Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Ceftazidime avibactam(CAZ-AVI)
Study Code	D4280C00018
Date	[redacted]
Protocol Dated	[redacted]

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime Avibactam (CAZ-AVI) Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This amendment affects all centres in the study.

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

1. Added name, address, and telephone number of international coordinating investigator
2. Removal of genetic and biomarker sampling from study design
3. Modification and clarification of analysis sets
4. Refinement of entry criteria with respect to abdominal wounds, and septic shock
5. Addition of detail on presentation of PK results
6. Revised definitions of “superinfection” and “new infection”

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

8. Additional clarifications for concomitant antibiotic therapy, follow-up of patients who discontinue the study therapy, staged abdominal repair, removal of duplicate paragraph in Section 5.5.2.3 , study participation by those who fail to meet entry criteria after study initiation, use of clinical information obtained as part of standard of care before the informed consent is signed, determining APACHE II score based on most recent parameters available, collection of blood for Coombs test and culture, definition of "persistence with increasing MIC", revised blood volume collection per amended items, and the purpose and use of the PREGREP and PREGOUT modules

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

10. Administrative changes

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

1. CHANGES REQUIRED FOR INTERNATIONAL COORDINATING INVESTIGATOR

Section of protocol affected:

International Coordinating Investigator or Principal Investigator or National Co-ordinating Investigator

Previous text:

International Coordinating Investigator or Principal Investigator or National Co-ordinating Investigator

[redacted] [redacted] (To be confirmed)

Revised text:

International Coordinating Investigator

[redacted]

[redacted]

Reason for Amendment:

[redacted] was identified as the international coordinating investigator for this study

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

2. CHANGES REQUIRED FOR REMOVAL OF GENETIC AND BIOMARKER SAMPLING FROM STUDY DESIGN

Section of protocol affected:

Protocol synopsis, Exploratory objectives & Section 2.3; List of Appendices; Section 4.1, Inclusion criteria 5; Section 4.2, Exclusion criteria 31 and 32; Section 6.2.2, Item 9 and 10; Section 6.2.3, item 11; Section 6.2.4, item 10; Section 6.3.8; Section 6.3.9; Table 9; Section 6.7; Section 6.8; Section 7.2.2; Section 7.5; Section 10; Section 11.5; Appendix D

Previous text,Protocol Synopsis Exploratory objectives & Section 2.3:

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

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

Revised text, Protocol Synopsis Exploratory objectives & 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** Calculation of Estimated Creatinine Clearance

Appendix **E** APACHE II Classification System

Appendix **F** Actions Required in Cases of Combined Increase of Alanine or Aspartate Aminotransferase and Total Bilirubin – Hy's Law

Previous text, Section 4.1, Inclusion criteria 5:

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

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

Revised text, Section 4.1, Inclusion criterion 5:

Item deleted.

Previous text, Section 4.2, Exclusion criteria 31 and 32:

In addition, the following are considered criteria for exclusion from the genetic research (not applicable in China):

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

32. Patient has previous allogenic bone marrow transplant.

Revised text, Section 4.2, Exclusion criteria 31 and 32:

Item deleted.

Previous Text, Section 6.2.2, Item 9 and 10

9. Collecting blood samples for pharmacogenetic research (PGx) analysis (only from patients who signed the separate PGx informed consent and will receive IV study therapy) (not applicable in China)

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

Revised Text, Section 6.2.2, Item 9 and 10

Items deleted.

Previous Text, Section 6.2.3, Item 11:

11. Obtaining a blood sample for biomarker analysis 24 hours after the beginning of IV study therapy infusion (only from those patients consenting to biomarker sample collection/analysis)

Revised Text, Section 6.2.3, Item 11:

Item deleted.

Previous Text, Section 6.2.4, Item 10:

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

Revised Text, Section 6.2.4, Item 10:

Item deleted.

Previous text, Section 6.3.8 and Section 6.3.9

6.3.8 Pharmacogenetic outcome variables (not applicable in China):

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

6.3.9 Biomarker outcome variables

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

Revised text, Section 6.3.8 and Section 6.3.9

6.3.8 Pharmacogenetic outcome variables

No longer applicable as of Amendment 1..

6.3.9 Biomarker outcome variables

No longer applicable as of Amendment 1.

Previous text, Table 9:

Biomarker samples (banked specimen)

Revised text, Table 9:

Item deleted from table.

Previous text, Section 6.7 and Section 6.8

6.7 Pharmacogenetics (not applicable in China)

For details of PGx sampling, see Appendix D.

Blood samples for PGx sampling 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.

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 the [redacted] to ensure their arrival during working hours. A requisition sheet should accompany the shipment that details the study number, center number, enrollment number, randomization number, date of sample collection, and unique identifier for each of the samples in the shipment. Refer to the laboratory manual for detailed instructions for sample processing and shipping.

6.8.2 Summary of biomarker assessments and analysis

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

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

Revised text, Section 6.7 and Section 6.8

6.7 Pharmacogenetics

No longer applicable as of Amendment 1.

6.8 Collection of samples for biomarker research

No longer applicable as of Amendment 1.

Previous text, Section 7.2.2

7.2.2 Pharmacogenetic samples (not applicable in China)

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 as of Amendment 1.

Previous text, Section 7.5

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research. As collection of the

biological samples (for the genetic and biomarker research) is an optional part of the study, the patient may continue in the study.

The investigator:

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

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

Revised text, Section 7.5

7.5 Withdrawal of informed consent for donated biological samples

No longer applicable as of Amendment 1.

Previous text, Section 10

Any genotype data generated in this study will be stored in the AstraZeneca genotyping [redacted] database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze samples.

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

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

Revised text, Section 10

Text deleted.

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 as of Amendment 1.

Previous text:

Appendix D, Pharmacogenetic Research

Revised text:

Appendix deleted.

Reason for Amendment:

To remove collection of optional biomarker and genetic samples from the study

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3. CHANGES REQUIRED FOR MODIFICATION AND CLARIFICATION OF ANALYSIS SETS

3.1 Addition of extended ME analysis set

Section of protocol affected:

Protocol synopsis; Section 6.3.4; Section 12.1.1.4

Previous text, synopsis and Section 6.3.4:

Secondary objectives

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to clinical cure at the end of treatment (EOT) with intravenous (IV) study therapy, TOC, and at the late follow-up (LFU) in patients who are microbiologically evaluable (ME)

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to the clinical cure at EOT with IV study therapy, TOC, and at the LFU in patients who have at least 1 identified pathogen (mMITT)

- To determine the efficacy of CAZ-AVI plus metronidazole compared to meropenem with respect to the clinical cure at EOT, and LFU in patients who are CE

- To determine the per-patient and per-pathogen microbiologic response of CAZ-AVI plus metronidazole compared to meropenem at EOT, TOC, and LFU in patients in mMITT and patients who are ME

- To evaluate the efficacy of CAZ-AVI plus metronidazole versus meropenem in pathogens resistant to ceftazidime

- To compare the time to first defervescence of CAZ-AVI plus metronidazole versus meropenem in patients who are on IV study therapy and who have fever at study entry both in patients who are CE and in patients who are ME

- To evaluate the safety and tolerability profile of CAZ-AVI plus metronidazole compared to meropenem in the treatment of patients with cIAI in the safety analysis set

- To evaluate the pharmacokinetics of the individual components of CAZ-AVI (avibactam and ceftazidime) in patients with cIAI

- To evaluate CAZ-AVI exposure and the antimicrobial response relationship in patients with cIAI.

Revised text, synopsis and Section 6.3.4:

The secondary efficacy outcome variables include the following:

- Proportion of patients with clinical cure at the EOT, TOC and LFU visits in the ME**, extended ME** and the mMITT analysis sets

- Proportion of patients with clinical cure at EOT and LFU in the CE analysis set

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

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

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

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

- Proportion of patients with a favorable per pathogen microbiological response at the TOC visit for patients infected with ceftazidime-resistant pathogens in the mMITT, ME **and extended ME** analysis sets

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

Previous text, Synopsis and Section 12.1.1.4:

None

Revised text, Synopsis and Section 12.1.1.4:

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

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

  - **Included in a subset of CE patients in EOT, TOC, or LFU, respectively.**

  - **Had at least 1 etiologic pathogen in the initial/prestudy culture regardless of susceptibility.**

Reason for Amendment:

To provide a microbiological evaluable population that removes the requirement for at least 1 pathogen that is susceptible to both study arms. This population may be useful for determining the microbiological breakpoints for CAZ-AVI.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.2 Definition of the mMITT analysis set

Sections of protocol affected:

Synopsis; Section 12.1.1.2

Previous text, Synopsis and Section 12.1.1.2:

- Microbiological modified intent-to-treat analysis set

  The mMITT analysis set includes all patients who:

  - Met the disease definition of cIAI and have at least 1 etiologic pathogen identified at study entry regardless of susceptibility

Revised text, Synopsis and Section 12.1.1.2:

- Microbiological modified intent-to-treat analysis set

  The mMITT analysis set includes all patients who:

  - Met the disease definition of cIAI and have at least 1 **Gram negative** pathogen identified at study entry **(**regardless of **isolate** susceptibili**ties). Patients with a bacterial species typically not expected to respond to both study drugs (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.) will be excluded**.

Reason for Amendment:

To exclude patients with a bacterial species that is typically unresponsive to both study treatments from the mMITT analysis set.

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3.3 Cross-tabulation for the mMITT, ME, and extended ME analysis sets and summary analyses for per-pathogen response and clinical cure at TOC

Section of protocol affected:

Section 12.2.2

Previous text, Section 12.2.2:

The definitions for the outcomes are presented in Section 6.3. The clinical cure analyses will be presented for the mMITT, ME and CE analysis sets. The analysis for clinical cure at TOC in the CE analysis set will also be presented by subgroups according to baseline characteristics as for the primary efficacy variable. The microbiologic response analyses will be presented for the mMITT and ME analysis sets. A clinical response per-pathogen will also be presented for the mMITT and ME analysis sets. If a patient has more than 1 unique baseline pathogen

identified and has a response of clinical cure, then the patient's clinical response will be a clinical cure for all of the baseline pathogens. Conversely, if the patient is a clinical failure, the patient's clinical response will be clinical failure for all of the baseline pathogens.

Revised text, Section 12.2.2:

The definitions for the outcomes are presented in Section 6.3. The clinical cure analyses will be presented for the mMITT, ME, **extended ME,** and CE analysis sets. The microbiologic response analyses will be presented for the mMITT, ME, and **extended ME** analysis sets. **A cross-tabulation of** clinical response **by baseline** pathogens will also be presented for the mMITT, ME, and **extended ME** analysis sets. If a patient has more than 1 unique baseline pathogen identified and has a response of clinical cure, then the patient's clinical response will be a clinical cure for all of the baseline pathogens. Conversely, if the patient is a clinical failure, the patient's clinical response will be clinical failure for all of the baseline pathogens.

Additionally, the per-pathogen response at TOC and clinical cure at TOC will be summarized by treatment group for patients whose reason for exclusion from the ME analysis set is that the patient did not have at least 1 Gram negative pathogen susceptible to both arms but did have 1 Gram negative pathogen susceptible to the treatment they received.

Reason for Amendment:

To clarify that the clinical response by baseline pathogen summary will be a cross-tabulation and to add an additional summary of the ME analysis set where susceptibility is based on the treatment they received rather than both arms.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

4. CHANGES REQUIRED FOR REFINEMENT OF ENTRY CRITERIA

4.1 Abdominal wounds

Section of protocol affected:

Section 4.1, Inclusion criterion 4; Section 4.2, Exclusion criterion 17; Figure 2; Section 6.2.4; Section 6.2.5; Section 6.4.8

Previous text, Section 4.1, Inclusion criterion 4:

4. EITHER:

Intra-operative/post-operative enrollment with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic

surgery. Specimens from the surgical intervention must be sent for culture. The patient must have 1 of the following diagnoses:

Revised text, Section 4.1, Inclusion criterion 4:

4. EITHER:

Intra-operative/post-operative enrollment with visual confirmation (presence of pus within the abdominal cavity) of an intra abdominal infection associated with peritonitis. Surgical intervention includes open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. Specimens from the surgical intervention must be sent for culture. **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.** The patient **has at least 1** of the following diagnose**d during the surgical intervention**:

Previous text, Section 4.2, Exclusion criterion 16 (formerly Exclusion criterion 17):

17. Patient has received systemic antibacterial agents within the 72-hour period prior to study entry, unless either of the following pertains:

    (a) Patient has a new infection (not considered a treatment failure) and both of the following are met:

    - Patient received no more than 24 hours of total prior antibiotic therapy
    - Patient received ≤1 dose of a treatment regimen post operatively and antibiotics were not received more than 6 hours post procedure (defined as 6 hours from the time of skin closure for surgical procedures)

Revised text, Exclusion criterion 16 (formerly Exclusion criterion 17):

16. Patient has received systemic antibacterial agents within the 72-hour period pristudy entry, unless either of the following pertains:

    (a) Patient has a new infection (not considered a treatment failure) and both of the following are met:

    - Patient received no more than 24 hours of total prior antibiotic therapy
    - Patient received ≤1 dose of a treatment regimen postoperatively and antibiotics were not received more than 6 hours post procedure. (defined as 6 hours from the time of skin closure **or, if skin closure is not performed, 6 hours from the time the wound dressing is applied).**

Previous text, Figure 2:

None

Revised text, Figure 2:

Note: 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. The use of negative pressure wound therapy in an open skin wound is permissible.

Previous text, Section 6.2.4, Items 2 and 3, and Section 6.2.5, Items 2 and 3:

2. Performing complete physical examination as defined in Section 6.4.8.

3. Assessing abdominal signs and symptoms plus abdominal and wound examinations postoperatively.

Revised text, Section 6.2.4, Items 2 and 3, and Section 6.2.5, Items 2 and 3:

2. Performing complete physical examination, **to include** assessing abdominal signs and symptoms plus abdominal and wound examinations postoperatively as defined in Section 6.4.8.

Previous text, Section 6.4.8:

The timing of individual examinations is indicated in Table 1.

A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen including wound examination, musculoskeletal, and neurological systems.

If pathologic findings emerge or worsen from the baseline physical examination, a nonserious AE page of the eCRF should be completed for these findings. If the findings meet the criteria for an SAE, procedures for reporting such events should be followed (refer to Section 6.4.5).

Height and weight will be measured at the Screening visit. Body mass index will be calculated. After the screening visit, weight should be measured as clinically indicated.

A detailed abdominal assessment will be performed at Screening, Day 1 (Baseline), daily during treatment with IV study therapy, at the EOT, TOC, and LFU visits.

Revised text, Section 6.4.8:

The timing of individual examinations is indicated in Table 1.

A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen including wound examination, musculoskeletal, and neurological systems. **The use of negative pressure wound therapy in an open skin wound is permissible. Surgical wound examination should occur daily even**

if inspection is limited by the presence of a negative pressure wound therapy device. A thorough wound evaluation should occur when a full dressing change is performed.

Assessment of abdominal signs and symptoms plus postoperative abdominal and wound examinations (infection-related focused physical examination) will be conducted at Screening, Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, and LFU visits as outlined in the study plan (Table 1).

If pathologic findings emerge or worsen from the baseline physical examination, a nonserious AE page of the eCRF should be completed for these findings. If the findings meet the criteria for an SAE, procedures for reporting such events should be followed (refer to Section 6.4.5).

Height and weight will be measured at the Screening visit. Body mass index will be calculated. After the screening visit, weight should be measured as clinically indicated.

Reason for Amendment:

To clarify that the skin incision may be left open for purposes of wound management as long as complete fascial closure is accomplished, and to explain the assessment of abdominal signs and symptoms and abdominal and wound examinations with respect to frequency and the use of negative pressure wound therapy

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

4.2 Septic shock

Sections of protocol affected:

Section 4.2 Exclusion criteria 7 and Exclusion criteria 14 (formerly 15)

Previous text, Exclusion criteria 7 and Exclusion criteria 14 (formerly 15)

7. Patient has evidence of sepsis with shock not responding to IV fluid challenge or anticipated to require the administration of vasopressors for >12 hours

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

Revised text, 4.2 Exclusion criteria 7 and Exclusion criteria 14 (formerly 15)

7. **Item 7 deleted.**

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

Reason for Amendment:

The former wording has been deleted due to feedback from medical experts that it is imprecise, and it will be not possible for clinical investigators to accurately predict which patients are anticipated to require the administration of vasopressors for >12 hours. Instead, new wording has been added to exclusion criterion 14 (formerly exclusion criterion 15) to clarify excluding patients who have a rapidly progressive or terminal illness, including septic shock that is associated with a high risk of mortality. The added language provides clarification that septic shock that is associated with a high risk of mortality is considered to be a rapidly progressive illness.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

5. CHANGES REQUIRED FOR PRESENTATION OF PK RESULTS

Section of protocol affected:

Protocol Synopsis, Pharmacokinetic analysis; Section 11.3

Previous text, Synopsis:

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

Revised text, Synopsis:

Descriptive statistics of individual plasma concentrations for ceftazidime and avibactam will be summarized and listed according to the nominal sampling windows after dosing for the PK analysis set and will be reported in the CSR. **Ceftazidime and avibactam compartmental PK parameters derived from population PK analysis and potential**

PK/PD relationships will be reported separately. Individual compartmental PK parameters of avibactam and ceftazidime for cIAI patients will be derived via a population modeling approach.

The avibactam and ceftazidime concentration, patient demographic, and disease status data, will be combined with the data from appropriate previous clinical studies for the population PK analysis. Individual compartmental PK parameters for patients with avibactam and ceftazidime plasma concentration data available will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters, such as maximum concentration (C_{max}), minimum concentration, area under the plasma concentration-time curve at steady state, and terminal half-life will be derived from the predicted avibactam and ceftazidime concentration time courses. The appropriate avibactam and ceftazidime exposure outcome variables predicted by the population PK modeling will be used for a PK/PD modeling for appropriate microbiological or clinical cure outcome variables.

Previous text, Section 11.3:

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

Revised text, Section 11.3:

Descriptive statistics of individual plasma concentrations for ceftazidime and avibactam will be summarized and listed according to the nominal sampling windows after dosing for the PK analysis set and will be reported in the CSR. **Ceftazidime and avibactam compartmental PK parameters derived from population PK analysis, and potential PK/PD relationships will be reported separately.** The pharmacokinetics of avibactam and ceftazidime will be assessed by population PK modeling. The actual dosing and plasma sampling times will be used in the population PK modeling.

Reason for Amendment:

The revised wording provides greater clarity and more detail on how the PK results will be presented.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6. CHANGES REQUIRED FOR DEFINITION OF SUPERINFECTION AND NEW INFECTION

Section of protocol affected:

Section 6.3.2.5, Table 8

Previous text, Table 8:

Table 8 Emergent infections

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

Revised text, Table 8:

Table 8 Emergent infections

Emergent infection	Definition
Superinfection	**Isolation** of **a** new pathogen **or pathogens (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**
New infection	**Isolation** of **a** new pathogen **or pathogens (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**

Reason for Amendment:

To revise the definition of superinfection and new infection so that they relate specifically to intra-abdominal cultures only

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7. CHNAGES REQUIRED FOR CORRECTION OF APACHE II FORM

Section of protocol affected:

Appendix F APACHE II Score Form

Previous text, Appendix F:

1. Oral Temperature (°C)

4. Respiratory rate (non-ventilated or ventilated), +4 Low Abnormal Range: <5

5. Oxygenation A-aDO_2 or PaO_2 (mmHg)

   a) FiO_2 >0.5:record A-aDO_2

7. Serum Sodium, 0 [normal range]: 130-139

8. Serum Potassium, +1 High Abnormal Range: 5.6-5.9

* Serum HCO3 (venous-mMol/L)

   Not preferred, use if no ABGs, +4 High Abnormal Range: <52

Revised text, Appendix E:

1. Temperature (°C)

4. Respiratory rate (non-ventilated or ventilated), +4 Low Abnormal Range: **≤**5

5. Oxygenation A-aDO_2 or PaO_2 (m**m H**g)

   a) FiO_2 **≥**0.5:record A-aDO_2

7. Serum Sodium **(mmol/L)**, 0 [normal range]: 130-1**4**9

8. Serum Potassium **(mmol/L)**, +1 High Abnormal Range: 5.**5**-5.9

* Serum HCO_3 (venous-m**m**ol/L)

   Not preferred, use if no ABGs, +4 High Abnormal Range: **≥**52

Reason for Amendment:

To correct physiologic variable and reference range errors on the APACHE II Score Form.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8. CHANGES REQUIRED FOR CLARIFICATIONS

8.1 Concomitant antibiotic therapy

Section of protocol affected:

Synopsis and Section 12.1.1.1

Previous text, Synopsis and Section 12.1.1.1:

The CE analysis set at the EOT, TOC, and LFU visits, respectively, includes all patients meeting the following criteria:

> Did not receive concomitant antibiotic therapy with potential activity against the baseline pathogen between the time of randomization and the time of the EOT, TOC, or LFU culture, respectively, except for protocol allowed antibiotics for the coverage of *Enterococcus* spp. and methicillin-resistant *Staphylococcus aureus*. This does not include patients who have failed and require additional antibiotic therapy.

Revised text, Synopsis and Section 12.1.1.1:

The CE analysis set at the EOT, TOC, and LFU visits, respectively, includes all patients meeting the following criteria:

> Did not receive concomitant antibiotic therapy with potential activity against **any of** the baseline pathogen**s** between the time of randomization and the time of the EOT, TOC, or LFU culture, respectively, except for protocol allowed antibiotics for the coverage of *Enterococcus* spp. and methicillin-resistant *Staphylococcus aureus*. This does not include patients who have failed and require additional antibiotic therapy. **Topical antibacterials and antifungals are permitted except that they may not be applied to the surgical site.**

Reason for Amendment:

To clarify that patients who receive topical antibacterials and antifungals on sites other than the surgical site will be included in the CE analysis set.

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.2 Follow-up for patients who discontinue the study therapy or have a change in fulfillment of entry criteria

Sections of protocol affected:

Section 4, Patient Selection Criteria; Section 5.3

Previous text, Section 4, Patient Selection Criteria:

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 or receive IV study therapy. There can be no exceptions to this rule.

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the investigator should inform the AstraZeneca physician immediately, (see Section 5.3). The AstraZeneca physician is to ensure all such contacts are appropriately documented.

Revised text, Section 4, Patient Selection Criteria:

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

Where patients **who** do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients **who** subsequently fail to meet the study criteria **after** initiation, the investigator should inform the AstraZeneca physician immediately, (see Section 5.3). **The patient may continue to receive study therapy or be discontinued from study therapy at the investigator's discretion.** The AstraZeneca physician is to ensure **that** all such contacts are appropriately documented.

Previous text, Section 5.3, Procedures for handling patients incorrectly enrolled or randomized:

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

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

Revised text, Section 5.3, Procedures for handling patients incorrectly enrolled or randomized:

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There will be no exceptions to this rule. **Patients discontinued from the study therapy should be followed for safety.**

Where patients **who** do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria **after initiation,** the investigator should inform the AstraZeneca physician immediately. **The patient may continue to receive study therapy or be discontinued from study therapy at the investigator's discretion.** The AstraZeneca physician is to ensure **that** all such contacts are appropriately documented.

Reason for Amendment:

To clarify that patients discontinued from the study therapy be followed for safety, and that study participation by those who fail to meet criteria after study initiation is at the discretion of the investigator.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.3 Clarification on staged abdominal repair

Section of protocol affected:

Section 4.2, Exclusion criteria 4

Previous text:

Patient's surgery will include staged abdominal repair, or "open abdomen" technique, or marsupialization

Revised text:

Patient whose surgery will include staged abdominal repair, or "open abdomen" technique, or marsupialization. **This criterion is intended to exclude patients in whom the abdomen is left open, particularly those for whom reoperation is planned**

Reason for Amendment:

The expanded wording provides clarification that patients undergoing a staged abdominal repair should be excluded from entering the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.4 Removal of duplicate paragraph

Section of protocol affected:

Section 5.5.2.3 Dose regimen adjustments for patients whose CrCl drops below 31 mL/min while on IV study therapy

Previous text:

If subsequent to study entry and while still on IV study therapy, a patient's estimated creatinine clearance falls below the threshold for study inclusion (ie, estimated creatinine clearance falls below 31 mL/min), an immediate retest should be performed with results obtained within 4 hours. If the results of the retest confirm that creatinine clearance has fallen below the threshold for study entry and the investigator considers that the patient should continue therapy, they should inform the dispensing pharmacist immediately. The pharmacist should then provide the appropriate dose adjustments as outlined in the handling instructions, to allow the patient to continue blinded study therapy.

Revised text:

The paragraph was deleted.

Reason for Amendment:

Remove the duplicate paragraph.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.5 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 (Table 1) and discussed by visit in Sections 6.2.1 to 6.2.6.

Revised text, Section 6.2:

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

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

8.6 Basis of APACHE II score

Section of protocol affected:

Section 6.2.1

Previous text, Section 6.2.1, Item 10:

10. Determining APACHE II score (see Appendix F).

Revised text, Section 6.2.1, Item 10:

10. Determining APACHE II score (see Appendix **E**) **using the most recent parameters available**.

Reason for Amendment:

To clarify basis for APACHE II scoring.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.7 Collection of blood for Coombs test and culture

8.7.1 Coombs test

Section of protocol affected:

Section 6.2.2, Item 6; Section 6.2.4, Item 8 (formerly Item 9); and Section 6.2.5, Item 7 (formerly Item 8)

Previous text, Section 6.2.2, Item 6:

6. Obtaining a blood sample for blood cultures if clinically indicated.

Revised text, Section 6.2.2, Item 6:

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

Previous text, Section 6.2.4, Item 8 (formerly Item 9) and Section 6.2.5, Item 7 (formerly Item 8):

Obtaining blood and urine samples for safety analysis (central reference laboratory).

Revised text, Section 6.2.4, Item 8 (formerly Item 9) and Section 6.2.5, Item 7 (formerly Item 8):

Obtaining blood and urine samples for safety analysis (central reference laboratory) **and direct Coombs test (performed locally)**.

Reason for Amendment:

To add Coombs test to text listing of assessments

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.7.2 Collection of blood for culture

Section of protocol affected:

Section 6.2.3, Item 7; Section 6.2.4, Item 7 (formerly Item 8); Section 6.2.5, Item 6 (formerly Item 7), and Section 6.2.6, Item 6 (formerly Item 7):

Previous text, Section 6.2.3, Item 7:

7. Obtaining a blood sample for blood cultures if previous blood cultures were positive or if clinically indicated.

Revised text, Section 6.2.3, Item 7:

7. If **a** previous blood culture **result was** positive, **repeat samples must be collected at least every 3 days** until **clearance of bacteremia has been documented. Blood cultures may also be obtained as** clinically indicated.

Previous text, Section 6.2.4, Item 7(formerly Item 8):

8. Obtaining blood samples for blood cultures if previous blood cultures were positive or if clinically indicated.

Revised text, Section 6.2.4, Item 7(formerly Item 8):

7. If repeat blood **culture results have not been finalized negative by the time of the EOT visit, a set of repeat** blood cultures **should be obtained at the EOT visit**.

Previous text, Section 6.2.5, Item 6 (formerly Item 7) and Section 6.2.6, Item 6 (formerly Item 7):

7. Obtaining blood samples for blood cultures if previous blood cultures were positive or if clinically indicated.

Revised text, Section 6.2.5, Item 6 (formerly Item 7) and Section 6.2.6, Item 6 (formerly Item 7):

6. If **a** previous blood culture **result was** positive, **repeat samples must be collected at least every 3 days** until **clearance of bacteremia has been documented. Blood cultures may also be obtained as** clinically indicated.

Reason for Amendment:

To clarify collection of blood cultures

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.8 Definition of clinical cure

Section of protocol affected:

Section 6.3, Table 6

Previous text, Table 6:

Table 6 Definitions of clinical response at the EOT, TOC, and LFU 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. Note: Patients who receive coverage for MRSA or *Enterococcus,* as allowed per protocol, can still have a response definition of cure.

Revised text, Table 6:

Table 6 Definitions of clinical response at the EOT, TOC, and LFU visits

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further anti**bacterial** therapy, drainage, or surgical intervention is necessary. Note: Patients who receive coverage for MRSA or *Enterococcus* spp.*,* as allowed per protocol, can still have a response definition of cure.

Reason for Amendment:

Clarification of the definition of clinical cure to make it clear that no further therapy refers to only antibacterial therapy and not other forms of antimicrobial therapy eg. antifungals.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.9 Clarification of "persistence with increasing MIC"

Section of protocol affected:

Table 7

Previous text:

Persistence with increasing MIC	Continued presence of the causative organism in a culture of the intra-abdominal abscess, peritonitis, or surgical wound infection obtained during or upon completion of treatment with IV study therapy, and the pathogen that was susceptible to IV study therapy pre-treatment displays a ≥4-fold higher MIC to IV study therapy after treatment with IV study therapy.

Revised text:

Persistence with increasing MIC	Continued presence of the causative organism in a culture of the intra-abdominal abscess, peritonitis, or surgical wound infection obtained during or upon completion of treatment with IV study therapy, and displays a ≥4-fold higher MIC to IV study therapy after treatment with IV study therapy.

Reason for Amendment:

The revised wording clarifies the definition of "persistence with increasing MIC" removing the need for the pathogen to be susceptible to IV study treatment.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.10 Volume of blood

Section of protocol affected:

Section 7.1, Table 10

Previous text, Table 10:

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry	5	6	30
	Hematology	3	6	18
	Coagulation	4.5	5	22.5
Pharmacokinetic sample		two 4-mL tubes	3	24
Biomarker sample		10	4	40
Blood culture		20	4[a]	80
Pharmacogenetic sample		10	1	10
Total				224.5

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

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

Revised text, Table 10:

Table 10 Volume of blood to be drawn from each patient

Assessment		**Sample volume (mL)**	**Number of samples**	**Total volume (mL)**
Safety	Clinical chemistry	5	6	30
	Hematology	3	6	18
	Coagulation	4.5	**6**	**27**
Pharmacokinetic sample		**4**	**3**	**12**
Blood culture		**10 – 15**	4[a]	**40 – 60**
Total				**127 – 147**

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

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on CAZ-AVI become available. However, the maximum volume to be drawn from each patient over approximately 60 days should not exceed **422.5** ml.

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

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8.11 PREGREP and PREGOUT modules

Section of protocol affected:

Section 13.3.1

Previous text:

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:

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.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

9. CORRECTION OF STUDY PLAN PER AMENDED ITEMS

Section of protocol affected:

Table 1

Previous text, Table 1

Table 1 Study Plan

	Eligibility/ Screening	Treatment Period[a]			Follow-up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16 EOT Visit	Visit 17 TOC Visit	Visit 18 LFU Visit
Procedures and Assessments	**Days -1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Informed consent[d]	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical and surgical history	X					
Review prior and concomitant medications (including prior antibiotic therapy)	X	X	Daily	X	X	X
Complete physical examination[e]	X			X	X	X
Abdominal signs and symptoms plus abdominal wound examinations postoperatively	X	X[b]	Daily	X	X	X
Vital sign measurements[f]	X	X	Daily	X	X	X
12-Lead digital electrocardiogram		X[g]	X[h]	X		
Monitor adverse events[i]	X	X	Daily	X	X	X
APACHE II score (see Appendix F)	X					

Table 1 Study Plan

	Eligibility/ Screening	Treatment Period[a]			Follow-up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16 EOT Visit	Visit 17 TOC Visit	Visit 18 LFU Visit
Procedures and Assessments	**Days -1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Culture from site of abdominal infection[j]	Mandatory at surgical intervention	---------- As clinically indicated ----------				
Blood cultures[k]	X (mandatory)	---------- Repeat daily if initial culture is positive and/or as clinically indicated ----------				
Blood and urine for safety analysis[l]	X	X[b]	Every 3 days	X	X	X
Estimate creatinine clearance[m]	X	X[b]	As clinically indicated			
Serum β-hCG for women of childbearing potential	X				X	X
Randomization		X[n]				
Blood for PK analysis[o]			X			
Pharmacogenetic blood sample[p]		X				
Biomarker sample[q]		X	X	X		
Description of operative procedures[r]	X	X	X	X	X	X
Administer IV study therapy[s]		X	X			
Clinical response assessment[t]				X	X	X
Record radiologic examination[u]	X					

Table 1 Study Plan

	Eligibility/ Screening	Treatment Period[a]			Follow-up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16 EOT Visit	Visit 17 TOC Visit	Visit 18 LFU Visit
Procedures and Assessments	**Days -1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Investigator case summary/operative notes/hospital discharge summary[v]				---------- Ongoing as available ----------		

[a] A minimum of 5 full days (15 doses for patients with normal renal function and patients with mild renal impairment) to a maximum of 14 full days, where a full day is defined as a 24-hour period.

[b] Repeat assessments are only required if Visit 1 and Visit 2 are separated by surgery OR are >12 hours apart.

[c] Patients who discontinue IV 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 IV dose.

[d] A separate informed consent form should be obtained 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.

[e] A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen, musculoskeletal, and neurological.

[f] Vital sign measurements including body temperature, heart rate, respiratory rate, and blood pressure should be assessed at Screening, Baseline, daily while the patient is receiving IV study therapy, at EOT, at TOC, and at the LFU visit. The patient should be resting in a supine position for at least 10 minutes before measuring blood pressure and heart rate. 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. Height will be measured at Screening only; weight will be measured at Screening and as clinically indicated thereafter.

[g] A digital electrocardiogram (ECG) must be performed prior to dosing on Day 1 (Baseline). The ECG measurement should be performed in triplicate.

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

[i] Patients will be monitored for non-serious adverse events and serious adverse events from the time when informed consent is obtained at Screening up to and including the LFU visit. If a patient experiences diarrhea during or after IV study therapy, *C. difficile* associated diarrhea may be present. When clinically indicated, the investigator should send a stool sample for *C difficile* toxin testing.

[j] These assessments will be used to determine microbiological outcome. 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.

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

[l] Laboratory specimens (see Table 9) will be obtained prior to dosing and sent to the central reference laboratory at Screening, every 3 days during IV study therapy, EOT, TOC, and LFU. Abnormal safety laboratory results obtained throughout the study, including the LFU, should be followed up as clinically indicated (see also Appendix G). Local laboratory test results will be used to qualify patients for randomization.

[m] Study center personnel will calculate the estimated creatinine clearance at Screening and when clinically indicated (eg, clinically relevant increase or decrease in serum creatinine clearance) using serum creatinine results from the local laboratory. See Appendix E for the calculation of the estimated creatinine clearance.

[n] On Day 1 (Baseline) before dosing.

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

[p] The pharmacogenetic sample should only be taken from consented patients prior to commencement of IV study therapy. If this 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.

[q] 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 IV study therapy infusion, 24 hours after the beginning of IV study therapy infusion, and at the EOT visit.

[r] With study entry and any subsequent procedures. If patient did not have surgery at Visit 1, details of the surgery need to be collected at Visit 2.

[s] If necessary, a 1-time dosing interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule 8 hours apart (±30 minutes). The dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose (ie, a –4 hour dosing window around the second dose). If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. Patients who remain on IV study therapy after 5 days (15 doses for patients with normal renal function or mild renal impairment) will receive their IV study therapy by study center personnel while in the hospital or qualified health care provider (eg, home health agency) as an outpatient. The patient is to return to the study center for their EOT, TOC and LFU visits following discharge from the hospital.

[t] If patients fail or relapse between scheduled visits, the assessment should be recorded as an unscheduled visit.

[u] Radiological examinations are not required for the study but the results should be recorded if done as part of the diagnosis. Radiological examinations include WBC scans, plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

[v] All documentation including surgical reports and imaging studies for any surgical intervention performed during the study must be submitted as it becomes available. For those patients whose surgical intervention was percutaneous drainage of an abscess, 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. See Section 3.1.1 for information regarding the Surgical Review Panel.

Revised text, Table 1:

Table 1 Study Plan

	Eligibility/ Screening	Treatment Period[a]			Follow-up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16 EOT Visit	Visit 17 TOC Visit	Visit 18 LFU Visit
Procedures and Assessments	**Days -1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Medical and surgical history	X					
Review prior and concomitant medications (including prior antibiotic therapy)	X	X	Daily	X	X	X
Complete physical examination[d]	X			X	X	X
Abdominal signs and symptoms plus abdominal **and** wound examinations postoperatively[e]	X	X[b]	Daily	X	X	X
Vital sign measurements[f]	X	X	Daily	X	X	X
12-Lead digital electrocardiogram		X[g]	X[h]	X		
Monitor adverse events[i]	X	X	Daily	X	X	X
APACHE II score (see Appendix **E**)	X					
Culture from site of abdominal infection[j]	Mandatory at surgical intervention	---------- As clinically indicated ----------				
Blood cultures[k]	X (mandatory)	---------**If screening blood cultures results are** positive, **repeat at least every 3 days until negative. Blood cultures may also be obtained** as clinically indicated.----------				
Blood and urine for safety analysis[l]	X	X[b]	Every 3 days	X	X	X

Table 1 Study Plan

	Eligibility/ Screening	Treatment Period[a]			Follow-up Period	
	Visit 1	Visit 2	Visits 3 to 15	Visit 16 EOT Visit	Visit 17 TOC Visit	Visit 18 LFU Visit
Procedures and Assessments	**Days -1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 14**	**Within 24 hours after last IV dose[c]**	**Day 28 visit**	**Day 42 visit**
Estimate creatinine clearance[m]	X	X[b]	As clinically indicated			
Serum β-hCG for women of childbearing potential	X[n]				X	X
Randomization		X[o]				
Blood for PK analysis[p]			X			
Description of operative procedures[q]	X	X	X	X	X	X
Administer IV study therapy[r]		X	X			
Clinical response assessment[s]				X	X	X
Record radiologic examination[t]	X					
Investigator case summary/operative notes/hospital discharge summary[u]				---------- Ongoing as available ----------		

[a] A minimum of 5 full days (15 doses for patients with normal renal function and patients with mild renal impairment) to a maximum of 14 full days, where a full day is defined as a 24-hour period.

[b] Repeat assessments are only required if Visit 1 and Visit 2 are separated by surgery OR are >12 hours apart.

[c] Patients who discontinue IV 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 IV dose.

[d] A complete physical examination will include an assessment of the following: general appearance including site of infection, skin, head and throat (head, eyes, ears, nose, and throat), lymph nodes, respiratory, cardiovascular, abdomen, musculoskeletal, and neurological.

[e] **The use of negative pressure wound therapy in an open skin wound is permissible. Surgical wound examination should occur daily even if inspection is limited by the presence of a negative pressure wound therapy device. A thorough wound evaluation should occur when a full dressing change is performed.**

[f] Vital sign measurements including body temperature, heart rate, respiratory rate, and blood pressure should be assessed at Screening, Baseline, daily while the patient is receiving IV study therapy, at EOT, at TOC, and at the LFU visit. The patient should be resting in a supine position for at least 10

minutes before measuring blood pressure and heart rate. 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. Height will be measured at Screening only; weight will be measured at Screening and as clinically indicated thereafter.

g A digital electrocardiogram (ECG) must be performed prior to dosing on Day 1 (Baseline). The ECG measurement should be performed in triplicate.

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

i 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 LFU visit. If a patient experiences diarrhea during or after IV study therapy, *C. difficile* associated diarrhea may be present. When clinically indicated, the investigator should send a stool sample for *C. difficile* toxin testing.

j These assessments will be used to determine microbiological outcome. 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.

k If the **screening** blood culture **results are** positive, **repeat** samples must be collected **at least every 3 day**s until **clearance of bacteremia has been documented**. I**f repeat cultures have not been finalized** negative **by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit**. When obtaining samples for blood cultures, 2 sets from 2 different sites must be collected (a total of 4 bottles; 2 aerobic and 2 anaerobic, each inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL of blood per collection). One set **should** be drawn through a venipuncture.

l Laboratory specimens (see Table 9) will be obtained prior to dosing and sent to the central reference laboratory at Screening, every 3 days during IV study therapy, EOT, TOC, and LFU. **A direct Coombs test should be performed at the study center at Baseline, EOT (IV), and TOC if the local laboratory is equipped to do so; study centers unable to perform direct Coombs testing will not be required to perform this test.** Abnormal safety laboratory results obtained throughout the study, including the LFU, should be followed up as clinically indicated (see also Appendix G). Local laboratory test results will be used to qualify patients for randomization.

m Study center personnel will calculate the estimated creatinine clearance at Screening and when clinically indicated (eg, clinically relevant increase or decrease in serum creatinine clearance) using serum creatinine results from the local laboratory. See Appendix E for the calculation of the estimated creatinine clearance.

n **If the results of the serum β-hCG test cannot be obtained prior to dosing of investigational product, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG test results must still be obtained.**

o On Day 1 (Baseline) before dosing.

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

q With study entry and any subsequent procedures. If patient did not have surgery at Visit 1, details of the surgery need to be collected at Visit 2.

r If necessary, a 1-time dosing interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule 8 hours apart (±30 minutes). The dosing interval adjustment must be such that the second dose is given a minimum of 4 hours and a maximum of 8 hours after the first dose (ie, a –4 hour dosing window around the second dose). If a 1-time dose adjustment is made for the second dose, all further dosing times will be calculated based on the time of the second dose. Patients who remain on IV study therapy after 5 days (15 doses for patients with normal renal function or mild renal impairment) will receive their IV study therapy by study center personnel while in the hospital or qualified health care provider

(eg, home health agency) as an outpatient. The patient is to return to the study center for their EOT, TOC and LFU visits following discharge from the hospital.

[s] If patients fail or relapse between scheduled visits, the assessment should be recorded as an unscheduled visit.

[t] Radiological examinations are not required for the study but the results should be recorded if done as part of the diagnosis. Radiological examinations include WBC scans, plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

[u] All documentation including surgical reports and imaging studies for any surgical intervention performed during the study must be submitted as it becomes available. For those patients whose surgical intervention was percutaneous drainage of an abscess, 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. See Section 3.1.1 for information regarding the Surgical Review Panel.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; β-hCG, β-human chorionic gonadotropin; EOT, End of Treatment; IV, intravenous; LFU, Late Follow-Up; PK, pharmacokinetic; QTcF, corrected QT interval using Fridericia formula; TOC, Test of Cure.

Reason for Amendment:

Revision of Table 1 to reflect global changes to protocol (clarification of blood culture collection, removal of genetic and biomarker sampling, clarification of pregnancy testing, negative pressure wound therapy, wound evaluation, Coombs test)

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

10. ADMINISTRATIVE CHANGES

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