Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Ceftazidime-Avibactam
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, S-151 85 Södertälje, Sweden

Centres affected by the Amendment:

This amendment affects all centers in the study

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

1. Amendment of the number of patients with a perforated appendix or appendiceal abscess

2. Clarification of the visit structure and timing of visits and assessments;

   - Updating of study Plan(Table 1) to incorporate changes
   - Clarification of ECG assessments required following completion of study drug;
   - Clarification of temperature recording assessments;
   - Amendment of duration for the safety analysis.

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

4. Correction of exclusion criteria on creatinine clearance;

5. Clarification of Exclusions from clinically evaluable population and correction of a typographical error

6. Correction of the definition of the mMITT analysis set

7. Clarification of the definitions of the ME and extended ME analysis sets

8. Amendment of inclusion criteria on female contraception and pregnancy

9. Amendment of Concomitant and post-study treatment(s)

10. Amendment of the SAE contacts information

1. AMENDMENT OF THE NUMBER OF PATIENTS WITH A PERFORATED APPENDIX OR APPENDICEAL ABSCESS

Section of protocol affected:

Synopsis; Section 3.1; section 5.2.1;

Previous text: Synopsis, Study design, paragraph3: (text to be deleted underlined)

After obtaining written informed consent and confirming eligibility, patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule. Patients will be stratified by baseline severity of disease (Acute Physiology and Chronic Health Evaluation II [APACHE II] score (Knaus et al 1985); levels: ≤10 or >10 and ≤30) (see Appendix E) and by country (China, non China). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to 25% of the study population.

Revised text: Synopsis, Study design, paragraph 3: (new text in bold and underlined)

After obtaining written informed consent and confirming eligibility, patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule. Patients will be stratified by baseline severity of disease (Acute Physiology and Chronic Health Evaluation II [APACHE II] score (Knaus et al 1985); levels: ≤10 or >10 and ≤30) (see Appendix E) and by country (China, non China). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to **approximately 40% of the study population.**

Previous text: section 3.1 overall study design and flow chart, paragraph 3: (text to be deleted underlined)

After obtaining written informed consent and confirming eligibility, patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule. Patients will be stratified by baseline severity of disease (APACHE II score; levels: ≤10 or >10 and ≤30) (see Appendix E) and by Country (China and non- China). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to 25% of the study population.

Revised text: section 3.1 overall study design and flow chart, paragraph 3: (new text in bold and underlined)

After obtaining written informed consent and confirming eligibility, patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio according to the central randomization schedule. Patients will be stratified by baseline severity of disease (APACHE II score; levels: ≤10 or >10 and ≤30) (see Appendix E) and by Country (China and non- China). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to **approximately 40% of the study population.**

Previous text: section 5.2.1 Procedures for Randomization, paragraph 3: (text to be deleted underlined)

Patients will be stratified by baseline severity of disease (APACHE II score; levels: ≤10 or >10 and ≤30) and by Country (China and non-China). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to 25% of the study population. Randomization codes will be assigned strictly sequentially to eligible patients (within each stratum).

Revised text: section 5.2.1 Procedures for Randomization, paragraph 3: (new text in bold and underlined)

Patients will be stratified by baseline severity of disease (APACHE II score; levels: ≤10 or >10 and ≤30) and by Country (China and non-China). Additionally, although not included as a stratification factor, the number of patients with a perforated appendix or appendiceal abscess will be limited to **approximately 40% of the study population.** Randomization codes will be assigned strictly sequentially to eligible patients (within each stratum).

Reason for Amendment:

Based on the current information from other cIAI studies and the proportion of subjects with appendicitis enrolled in clinical studies, including multiple registrational studies, the percentage of subjects having appendicitis with associated peritonitis will be adjusted to approximately 40%. The adjustment will be consistent with the global CAZ-AVI cIAI program's recent adjustment to approximately 40% appendicitis with associated peritonitis, which had received agreement from the US Food and Drug Administration.

2. CLARIFICATION OF THE VISIT STRUCTURE AND TIMING OF VISITS AND ASSESSMENTS;

Section of protocol affected:

Section 3.1, Section 6.4.9, Section 6.4.10.2, Section 12.3

Previous text: Section 3.1, Table 1: (text to be deleted underlined)

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

[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 F). 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 D 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.

Revised text: Section 3.1, Table 1: (new text in bold and underlined)

	Visit 1	Visit 2[a]	Visit 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
Procedures and assessments	**Eligibility/ Screening Assessments (Days -1 to 0)**	**Baseline Assessments plus Day 1[b] of study therapy**	**On therapy Assessments (Day 2 to 14)[b]**	**EOT Assessments (within 24 hours after completion of last dose of IV therapy)**	**TOC Assessments (28 calendar days from randomization)[c]**	**LFU Assessments (42 calendar days from randomization)[d]**
Informed consent	X					
Inclusion and exclusion criteria	X	X				
APACHE II[e]	X					
Demographics	X					
Medical and surgical history	X					
Prior and concomitant medications/antibiotics	X	X	Daily	X	X	X
Complete physical examination [f]	X			X	X	X
Abdominal signs/symptoms/examination; wound examination [g]	X	X [h]	Daily	X	X	X
Temperature [i]	**X**	**X**	**Daily**	**X**	**X**	**X**
Heart rate, blood pressure, respiratory Rate [j]	**X**	**X**	**Daily**	**X**	**X**	**X**
Height/weight	X	**Repeat weight only to calculate CrCl when clinically indicated.**				

	Visit 1	Visit 2[a]	Visit 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
Procedures and assessments	**Eligibility/ Screening Assessments (Days -1 to 0)**	**Baseline Assessments plus Day 1[b] of study therapy**	**On therapy Assessments (Day 2 to 14)[b]**	**EOT Assessments (within 24 hours after completion of last dose of IV therapy)**	**TOC Assessments (28 calendar days from randomization)[c]**	**LFU Assessments (42 calendar days from randomization)[d]**
12-lead ECG[k]		X	Day 3 and as clinically indicated	X		
Estimate creatinine clearance[l]	X	X[h]	**As clinically indicated: use local serum creatinine measurements**			
Serum and urine β-hCG[m]	X				X	X
Coombs test[n]		**X**		**X**	**X**	
Record available radiologic examinations[o]	X					
Blood cultures[p]	X	If blood cultures are positive, repeat at least every 3 days until negative. Blood cultures should also be performed as clinically indicated.				
Culture of abdominal infection site[p]	**Cultures must be obtained at initial qualifying procedure (performed within 24 hours of randomization). If additional procedures are performed, additional abdominal site cultures should be obtained. Cultures from the wound/procedure site should be obtained only if clinically indicated.**					
Description of operative procedure	**From initial qualifying procedure (performed within 24 hours of randomization) and any additional procedures performed during the study period.**					
Monitor AEs	X	X	X	X	X	X

	Visit 1	Visit 2[a]	Visit 3 to 15	Visit 16	Visit 17[c]	Visit 18[d]
Procedures and assessments	**Eligibility/ Screening Assessments (Days -1 to 0)**	**Baseline Assessments plus Day 1[b] of study therapy**	**On therapy Assessments (Day 2 to 14)[b]**	**EOT Assessments (within 24 hours after completion of last dose of IV therapy)**	**TOC Assessments (28 calendar days from randomization)[c]**	**LFU Assessments (42 calendar days from randomization)[d]**
Randomization		X				
Administer IV therapy [q]		X [a,b]	X			
Blood and urine for safety to central lab[r]	X		Day2, then every 3 days while on IV therapy	X	X	X
Blood for PK to central lab [s]			Day 3			
Clinical response assessment [t]				X	X	X
Investigator case summary/operative notes/discharge summary [u]	When available					

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

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

c) **For example, if a patient is randomized on the first of the month, the TOC visit should be performed on the 28th of the month. If it is not possible to perform the TOC visit 28 calendar days from randomization, the allowed visit window is 28 to 35 calendar days after randomization.**

d) **If it is not possible to perform the LFU visit 42 calendar days from randomization, the allowed visit window is 42 to 49 calendar days from randomization.**

e) **Calculate APACHE II using most recent local laboratory results. Use of temperature obtained rectally in determining the APACHE II score is preferred but not mandatory. See Appendix E. If an arterial blood gas is not clinically indicated, the APACHE II score should be calculated using serum bicarbonate and oxygenation should be presumed normal.**

f) **As note in Section 6.4.8, this includes an assessment of the followings: 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.**

g) **Surgical wound examination should occur daily even if inspection is limited by the presence of the operative dressing (in the first 24 to 48 hours after surgery) or the presence of a negative pressure wound therapy device. A full inspection of the wound unimpeded by the surgical dressing should occur starting approximately 24 to 48 hours after surgery or earlier if the surgeon feels it is safe to remove the dressing. For patients with negative pressure wound therapy**

devices, a thorough wound evaluation should occur when a full dressing change is performed.

h) Assessment is only required at Visit 2 if Visit 1 and Visit 2 are separated by surgery or are >12 hours apart.

i) Temperature should be assessed at all visits and twice daily during IV therapy (suggested at least 8 hours apart). See Section 6.4.10.2.

j) Assess heart rate and blood pressure after patient is resting in supine position for at least 10 minutes (see Sections 6.4.10.1 and 6.4.10.3). Assess heart rate, blood pressure and respiratory rate at all scheduled visits (ie, Visit 1 [screening], Visit 2 [baseline], Visits 3 to 18 [Day 2 through end of IV treatment], EOT, TOC, and LFU)

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

l) Calculate estimated creatinine clearance using Cockcroft-Gault formula (See Appendix D). For details regarding dosing in renal impairment see Section 5.5.2.

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

n) Coombs test is to be performed locally where possible.

o) 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.

p) For instructions on collection and processing of abdominal cultures and blood cultures see Section 3.1.2.1.

q) 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.

r) Safety labs should be collected at screening, baseline (only if surgery occurs between screening and baseline visits or if >12 hours has passed between the screening and baseline visit), every 3 days while on IV therapy (Day 2, Day 5, Day 8, etc), EOT, TOC, and LFU. See Section 6.4.6.

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

t) If a patient fails or relapses between scheduled visits, the assessment should be recorded as an unscheduled visit.

u) All documentation including surgical reports and imaging studies results 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 film results 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: AE, adverse event; APACHE II, Acute Physiology and Chronic Health Evaluation II; β-hCG, β-human chorionic gonadotropin; ECG, echocardiogram; EOT. End of Treatment; IV, intravenous; LFU, Late Follow-Up; PK, pharmacokinetic; QTcF, corrected QT interval using Fridericia formula; TOC, Test of Cure

Previous text, Section 6.4.9 Resting ECG:

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. Electrocardiograms should be performed after the next dose of study drug then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to baseline (Day 1 prior to receiving any study drug). Assessments should be performed after the completion of study drug administration and be recorded as unscheduled assessments.

Revised text, Section 6.4.9 Resting ECG: (new text in bold and underlined)

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. Electrocardiograms should be performed after the next dose of study drug then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to baseline (Day 1 prior to receiving any study drug). Assessments should be performed after the completion of study drug administration and be recorded as unscheduled assessments.

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

Reason for Amendment:

To provide guidance regarding when ECGs may be discontinued after EOT

Previous text, Section 6.4.10.2 Body temperature (new text in bold and underlined)

Body temperature will be measured at the times indicated in Table 1, an automated thermometer should be used where available. The patient's body temperature will also be evaluated at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature collection will be recorded. Fever will be defined as a body temperature >38°C. For each individual patient, the method of temperature measurement should be consistent for the duration of the study.

Revised text, Section 6.4.10.2 Body temperature

Body temperature will be measured at the times indicated in Table 1, an automated thermometer should be used where available. The patient's body temperature will also be evaluated at **all visits. During the study therapy period, temperature should be evaluated** at least twice a day (suggested at least 8 hours apart) and the actual time of body temperature collection will be recorded. Fever will be defined as a body temperature >38°C. For each individual patient, the method of temperature measurement should be consistent for the duration of the study.

Reason for Amendment:

To clarify that the twice daily temperature recordings refer only to the study treatment period.

Previous text, Section 12.3 Safety and tolerability, Safety hypothesis paragraph 4 (text to be deleted underlined)

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

Revised text, Section 12.3 Safety and tolerability, Safety hypothesis paragraph 4 (new text in bold and underlined)

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

Reason for Amendment:

Given the short half life of the study drugs, it is appropriate to summarize AEs up to LFU, and then summarize those AEs that occurred up to EOT (IV). This is considered the more appropriate time point to evaluate safety findings that might be considered related to study therapy.

3. CLARIFICATION OF THE TIMING FOR FOLLOW-UP IF A PATIENT DISCONTINUES INVESTIGATIONAL PRODUCT OR WITHDRAWS FROM THE STUDY

Section of protocol affected:

Section 5.8.1 and Section 5.9

Previous text, Section 5.8.1 Procedures for discontinuation of a patient from investigational product:

A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of discontinuation from the IP and at the LFU visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and Section 6.4.5); and all IV study drugs (CAZ-AVI plus metronidazole, and meropenem) should be returned by the investigator.

Revised text, Section 5.8.1 Procedures for discontinuation of a patient from investigational product: (new text in bold and underlined)

A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of discontinuation from the IP**, at TOC** and at the LFU visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and Section 6.4.5); and all IV study drugs (CAZ-AVI plus metronidazole, and meropenem) should be returned by the investigator.

Previous text, Section 5.9 Withdrawal from study: (text to be deleted underlined)

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of withdrawal and at the LFU visit. Adverse events and SAEs will be followed up (See Sections 6.4.3 and 6.4.5).

Revised text, Section 5.9 Withdrawal from study:

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of withdrawal. Adverse events and SAEs will be followed up (See Sections 6.4.3 and 6.4.5).

Reason for Amendment:

To clarify discrepant wording in the protocol regarding timing of assessments; whether TOC and LFU versus LFU only assessments are required after premature discontinuation.

4. CORRECTION OF EXCUSION CRITERIA ON CREATININE CLEARANCE

Section of protocol affected:

Section 4.2

Previous text, exclusion criteria 11(a): (text to be deleted underlined)

11. Patient has any of the following laboratory values as defined below:

(a) Estimated creatinine clearance <30 mL/min calculated by Cockcroft-Gault method (Cockcroft et al 1976). Refer to Appendix D for calculation information.

Revised text, exclusion criteria 11(a): (new text in bold and underlined)

11. Patient has any of the following laboratory values as defined below:

(a) Estimated creatinine clearance **≤30 mL/min** calculated by Cockcroft-Gault method (Cockcroft et al 1976). Refer to Appendix D for calculation information.

Reason for Amendment:

To correct the exclusion criteria for creatinine clearance

5. CLARIFICATION OF EXCLUSIONS FROM CLINICALLY EVAUABLE POPULATION

Sections of protocol affected:

Synopsis and Section 12.1.1.1 Item 6

Previous text, Synopsis and Section 12.1.1.1 Clinically evaluable analysis set at the EOT, TOC, and LFU visits: (text to be deleted underlined)

- Did not receive any prior antibiotics other than protocol allowed antibiotics with specified duration in Section 4.2 exclusion criterion 17.

- Did not receive concomitant antibiotic therapy with potential activity against any of the baseline pathogens 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 MRSA. 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.

Revised text, Synopsis and Section 12.1.1.1 Clinically evaluable analysis set at the EOT, TOC, and LFU visits: (new text in bold and underlined)

- Did not receive any prior antibiotics other than protocol allowed antibiotics with specified duration in Section 4.2 exclusion criterion **16.**

- Did not receive concomitant antibiotic therapy with potential activity against any of the baseline **aerobic** pathogens 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 MRSA. 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 correct a typographical error

To clarify that receipt of antibiotics active against aerobic baseline pathogens will result in exclusion from the clinically evaluable analysis set.

6. CORRECTION THE DEFINITION OF THE mMITT ANALYSIS SET

Sections of protocol affected:

Synopsis and Section 12.1.1.2

Previous text, Synopsis and Section 12.1.1.2, Microbiological modified intent-to-treat

analysis set: (text to be deleted underlined)

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 susceptibilities). Patients with a bacterial species typically not expected to respond to both study drugs (eg, *Acinetobacter* spp., *Stenotrophomonas* spp.) will be excluded.

Revised text, Synopsis and Section 12.1.1.2, Microbiological modified intent-to-treat analysis set: (new text in bold and underlined)

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 isolate susceptibilities). 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 correct the definition of the mMITT analysis set. The restriction to include only patients with a Gram negative pathogen was intended to be applied to the ME analysis set only and not the mMITT analysis set.

7. CLARIFICATION OF THE DEFINITIONS OF THE ME AND EXTENED ME ANALYSIS SETS

Sections of protocol affected:

Synopsis and Section 12.1.1.3, Section 12.1.1.4

Previous text:

Synopsis and 12.1.1.3 Microbiologically evaluable analysis set at the EOT, TOC, and LFU visits

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

1. Included in a subset of CE patients at EOT, TOC, or LFU, respectively

2. Had at least 1 Gram negative pathogen in the initial/prestudy culture that is susceptible to both study agents

Synopsis and 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:

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

2. Had at least 1 Gram negative pathogen in the initial/prestudy culture regardless of susceptibility.

Revised text (<u>new text in bold and underlined</u>)

Synopsis and 12.1.1.3 Microbiologically evaluable analysis set at the EOT, TOC, and LFU visits

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

1. Included in a subset of CE patients at EOT, TOC, or LFU, respectively

2. Had at least 1 Gram negative **<u>aerobic</u>** pathogen in the initial/prestudy culture that is susceptible to both study agents

Synopsis and 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:

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

2. Had at least 1 Gram negative **<u>aerobic</u>** pathogen in the initial/prestudy culture regardless of susceptibility.

Reason for Amendment:

Clarification that the definitions of the ME and extended ME analysis sets include gram negative aerobic pathogens.

8. AMENDMENT OF INCLUSION CRITERIA ON FEMALE CONTRACEPTION AND PREGNANCY

Section of protocol affected:

Section 4.1, Inclusion criteria

Previous text, Section 4.1 Inclusion criterion 3: <u>(text to be deleted underlined)</u>

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

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

<u>OR</u>

(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 ß-human chorionic gonadotropin [ß-hCG]) within 1 day prior to study entry (if the results of the serum ß-hCG cannot be obtained prior to dosing of the investigational product (IP), a patient may be enrolled on the basis of a negative urine pregnancy test, though serum ß-hCG must still be obtained), and
- Must be willing, during treatment and for at least 7 days after last dose of IV study therapy, to practice highly effective methods of birth control, such as intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), and medroxyprogesterone injections (Depo-Provera®), or remain sexually abstinent. Oral contraceptives should not be used as the sole method of birth control because the effect of CAZ-AVI on the efficacy of oral contraceptives has not yet been established. Barrier methods (such as male condom or diaphragm with spermicide) can be used if another method of acceptable contraception (not oral contraceptives) is also used.

Revised text, Section 4.1 Inclusion criterion 3: (new text in bold and underlined)

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

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

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

(c) Age <50 years 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 ß-human chorionic gonadotropin [ß-hCG]) within 1 day prior to study entry (if the results of the serum ß-hCG cannot be obtained prior to dosing of study therapy, a patient may be enrolled on the basis of a negative urine pregnancy test, though serum ß 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 therapy and for a period of** 7 days after the last dose of study therapy (IV and oral), and agrees to the use of the following acceptable methods **of contraception: prior to and during the study, use** of an intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), regular medroxyprogesterone injections (Depo-Provera®)**, or sexual intercourse with only 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 effective contraception (not oral contraceptives) is also used.

Reason for Amendment:

Clarification of the entry criteria for female patients to participate in the study with regards to methods of ascertaining childbearing potential, contraception, and confirmation that the patient is not pregnant

9. AMENDMENT OF CONCOMITANT AND POSTSTUDY TREATMENTS

Section of protocol affected:

Section 5.6

Previous text, Section 5.6 Concomitant and post-study treatment(s):

The use of other systemic antimicrobials not specified by this protocol is not permitted during the study. Antibiotic peritoneal lavage is not permitted (peritoneal lavage with saline or other non-antibacterial containing solution is allowed). Topical antibacterial and antifungals are permitted except that they may not be applied to the surgical site.

Revised text, Section 5.6 Concomitant and post-study treatment(s): (new text in bold and underlined)

The use of other systemic antimicrobials not specified by this protocol is not permitted during the study. **However, if a new infection develops at a remote site (ie, outside of the abdomen) between the date and time of randomization and the LFU visit, and the investigator considers addition of nonstudy antibiotics essential to the safety and wellbeing of the patient, additional antibiotics may be added. If possible, the investigator should attempt to choose antibiotics that will not have antibacterial activity against the patient's cIAI baseline pathogens to avoid confounding the assessment of the effect of study therapy.** Antibiotic peritoneal lavage is not permitted (peritoneal lavage with saline or other nonantibacterial containing solution is allowed). Topical antibacterial and antifungals are permitted except that they may not be applied to the surgical site. **It is anticipated that in instances of clinical failure, alternative "rescue" antibacterial therapy to treat the cIAI would be instituted. Antifungal therapy to treat the cIAI should be avoided unless**

clinically indicated. A known requirement for antifungal therapy at randomization would exclude the patient from enrollment based on exclusion criterion 6.

Reason for Amendment:

To clarify that the concomitant antibiotics should not be withheld if it puts the patients at risk.

10. AMENDMENT OF THE SAE CONTACTS INFORMATION

Sections of protocol affected:
Section 13.1

Previous text (text to be deleted underlined)

Name	Role in the study	Address and telephone number
[redacted]	Study Physician	[redacted]
[redacted]	Study Leader	[redacted]

Revised text (new text in bold and underlined)

Name	Role in the study	Address and telephone number
[redacted]	Study Physician AstraZeneca China	[redacted]
[redacted]	Study Leader	[redacted]

Persons who initiated the Amendment:

The Study Delivery Team (SDT).