bottles) for aerobic and anaerobic incubation. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. At least 1 set of blood cultures should be obtained through a venipuncture.

Abdominal culture for patients with cIAI

Adequate abdominal culture specimen(s) (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) are collected from the site of abdominal infection and from other clinically relevant intra-abdominal sites, as appropriate.

Urine culture for patients with cUTI

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

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

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

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

Previous text, Section 3.1.2.2:

3.1.2.2 Shipment of isolates

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

Revised text, Section 3.1.2.2

3.1.2.2 Isolate collection

Abdominal culture for patients with cIAI

The ceftazidime-resistant Gram-negative bacterial isolate from the study-qualifying culture must be sent to the central microbiology laboratory for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics. If available, additional pathogens identified in the study-qualifying culture should also be sent to the central microbiology laboratory. Pathogens identified from intra-abdominal or surgical site cultures at any time during the study should also be sent to the central microbiology laboratory. All pathogens should be kept by the local laboratory at –20°C or colder (preferably at –70°C) until the end of the study or when contacted by the central microbiology laboratory.

Urine culture for patients with cUTI

The following must be sent to the central microbiology laboratory for confirmation of identification:

- **From the study-qualifying culture: the ceftazidime-resistant Gram-negative bacterial uropathogens at $\geq 10^5$ CFU/mL**
- **From the supplementary urine culture: all uropathogens identified regardless of colony count**

- **From follow-up cultures at EOT, TOC, FU1, and FU2: all uropathogens quantified at ≥10^4 CFU/mL**

All uropathogens being sent to the central microbiology laboratory should also be kept by the local laboratory at –20°C or colder (preferably at –70°C) until the end of the study or when contacted by the central microbiology laboratory.

Blood cultures for all patients (cIAI and cUTI)

Any ceftazidime-resistant blood **pathogens identified at the time of initial diagnosis of cUTI or cIAI (ie, within 24 hours** prior to study-**qualifying culture and up to screening) should be sent to the central microbiology laboratory, if available. All** blood **pathogens identified during screening and** after randomization, **regardless of ceftazidime susceptibility should be sent to the central microbiology laboratory.**

All blood pathogens being sent to the central microbiology laboratory should also be kept by the local laboratory at –20°C or colder (preferably at –70°C) until the end of the study or when contacted by the central microbiology laboratory.

Organisms isolated in the blood from a blood study-qualifying culture will be assigned a microbiological response similar to those given for pathogens isolated from abdominal cultures (cIAI) and to those given for uropathogens isolated from urine cultures as noted in , except that specification for quantity will not apply for blood isolates. The blood study-qualifying microbiological isolate will be utilized as the isolate to determine microbiological response. Details concerning the collection of blood cultures are provided in the laboratory manual.

Previous text, Section 3.1.2.3:

3.1.2.3 Analysis of isolates

For patients with cIAI, the local laboratory must identify all aerobic bacterial pathogens to the genus and species level using confirmatory, not presumptive, identification methods from blood and abdominal specimens. All isolated Gram-negative organisms, including the study-qualifying isolate, that are resistant to ceftazidime should be sent to the central reference laboratory for confirmation of identification and susceptibility testing. All anaerobic bacterial pathogens, including the study-qualifying isolate, must be identified to at least the genus level. All anaerobic isolates should be sent to the central reference laboratory for confirmation of identification and susceptibility testing.

For patients with cUTI, all Gram-negative pathogens resistant to ceftazidime meeting the criteria of ≥10^5 CFU/mL from study-qualifying cultures and at EOT, TOC, FU1, and FU2 and all Gram-negative pathogens resistant to ceftazidime isolated from urine cultures collected at Baseline (the supplementary culture) regardless of quantification, must be identified to the genus and species level using confirmatory, not presumptive, identification methods. All isolated Gram-negative pathogens resistant to ceftazidime should be sent to the central reference laboratory for confirmation of identification and susceptibility testing.

The investigator should record information on all specimens according to the investigator's manual supplied by the central reference laboratory. The central reference laboratory will confirm pathogen identifications and susceptibility test results on all reported Gram-negative isolates that are resistant to ceftazidime and shipped by the local laboratory. If discrepancies occur between the results obtained at the central reference laboratory and those obtained at the study center's local laboratory, a [redacted] representative will request that a second sample of the isolate in question be shipped. In the instance of differences in pathogen identification or susceptibilities, the central reference laboratory results will take precedence over the local laboratory result. If microorganisms that are isolated at the local laboratory do not survive shipping to the central reference laboratory, a [redacted] representative will request that a second sample of the isolate in question be shipped. Local laboratory results may be used if a microorganism does not survive shipping from the local laboratory to the central reference laboratory, or a microorganism is not recoverable from the local laboratory and therefore cannot be reshipped to the central reference laboratory.

Revised text, Section 3.1.2.3 and Addition of Section 3.1.2.4:

3.1.2.3 Shipment of isolates

The central **microbiology** laboratory will supply the local laboratory with all media containing transport vials and instructions for shipment of isolates to the central **microbiology** laboratory. The central **microbiology** laboratory will monitor and verify resistant isolates reported by the local laboratory. All shipment documentation for samples sent from the local laboratory to the central **microbiology** laboratory should be maintained and available for review by the [redacted] representative.

3.1.2.4 Analysis of Isolates

For patients with cIAI, the local laboratory must identify all aerobic bacterial pathogens to the genus and species level using confirmatory, not presumptive, identification methods from blood and abdominal specimens. All isolated Gram-negative **pathogens**, including the study-qualifying isolate, that are resistant to ceftazidime should be sent to the central **microbiology** laboratory for confirmation of identification and susceptibility testing. **If possible,** all anaerobic bacterial pathogens, including the study-qualifying isolate, must be identified to at least the genus level. **If possible,** all anaerobic isolates should be sent to the central **microbiology** laboratory for confirmation of identification and susceptibility testing.

For patients with cUTI, Gram-negative **uropathogens** must be identified to the genus and species level using confirmatory, not presumptive identification methods **and** be sent to the central **microbiology** laboratory **if present at $\geq 10^5$ CFU/ml in the study-qualifying culture, if present at any quantification at baseline and if present at $\geq 10^4$ CFU/ml at any follow-up visit.**

Susceptibility testing **for CAZ-AVI will be performed by the disk diffusion method at the local laboratory using recommended CLSI methodology on all pathogens being**

submitted to the central microbiology laboratory, as outlined in the microbiology laboratory manual. Susceptibility disks will be provided by the sponsor.

The investigator should record information on all specimens according to the investigator's manual supplied by the central **microbiology** laboratory. The central **microbiology** laboratory will confirm pathogen identifications and susceptibility test results on all reported Gram-negative isolates that are resistant to ceftazidime and shipped by the local laboratory. If discrepancies occur between the results obtained at the central **microbiology** laboratory and those obtained at the study center's local laboratory, a [redacted] representative will request that a second sample of the isolate in question be shipped. In the instance of differences in pathogen identification or susceptibilities, the central **microbiology** laboratory results will take precedence over the local laboratory result. If microorganisms that are isolated at the local laboratory do not survive shipping to the central **microbiology** laboratory, a [redacted] representative will request that a second sample of the isolate in question be shipped. Local laboratory results may be used if a microorganism does not survive shipping from the local laboratory to the central **microbiology** laboratory, or a microorganism is not recoverable from the local laboratory and therefore cannot be reshipped to the central **microbiology** laboratory.

Reason for Amendment:

To clarify the criteria for handling and identification of the isolates.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

5. DEFINITION OF EMERGENT INFECTIONS

Section of protocol affected:

Section 6.3.2.5, Table 6

Previous Text: Table 6 Emergent infections

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

Previous Text: Table 6 Emergent infections

Emergent infection	Definition

Revised Text: Table 6 Emergent infections

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

Reason for Amendment:

To clarify the definition of emergent infection to ensure that only pathogens identified from intra-abdominal cultures and urine cultures are considered for cIAI and cUTI patients, respectively.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6. CLARIFICATIONS

6.1 Update to Introduction

Section of protocol affected:

Section 1.1.6; Section 1.1.7; Section 1.3

Previous text, Section 1.1.6:

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

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

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

Revised text, Section 1.1.6:

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

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

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

Previous text, Section 1.1.7:

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

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

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

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

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

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

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

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

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

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

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

Revised text, Section 1.1.7:

At the time of this protocol, **7** clinical pharmacology studies have been completed:

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

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

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

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

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

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

- **A Phase I open-label, single dose study to investigate the excretion and metabolism of [^{14}C] avibactam in healthy subjects (Study D4280C00008).**

The Phase I studies completed to date have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly male and female subjects. **The [^{14}C] avibactam study D4280C00008 showed that an average of 97% (range 95% to 98%) of administered radioactivity was recovered from the urine, over 95% within 12 hours of dosing. Avibactam is predominantly renally cleared with little contribution from metabolism. An average of 85% (range 67% to 101%) of administered avibactam was recovered from the urine during the study, with >50% being recovered within 2 hours of the start of the infusion. Renal clearance was**

158 mL/min suggesting active tubular secretion. The PK and tolerability of avibactam have also been determined in patients with different degrees of renal impairment (Study NXL104/1003). The relationship between avibactam renal clearance and calculated creatinine clearance (CrCl) was found to be linear, consistent with the predominantly renal excretion of avibactam. Based on the data from Study NXL104/1003, dosage adjustments will be required in patients with moderate or severe renal impairment. Population PK and PK/pharmacodynamic (PD) modeling support adjustments in the dose amount and frequency of administration for ceftazidime-avibactam (CAZ-AVI, formerly [redacted]) that are consistent with those already recommended for ceftazidime (see Section 5.5.2.2).

Based on the data from Study NXL104/1004, dose adjustments based on age (young adult or elderly) or gender are not required. Overall, preliminary data indicate that there were no major safety and tolerability concerns identified in this study. Additional details can be found in Section 5.1 of the CAZ-AVI Investigator's Brochure.

In Study D4280C00007, a supratherapeutic dose of **avibactam was investigated for QT effects in combination with** ceftazidime **and ceftaroline fosamil, with moxifloxacin as a positive control. A single IV dose of avibactam** 2000 mg **and ceftazidime 3000 mg or avibactam 2000 mg and ceftaroline fosamil 1500 mg did** not prolong QTcF beyond 10 ms. There were no QTcF **intervals** greater than 450 ms nor were there any QTcF **interval** changes from Baseline greater than 30 ms after a single IV dose of **avibactam 2000 mg/ceftazidime 3000 mg or avibactam 2000 mg/ceftaroline fosamil 1500 mg**.

Previous text, Section 1.3:

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

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

Revised text, Section 1.3:

In regard to hypersensitivity reactions, there was 1 report in the CAZ-AVI clinical trials, where the clinical investigator considered the events of skin rash and elevated liver function tests to be a possible hypersensitivity reaction because of the temporal relationship of the

events to study therapy administration. In the CAZ-AVI development program, rashes have been reported. Elevations of liver enzymes independent of skin rashes or other potential signs of hypersensitivity have also been reported. **Drug-induced liver injury is considered an important potential risk (see Section 1.1.7).**

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

Reason for Amendment:

To update the background and benefit/risk information with the most current information.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.2 Start of study treatment

Section of protocol affected:

Synopsis; Section 3.1

Previous text, Synopsis and Section 3.1:

Study periods

Eligibility/Screening Period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0
Treatment Period	
Visit 2 (Baseline/randomization)	Day 1
Visits 3 to 22 (Days 2 to 21)	While on therapy
End of Treatment (EOT with study therapy)	Within 24 hours after the completion of the last infusion of study therapy[a]
Follow-Up Period	
Test of Cure Visit (TOC)[b]	
cUTI	7 days after the last infusion of study therapy
cIAI	7 days after the last infusion of study therapy
Follow-Up 1 (FU1)[c]	
cUTI	Day 21[d]
cIAI	Day 28[e]
Follow-Up 2 (FU2)	
cUTI[f]	Day 28[g]
cIAI	No additional visit required

[a] Patients who discontinue study therapy should continue the study schedule as planned whenever possible; however, they should be scheduled for the EOT visit within 24 hours after the last infusion of study therapy.
[b] The TOC visit may occur 7 to 10 days after the last infusion of study therapy.
[c] If it is not possible to perform the FU1 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 21 to Day 25 and for cIAI is Day 28 to Day 35.
[d] The designated windows for the TOC (7 to 10 days after the last infusion of study therapy) and FU1 (Day 21 to Day 25) visits may overlap depending upon the number of days the cUTI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU1 visits need to be performed only once.
[e] The designated windows for the TOC (7 to 10 days after last infusion of study therapy) and FU1 (Day 28 to Day 35) visits may overlap depending upon the number of days the cIAI patient receives study therapy. In those instances, the TOC and FU1 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU1 visits need to be performed only once.
[f] If it is not possible to perform the FU2 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is Day 28 to Day 32.
[g] The designated windows for the TOC (7 to 10 days after last infusion of study therapy) and FU2 (Day 28 to Day 32) visits for a cUTI patient may overlap depending upon the number of days the patient receives study therapy. In those instances, the TOC and FU2 visits may be combined on the same day. All assessments for both visits must be performed (Table 1). In this instance, assessments that are required at both the TOC and FU2 visit only need to be performed once.

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

Revised text, Synopsis and Section 3.1:

Study periods

Eligibility/Screening Period	
Visit 1 (Eligibility/Screening)	Day –1 to Day 0[a]
Treatment Period	
Visit 2 (Baseline/randomization)	Day 1
Visits 3 to 22 (Days 2 to 21)	While on therapy
End of Treatment (EOT with study therapy)	Within 24 hours after the completion of the last infusion of study therapy[b]
Follow-Up Period	
Test of Cure Visit (TOC)[c]	
cUTI	7 days after the last infusion of study therapy
cIAI	7 days after the last infusion of study therapy
Follow-Up 1 (FU1)[d]	
cUTI	Day 21[e]
cIAI	Day 28[f]
Follow-Up 2 (FU2)	
cUTI[g]	Day 28[h]
cIAI	No additional visit required

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

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

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

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

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

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

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

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

Reason for Amendment:

To clarify that Day −1 and Day 0 may be the same calendar day as Day 1

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.3 Following patients discontinued prematurely

Section of protocol affected:

Section 5.3

Previous text, Section 5.3:

Where patients that do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the [redacted] physician immediately. The [redacted] physician is to ensure that all such contacts are appropriately documented.

Revised text, Section 5.3:

Where patients **who** do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the [redacted] physician immediately. **Except for those criteria outlined in Section 5.8, the patient may continue to receive study therapy or be discontinued from study therapy at the investigator's discretion. Whenever a patient discontinues study therapy prematurely, they should remain in the study and complete all assessments wherever possible.** The [redacted] physician is to ensure that all such contacts are appropriately documented.

Reason for Amendment:

To clarify handling of patients who discontinue prematurely

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.4 Order of infusions for CAZ-AVI and metronidazole

Section of protocol affected:

Section 5.5.2.3

Previous text, Section 5.5.2.3:

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

Revised text, Section 5.5.2.3:

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

Reason for Amendment:

To clarify order of infusions in instances where the timing coincides

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.5 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 6.2.7.

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 6.2.7.

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

6.6 Collection of blood for Coombs test

Sections of protocol affected:

Section 6.2.2; Section 6.2.4

Previous text, Section 6.2.2, Item 9

9. Obtaining a blood sample for blood culture if a blood culture had not been previously obtained or if blood cultures were positive, but repeat blood cultures had not yet shown clearance of bacteremia

Revised text, Section 6.2.2, Item 9

9. Obtaining a blood sample for blood culture if a blood culture had not been previously obtained or if blood cultures were positive, but repeat blood cultures had not yet shown clearance of bacteremia**, and a blood sample for a direct Coombs test (to be performed locally)**

Previous text, Section 6.2.4, Item 12

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

Revised text, Section 6.2.4, Item 12

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

Reason for Amendment:

To clarify collection of Coombs test.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.7 Clarification of randomization and enrollment into the study

Section of protocol affected:

Section 4.0

Previous text, Section 4.0:

Investigators should keep a record, the patient screening log, of patients who entered Screening. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled into the study or receive study therapy. There can be no exceptions to this rule. Patients discontinued from the study should be followed for safety.

Revised text, Section 4.0:

Investigators should keep a record, the patient screening log, of patients who entered Screening. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled **(randomized)** into the study or receive IV study therapy. There can be no exceptions to this rule. Patients discontinued from the study should be followed for safety.

Reason for Amendment:

To clarify when enrollment and randomization are equivalent.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.8 Volume of blood

Section of protocol affected:

Section 7.1, Table 8

Previous text, Table 8:

Table 8 Volume of blood to be drawn from each patient

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

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

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

Revised text, Table 8:

Table 8 Volume of blood to be drawn from each patient

Assessment		**Sample volume (mL)**	**Number of samples**	**Total volume (mL)**
Safety	Clinical chemistry	5	12[a]	60[a]
	Hematology	3	12[a]	36[a]
	Coagulation	4.5	12[a]	54
Pharmacokinetic sample		4	3	12
Blood culture		**10 – 15**	4[a,b]	**40 – 60**[a,b]
Total				**202-222**

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

[b] **When obtaining samples for blood cultures, 2 sets should be collected. If a blood culture prior to study entry also grew the same pathogen as the study-qualifying microbiological isolate from the disease under study, then this blood culture study-qualifying isolate will be utilized as the isolate to determine microbiological response for positive blood cultures. If blood cultures had not been performed previously or if previous blood cultures were positive, but repeat cultures had not yet shown clearance of bacteremia, an additional blood culture must be obtained at Baseline/Randomization as described in Section 3.1.2.1**

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

6.9 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

6.10 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, TOC, FU1, and FU2 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

6.11 Anaerobic coverage for IAI patients

Section of protocol affected:

Section 5.5.3

Previous text, Section 5.5.3:

Patients randomized to receive the investigator-determined BAT will receive doses based on the investigator's standard of care and the local label recommendation. The preferred BAT options for cUTI are meropenem, imipenem, doripenem, and colistin. The preferred BAT

options for cIAI are meropenem, imipenem, doripenem, tigecycline, and colistin. Colistin does not cover anaerobes, if colistin is the therapy of choice, then the addition of metronidazole should be considered for anaerobic coverage.

Revised text, Section 5.5.3:

Patients randomized to receive the investigator-determined BAT will receive doses based on the investigator's standard of care and the local label recommendation. The preferred BAT options for cUTI are meropenem, imipenem, doripenem, and colistin. The preferred BAT options for cIAI are meropenem, imipenem, doripenem, tigecycline, and colistin. Colistin does not cover anaerobes, if colistin is the therapy of choice, then the addition of metronidazole should be considered for anaerobic coverage **for patients entering with a cIAI diagnosis.**

Reason for Amendment:

To clarify anaerobic coverage for IAI patients.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.12 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 FU 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.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.13 Remove central reader interpretation for 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

6.14 Clarify when body temperature is to be measured during the study

Section of protocol affected:

Section 6.4.10.2

Previous text, Section 6.4.10.2:

Body temperature will be measured using an automated thermometer at the times indicated in Table 1. The patient's body temperature will also be evaluated at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature collection will be recorded.

Revised text, Section 6.4.10.2:

Body temperature will be measured using an automated thermometer at the times indicated in Table 1. The patient's body temperature will also be evaluated at least twice a day **while on**

study therapy (suggested at least 8 hours apart), and the actual time of body temperature collection will be recorded.

Reason for Amendment:

To clarify that twice daily measurement of body temperature is only required during the treatment period, when the patient is receiving study therapy

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.15 Possibly extend recruitment to meet study objectives

Sections of protocol affected:

Synopsis; Section 12.3

Previous text, Synopsis:

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

Revised text, Synopsis:

Recruitment may be extended by a further 100 patients, if insufficient numbers of certain specific organisms or resistance mechanisms are obtained.

Previous text, Section 12.3:

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

Revised text, Section 12.3:

Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal power calculations have been performed for this study; therefore, the sample size is based on practical considerations. Approximately 200 patients per treatment group will be recruited for this trial. This will provide sufficient data that the 95% CI for the cure rate within each treatment group will extend at most approximately 7%

on either side of the observed proportion in the overall summary, or at most 17% on either side for each separate pathogen infecting at least 30 patients, or 13% on either side for pathogens infecting at least 60 patients.

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

Reason for Amendment:

To clarify that recruitment may be extended if there are insufficient numbers of certain specific organisms or resistance mechanisms to meet the study objectives.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6.16 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. CLARIFY IN DEFINITION OF CLINICAL RESPONSE THAT PER-PROTOCOL ANTIBACTERIAL THERAPY IS ALLOWED

Previous text, Section 6.3.1, Table 4

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

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antimicrobial therapy, drainage, or surgical intervention is necessary.
Failure	Patients who meet any 1 of the following criteria will be considered a treatment failure: • Death related to the index infection • Patient who received treatment with additional antibiotics for ongoing symptoms of index infection (including patients prematurely discontinued from study therapy due to an adverse event who require additional antibiotics for the index infection) • Patient previously met criteria for failure (not applicable for EOT). In addition, patients with cIAI will be considered a treatment failure in the following conditions: • Persisting or recurrent infection within the abdomen documented by the findings at re‑intervention either percutaneously or operatively • Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or nonroutine wound care
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response cannot be made • Death where index infection is clearly noncontributory • Circumstances that preclude classification as a cure or failure.

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

Revised text, Section 6.3.1, Table 4

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

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further **antibacterial** therapy **(other than those allowed per protocol)**, drainage, or surgical intervention is necessary.
Failure	Patients who meet any 1 of the following criteria will be considered a treatment failure: • Death related to the index infection • Patient who received treatment with additional antibiotics **(other than those allowed per protocol)** for ongoing symptoms of index infection (including patients prematurely discontinued from study therapy due to an adverse event who require additional antibiotics for the index infection) • Patient previously met criteria for failure (not applicable for EOT). In addition, patients with cIAI will be considered a treatment failure in the following conditions: • Persisting or recurrent infection within the abdomen documented by the findings at re‑intervention either percutaneously or operatively • Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or nonroutine wound care
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response cannot be made • Death where index infection is clearly noncontributory • Circumstances that preclude classification as a cure or failure.

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

Reason for Amendment:

To clarify that patients receiving antibacterial therapy/antibiotics allowed per-protocol will not be defined as failures.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8. UPDATE SAFETY LABORATORY VARIABLES

Section of protocol affected:

Section 6.4.6, Table 7

Previous text, Section 6.4.6, Table 7:

Table 7 Laboratory variables

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

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

Revised text, Section 6.4.6, Table 7:

Table 7 Laboratory variables

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

Note: Local laboratory test results will be used to qualify patients for randomization.

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

Reason for Amendment:

Update the safety laboratory variables collected in the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

9. CHANGED THE MODIFIED INTENT-TO-TREAT (MITT) ANALYSIS POPULATION TO THE MICROBIOLOGICAL MODIFIED INTENT-TO-TREAT (mMITT) ANALYSIS POPULATION

Sections of protocol affected:

Synopsis; Section 6.3.2; Section 12.1.1.1

Previous text, Synopsis

- Primary efficacy outcome variable

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

Revised text, Synopsis

- Primary efficacy outcome variable

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

Previous text, Section 6.3.2:

The per patient and per pathogen microbiological response of CAZ-AVI and BAT in the modified intent-to-treat (MITT) and extended ME analysis sets for patients with the index infection at the EOT, TOC, FU1, and FU2 visits is a secondary outcome.

Revised text, Section 6.3.2:

The per patient and per pathogen microbiological response of CAZ-AVI and BAT in the **microbiological** modified intent-to-treat (mMITT) and extended ME analysis sets for patients with the index infection at the EOT, TOC, FU1, and FU2 visits is a secondary outcome.

Previous text, Section 12.1.1.1:

12.1.1.1 Modified intent-to-treat analysis set

The MITT analysis set includes all patients who:

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

Revised text, Section 12.1.1.1:

12.1.1.1 **Microbiological m**odified intent-to-treat analysis set

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

Reason for Amendment:

Modified the name of the population from MITT to mMITT to clarify that the patient must have a ceftazidime-resistant Gram-negative pathogen to be included in this population, as defined in inclusion criteria 4.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

10. CORRECTION OF APACHE II FORM

Section of protocol affected:

Appendix F APACHE II Score Form

Previous text, Appendix F:

1. Oral Temperature

2. Oxygenation A-aDO_2 or PaO_2 (mm Hg)
   a) FiO_2 ≥0.5:record A-aDO_2 (+2):
   b) FiO_2 <0.5:record only PaO_2 (+3): 200–349

3. Arterial pH – If no ABGs record Serum HCO_3 below (+3): 7.6-6.69

4. Abbreviation: GCS, Glasgow Coma Score.

Revised text, Appendix F:

1. Temperature

2. Oxygenation A-aDO_2 or PaO_2 (mm Hg)
   a) FiO_2 ≥0.5:record A-aDO_2 (+2): **200–349**
   b) FiO_2 <0.5:record only PaO_2 (+3):

3 Arterial pH – If no ABGs record Serum HCO_3 below (+3): 7.6-**7**.69

4. Abbreviations: **ABGs, arterial blood gases; CHP, Chronic Health Points; CV, cardiovascular;** GCS, Glasgow Coma Score; **PHT, pulmonary hypertension**.

Reason for Amendment:

Correct the criteria for the APACHE II Form.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

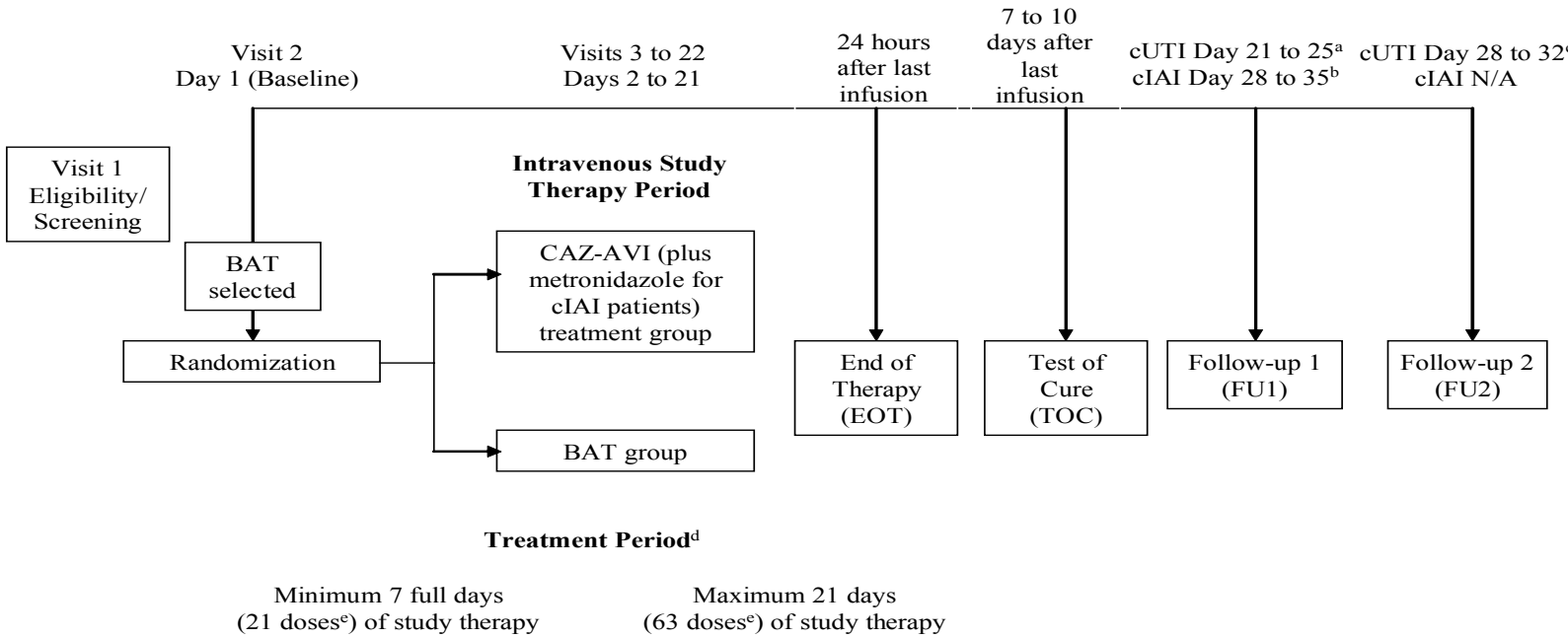
11. CORRECTION OF FIGURE 1

Section of protocol affected:

Section 3.1, Figure 1 – Study flow chart

Previous text, Figure 1:

Figure 1 Study flow chart



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

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

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

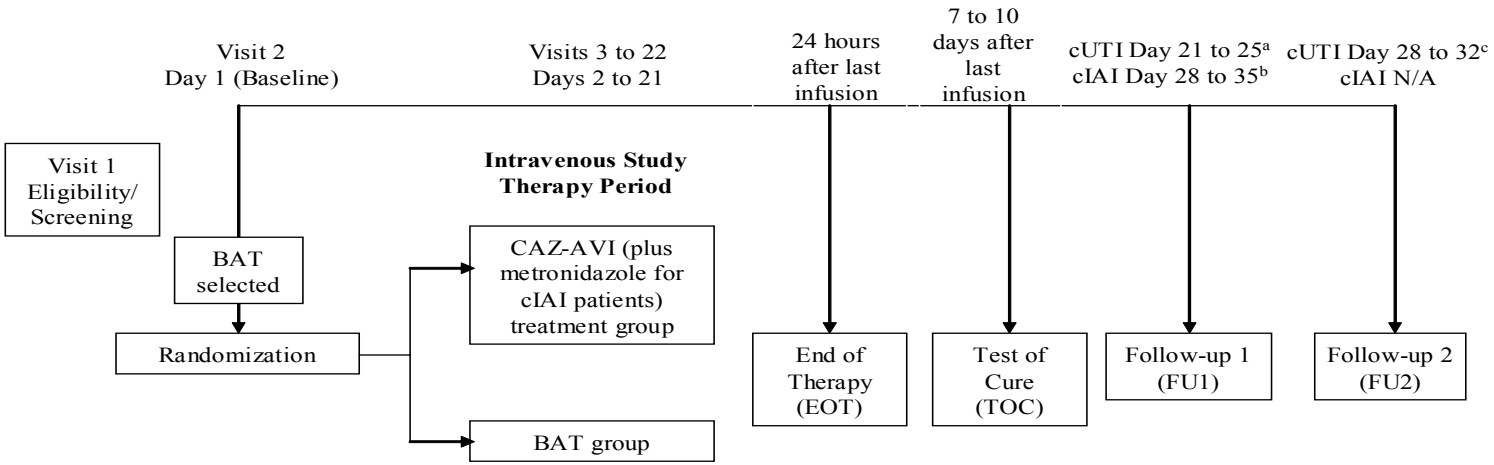
[d] Treatment Period doses are only for patients randomized to CAZ-AVI. Dosing intervals for BAT will be per the local standard of care.

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

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

Revised text, Figure 1:

Figure 1 Study flow chart



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

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

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

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

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

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

Reason for Amendment:

To correct Figure 1 (Study flow chart) to show that patients are to receive study therapy for a minimum of 5 days (15 doses).

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

12. CORRECTION OF STUDY PLAN PER AMENDED ITEMS

Section of protocol affected:

Table 1

Previous text, Table 1:

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

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

	Eligibility/ Screening	**Baseline[a]**	**Treatment Period[b]**				
	Visit 1	**Visit 2**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
Procedures and Assessments	**Days –1 to 0**	**Day 1**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Record radiologic examination if performed (for cIAI patients only)[cc]	X						
Investigator case summary/operative notes/hospital discharge summary (for cIAI patients only)[dd]				X		X	
Mortality assessment			X	X	X	X	X

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

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

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

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

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

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

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

[h] Infection-related signs and symptoms should be assessed daily while the patient is receiving study therapy. For cUTI patients, clinical signs and symptoms include fever or chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, suprapubic pain, and nausea or vomiting. For cIAI patients, clinical signs and symptoms include abdominal signs and symptoms plus abdominal and wound examinations.

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

[j] A digital ECG must be performed prior to dosing on Day 1 (Baseline) and on Day 3 at the end of study infusion CAZ-AVI and BAT). The ECG measurement should be performed in triplicate. If indicated, additional ECG assessments can be made at the discretion of the investigator; these assessments should be entered as an

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

unscheduled assessment. If any significant increase of QTcF (ie, increase from Baseline of ≥30 ms or QTcF >460 ms) is observed, then additional ECG assessments must be performed (see Section 6.4.9).

k Patients will be monitored for nonserious adverse events and serious adverse events from the time when informed consent is obtained at Screening up to and including the FU visits. Should a patient experience significant diarrhea during or after study therapy, the investigator should consider obtaining a stool sample and testing for *C. difficile* toxin.

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

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

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

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

p For cIAI patients with surgical specimens collected on or after the Baseline visit, both aerobic and anaerobic cultures should be performed on specimens collected from the site of abdominal infection and on specimens collected from other clinically relevant intra-abdominal sites.

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

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

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

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

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

v Investigator to choose BAT (including dose and dose interval) based on local susceptibility testing and document in the source documents prior to randomizing the patient. If a compound other than 1 of the 4 preferred options for cUTI (meropenem, imipenem, doripenem, and colistin) or 1 of the 5 preferred options for cIAI (meropenem, imipenem, doripenem, tigecycline, and colistin) is chosen, or more than 1 antibacterial is chosen to be co-administered, the investigator must document in the source documents the reason a nonpreferred therapy was chosen.

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

x Plasma samples for pharmacokinetic assessments will be collected on Day 3 following a dose administration that is convenient for plasma sample collection at the following time points: anytime within 15 minutes prior to or after stopping any infusion, anytime between 30 minutes and 90 minutes after stopping any infusion, and

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

anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping any infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient.

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

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

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

[bb] If necessary for patients receiving CAZ-AVI, a 1-time dosing interval adjustment can be made after the first dose of study therapy to create a suitable dosing schedule. For patients with normal renal function or with mild renal impairment (CrCl >50 mL/min), the dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose. If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. See Section 5.5.2.2 for additional guidance for patients with moderate or severe renal impairment (CrCl 50 to 6 mL/min).

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

[dd] For cIAI patients only, all documentation including surgical reports and imaging studies for any surgical intervention performed during the study must be submitted as soon as it becomes available. For those patients whose surgical intervention was percutaneous abscess drainage, the interventional radiology report serves as the operative note. Any follow-up films used to assess outcome should also be submitted as they become available.

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

Revised Text: Table 1 Study plan

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

Revised Text: Table 1 Study plan

	Eligibility/ Screening	Treatment Period[a]					
	Visit 1	**Visit 2**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
Procedures and Assessments	**Days –1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Blood cultures[n]		X[o]	**If screening blood cultures are positive, repeat at least every 3 days until negative. Blood cultures may also be obtained as clinically indicated**				
Intra-abdominal culture (cIAI patients only) p		As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Quantitative urine culture (cUTI patients only)[q]		X		X	X	X	X
Urine for microscopic white blood cell count (cUTI patients only)[r]		X					
Blood and urine for safety analysis[s]	X	X	Every 3 days	X	X	X	X
Estimate creatinine clearance[t]	X	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
Serum β-hCG for **females** of childbearing potential[u]	X					X (for cIAI patients)	X (for cUTI patients)
Determination of Best Available Therapy prior to randomization[v]		X					
Randomization		X[w]					
Pharmacokinetic sample[x]			X				
Description of operative procedures (cIAI patients only)[y]	As available	As available	As available	As available	As available	As available	
Administer study therapy[z]		X	X				
Clinical response assessment				X	X	X	X

Revised Text: Table 1 Study plan

	Eligibility/ Screening	Treatment Period[a]					
	Visit 1	Visit 2	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
Procedures and Assessments	**Days –1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Record radiologic examination if performed (for cIAI patients only)[aa]	X						
Investigator case summary/operative notes/hospital discharge summary (for cIAI patients only)[bb]				X		X	
Mortality assessment			X	X	X	X	X

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

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

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

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

e The overall consent covers sending the qualifying microbiological isolate obtained per routine standard of care to the central microbiology **laboratory** for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics.

f History will include surgical history for cIAI patients.

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

h Infection-related signs and symptoms should be assessed daily while the patient is receiving study therapy. For cUTI patients, clinical signs and symptoms include fever or chills, flank pain, **suprapubic and** costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, and nausea or vomiting. For cIAI patients, clinical signs and symptoms include abdominal signs and symptoms plus abdominal and wound examinations.

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

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

[k] Patients will be monitored for nonserious adverse events and serious adverse events from the time when informed consent is obtained at Screening up to and including the FU visits. Should a patient experience significant diarrhea during or after study therapy, the investigator should consider obtaining a stool sample and testing for C. difficile toxin.

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

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

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

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

[p] For cIAI patients with surgical specimens collected on or after the Baseline visit, both aerobic and anaerobic cultures should be performed on specimens collected from the site of abdominal infection and on specimens collected from other clinically relevant intra-abdominal sites.

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

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

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

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

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

[v] Investigator to choose BAT (including dose and dose interval) based on local susceptibility testing and document in the source documents prior to randomizing the patient. If a compound other than 1 of the 4 preferred options for cUTI (meropenem, imipenem, doripenem, and colistin) or 1 of the 5 preferred options for cIAI (meropenem, imipenem, doripenem, tigecycline, and colistin) is chosen, or more than 1 antibacterial is chosen to be

co-administered, the investigator must document in the source documents the reason a nonpreferred therapy was chosen.

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

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

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

[z] If necessary for patients receiving CAZ-AVI, a 1-time dosing interval adjustment can be made after the first dose of study therapy to create a suitable dosing schedule. For patients with normal renal function or with mild renal impairment (CrCl >50 mL/min), the dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose. If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. See Section 5.5.2.2 for additional guidance for patients with moderate or severe renal impairment (CrCl 50 to 6 mL/min).

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

[bb] For cIAI patients only, all documentation including surgical reports and imaging studies for any surgical intervention performed during the study must be submitted as soon as it becomes available. For those patients whose surgical intervention was percutaneous abscess drainage, the interventional radiology report serves as the operative note. Any follow-up films used to assess outcome should also be submitted as they become available.

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

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Reason for Amendment:

Revision of Table 1 to reflect changes to protocol (removal of genetic and biomarker sampling; clarification of pregnancy testing; Coombs test; removal home health care).

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

13. ADMINISTRATIVE CHANGES

- Edits to the List of Abbreviations for items added per amendment
- Changed MITT to mMITT throughout the document per revision
- Changed central microbiology vendor to central microbiology laboratory
- Changed central reference laboratory to central microbiology laboratory in appropriate sections
- Editorial, formatting, and style corrections