Clinical Study Protocol Amendment	
Amendment Number	3
Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00006
Date	[redacted]
Protocol Dated	[redacted]

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

Sponsor:

AstraZeneca AB, S-151 85 Södertälje, Sweden

Centers affected by the Amendment:

This amendment affects all centers in the study.

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

1. Update of study timetable and end of study.

2. Clarification of visit structure, timing of visits and assessments

   - Update of Study Plan (Table 1) to align with amended items in the protocol
   - Update of Figure 1 (Study flow chart) to align with amended items in the protocol.
   - Update of Visit 1 Eligibility/Screening (Days -1 to 0) assessment procedures

- Clarification of the laboratory results to be used for calculating the APACHE II score.
- Clarification of microbiological assessments
- Clarification of FU1 visit assessments
- Clarification of FU2 visit assessments
- Clarification of recording of adverse events procedures
- Clarification of physical examination procedures
- Clarification of the ECG assessments required following completion of study drug.
- Clarification of the timing of body temperature assessments during the study
- Clarification of the timing of plasma sample collection for pharmacokinetic assessments
- Clarification of the timing of wound assessments for patients with cIAI
- Clarification of safety and tolerability procedures
- Clarification of the timing of calculation of variables

3. Clarification of pharmacokinetic parameters
4. Clarification regarding cIAI patients who will be reviewed by the surgical review panel
5. Clarification of the analysis of isolates
6. Amendment of inclusion criteria
    - Clarification that prior to study entry means prior to Screening.
7. Amendment of the exclusion criteria
    - Clarification that the APACHE II score is only required for cIAI patients
    - Clarification that patients who are unlikely to survive the study period are not suitable for study entry

- Correction of a typographical error

8. Amendment of CAZ-AVI dosing regimen for patients who need to start intermittent haemodialysis

9. Clarification of treatment compliance procedures

10. Amendment of Concomitant and post study treatment(s)

    - Clarification that concomitant antibiotics should not be withheld if it puts the patient at risk

    - Clarification that co-administration of CAZ-AVI with probenecid is not recommended

11. Clarification of responsibilities for study drug destruction procedures.

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

13. Amendment of the failure criteria for cIAI patients.

14. Amendment of the method of calculating the confidence interval.

15. Administrative changes that include typographical and grammatical updates, removal of references that are no longer cited in the protocol, and addition of new references.

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

1. UPDATE OF STUDY TIMETABLE AND END OF STUDY

Section of protocol affected:

Protocol Synopsis, Section 9.5

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

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

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

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

Previous text, Section 9.5 Study timetable and end of study:

The end of the study is defined as the last visit of the last patient participating in the study.

The study is expected to start in the second quarter of [redacted] and to end by the fourth quarter of [redacted].

Revised text, Section 9.5 Study timetable and end of study

The end of the study is defined as the last visit of the last patient participating in the study.

The study is expected to start in the second quarter of [redacted] and to end by the **first quarter of [redacted].**

Reason for the Amendment:

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

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

2. CLARIFICATION OF VISIT STRUCTURE, TIMING OF VISITS AND ASSESSMENTS

Sections of protocol affected

Synopsis, Section 3.1, Section 3.1.2, Section 6.2.1, Section 6.2.2, Section 6.2.4, Section 6.2.6, Section 6.2.7, Section 6.4.3, Section 6.4.8, Section 6.4.9, Section 6.4.10.2, Section 6.5.1, Section 12.2.3

Previous text, Synopsis and Section 3.1 study periods table:

Study periods

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

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

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

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

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

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

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

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

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

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

Revised text, Synopsis and Section 3.1 study periods table:

Study periods

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

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

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

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

[d] If it is not possible to perform the FU1 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is **21 to 25 calendar days from randomization** and for cIAI is **28 to 35 calendar days from randomization.**

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

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

[g] If it is not possible to perform the FU2 visit on the designated day (eg, the patient is on holiday), the allowed visit window for cUTI is **28 to 32 calendar days from randomization**.

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

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

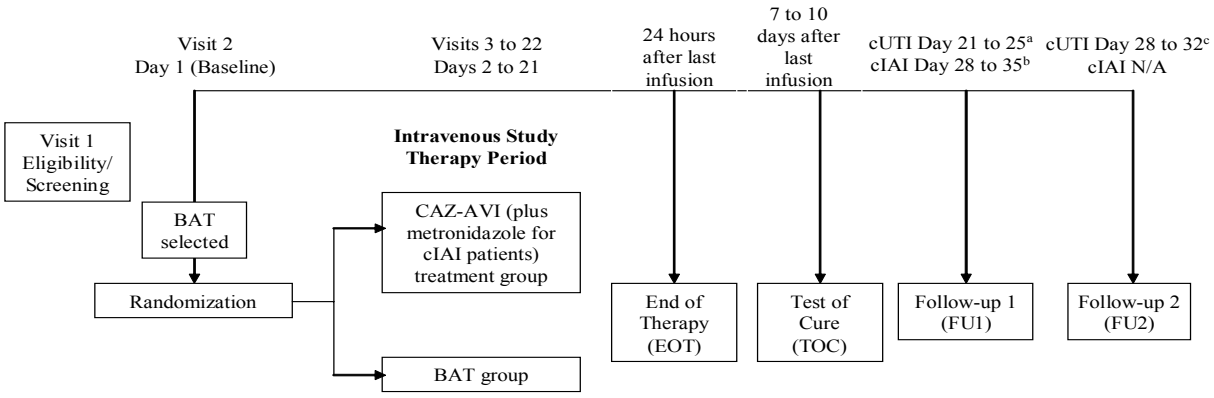
Previous text, Section 3.1 Overall study design and flow chart:

An overall clinical assessment, vital sign measurement, and assessment of infection-related signs and symptoms will be performed at Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, FU1, and FU2 visits. For cIAI patients, clinical signs and symptoms will include abdominal signs and symptoms plus abdominal and wound examinations. For cUTI, clinical signs and symptoms include fever or chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, suprapubic pain, and nausea or vomiting. The investigator is responsible for determining the appropriate duration of study therapy and assessing the relationship of AEs to study therapy.

Revised text, Section 3.1 Overall study design and flow chart:

An overall clinical assessment, vital sign measurement, and assessment of infection-related signs and symptoms will be performed **at all visits**. For cIAI patients, clinical signs and symptoms will include abdominal signs and symptoms plus abdominal and wound examinations. For cUTI, clinical signs and symptoms include fever or chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, suprapubic pain, and nausea or vomiting. The investigator is responsible for determining the appropriate duration of study therapy and assessing the relationship of AEs to study therapy.

Previous text, Section 3.1 Figure 1 Study flow chart:



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

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

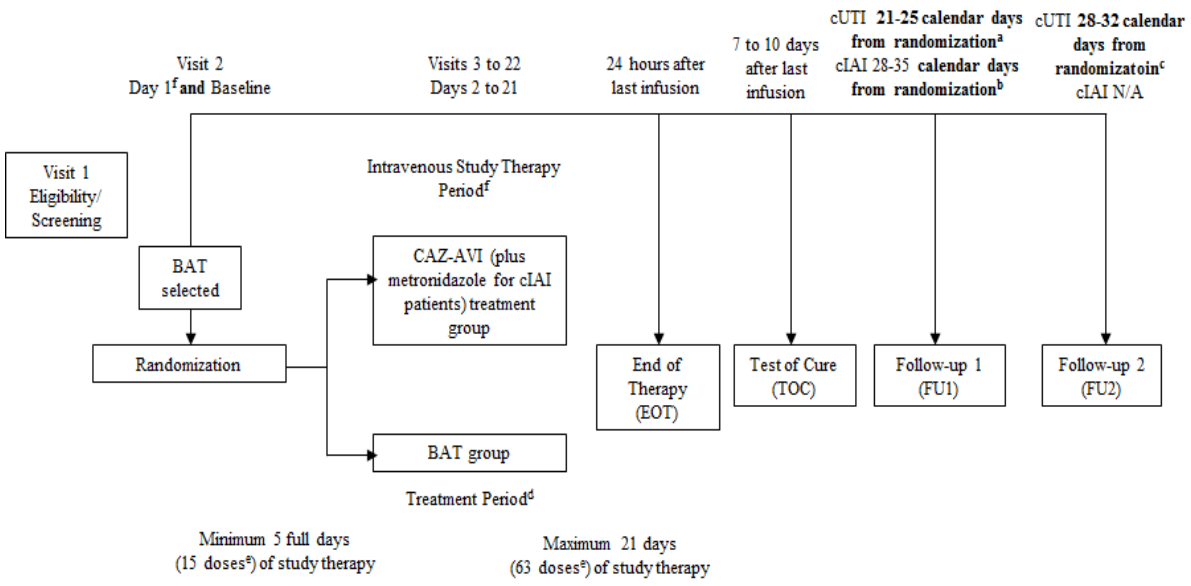
[c] The designated windows for the TOC (7 to 10 days after last dose of study therapy) and FU2 (Day 28 to Day 32) visits may overlap depending upon the number of days the cUTI patient receives study therapy. In those instances, the TOC and FU2 visits may be combined on the same day.

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

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

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

Revised text, Section 3.1 Figure 1 Study flow chart:



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

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

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

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

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

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

Reason for the Amendment:

Clarify visit structure and timing of visits

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

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

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

	Eligibility/ Screening	**Treatment Period[a]**					
	Visit 1	**Visit 2**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
Procedures and Assessments	**Days –1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
Monitor adverse events[k] APACHE II score (see Appendix F)[l]	X X	X	Daily	X	X	X	X
Obtain isolate from study-qualifying culture and send to central microbiology laboratory[m]	X						
Blood cultures[n] (if not previously documented as negative)		X[o]	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
Intra-abdominal culture (cIAI patients only)[p]		As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Quantitative urine culture (cUTI patients only)[q]		X		X	X	X	X
Urine for microscopic white blood cell count (cUTI patients only)[r]		X					
Blood and urine for safety analysis[s]	X	X	Every 3 days	X	X	X	X
Estimate creatinine	X	As clinically	As clinically	As clinically	As clinically	As clinically	As clinically indicated

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

	Eligibility/ Screening	**Treatment Period[a]**					
	Visit 1	**Visit 2**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
Procedures and Assessments	**Days –1 to 0**	**Day 1[b] (Baseline)**	**Days 2 to 21**	**Within 24 hours after last infusion**	**7 to 10 days after last infusion**	**cUTI Day 21 cIAI Day 28**	**cUTI Day 28 cIAI N/A**
clearance[t]		indicated	indicated	indicated	indicated	indicated	
Serum β-hCG for females of childbearing potential[u]	X					X (for cIAI patients)	X (for cUTI patients)
Determination of Best Available Therapy prior to randomization[v]		X					
Randomization		X[w]					
Pharmacokinetic sample[x]			X				
Description of operative procedures (cIAI patients only)[y]	As available	As available	As available	As available	As available	As available	
Administer study therapy[z]		X	X				
Clinical response assessment				X	X	X	X
Record radiologic examination if performed (for cIAI patients only)[aa]	X						
Investigator case summary/operative notes/hospital discharge summary (for cIAI				X		X	

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

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

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

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

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

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

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

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

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

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

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

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

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

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

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

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

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

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

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

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

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

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

[s] Local laboratory test results will be used to qualify patients for randomization. Laboratory specimens will be obtained prior to dosing and sent to the central reference laboratory. A direct Coombs test should be performed at the study center at Baseline, EOT, and TOC if the local laboratory is equipped to do so; study centers unable to perform direct Coombs testing will not be required to perform this test. For any clinically significant abnormal laboratory results at FU visits, additional laboratory tests should be performed and results followed until resolution or stabilization.

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

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

Abnormal laboratory results at TOC should be followed-up as clinically indicated. Local laboratory test results will be used to qualify patients for eligibility and randomization.

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

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

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

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

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

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

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

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

Previous text, Section 3.1 Table 1 Study Plan

Table 1 Study plan

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

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

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

Revised text, Section 3.1 Table 1:

Table 1 Study plan

	Visit 1	Visit 2[a]	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**
Informed consent[e]	X						

Table 1 Study plan

	Visit 1	**Visit 2[a]**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**
Inclusion and exclusion criteria	X	X					
APACHE II score **(cIAI patients only)[f]**	X						
Demographics	X						
Medical history[g]	X						
Review prior and concomitant medications/antibiotic	X	X	Daily	X	X	X	X
Complete physical examination[h]	X			X	X	X	X
Height/weight	**X**	**Repeat weight only to calculate the patient's estimated CrCl when clinically indicated**					
Assess infection signs and symptoms and perform focused physical examination[i]	X	X	Daily	X	X	X	X

Table 1 Study plan

	Visit 1	**Visit 2[a]**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**
Assess urinary device status (as appropriate for cUTI patients only)		X	X	X	X	X	X
Temperature[j]	**X**	**X**	**Daily**	**X**	**X**	**X**	**X**
Heart rate, blood pressure, respiratory rate[k]	**X**	**X**	**Daily**	**X**	**X**	**X**	**X**
12-lead digital ECG[l]		X	**Day 3 and as clinically indicated**	X			
Monitor adverse events[m]	X	X	Daily	X	X	X	X
Obtain **all pathogens f**rom study-qualifying culture and send to central microbiology laboratory[n]	X						
Blood cultures (if not previously documented as negative)[o]		**X[p]**	**As clinically indicated**				
Intra-abdominal culture (cIAI patients only)[q]		As clinically indicated					

Table 1 Study plan

	Visit 1	**Visit 2[a]**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**
Quantitative urine culture (cUTI patients only)[r]		X		X	X	X	X
Urine for microscopic white blood cell count (cUTI patients only)[s]		X					
Blood and urine for safety analysis[t]	X	X	**Day 2, then every 3 days while on IV therapy**	X	X	X	X
Coombs test[u]		**X**		**X**	**X**		
Estimate creatinine clearance[v]	X	As clinically indicated: **use local serum creatinine measurements**					
Serum **and urine** β-hCG for females of childbearing potential[w]	X					X (for cIAI patients)	X (for cUTI patients)
Determination of Best Available Therapy prior to randomization[x]		X					

Table 1 Study plan

	Visit 1	**Visit 2[a]**	**Visits 3 to 22**	**EOT[c]**	**TOC[d]**	**FU1[d]**	**FU2[d]**
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**
Randomization		X[y]					
Pharmacokinetic sample[z]			**Day 3**				
Description of operative procedures (cIAI patients only)	As available. **This includes any report from the procedure when the study qualifying isolate was obtained and with any subsequent surgical procedures.**						
Administer IV therapy[aa]		**X[a,b]**	X				
Clinical response assessment				X	X	X	X
Record radiologic examination if performed (for cIAI patients only)[bb]	X						
Investigator case summary/operative notes/ discharge summary (for cIAI patients only)[cc]				X		X	
Mortality assessment			X	X	X	X	X

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

Table 1 Study plan

	Visit 1	Visit 2[a]	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
	Eligibility/ Screening Assessment (Days –1 to 0)	Baseline assessments plus Day 1[b] of study therapy	On therapy assessments (Days 2 to 21)[b]	EOT assessments (Within 24 hrs after completion of dose of IV therapy)	TOC assessments (7 to 10 days after completion of last dose of IV therapy)	cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization	cUTI 28 calendar days from randomization cIAI N/A

[b] Study day 1 starts at the time of administration of first dose of IV study therapy and ends 24 hours later. Subsequent study days are based on 24-hour periods from the time of the first infusion. Study treatment duration is for a minimum of 5 days to a maximum of 21 days. Repeat assessments are not required for visits that occur on the same calendar day as the Eligibility/Screening visit.

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

[d] The TOC visit may occur 7 to 10 days after last infusion of study therapy. The FU visits are calculated from the date of randomization. For cUTI patients, the FU1 visit is 21 calendar days from randomization and for cIAI is 28 calendar days from randomization. For example, if a patient is randomized on the first of the month, FU1 should be performed on the 21st of the month (or 28th of the month for cIAI). If it is not possible to perform the FU1 visit on the designated day (eg. patient is on holiday), the allowed visit window for cUTI is 21 to 25 calendar days from randomization and for cIAI is 28 to 35 calendar days from randomization. The FU2 visit for cUTI patients may likewise be performed 28 to 32 calendar days from randomization and is not required for cIAI patients. Depending on the duration of study treatment, the FU1 and FU2 visit may fall within the window for the TOC visit, in which case the FU1 or FU2 visit may be combined with the TOC visit. All assessments for both visits must be performed. Assessments that are required at both the TOC and FU visits need to be performed only once.

[e] The overall consent covers sending all pathogens from the study the qualifying culture obtained per routine standard of care to the central microbiology laboratory for confirmation of identification and ceftazidime resistance and analysis of additional genotypic and phenotypic characteristics

[f] Calculate the APACHE II score using most recent local laboratory results. Use of temperature obtained rectally in determining the APACHE II score is preferred but not mandatory. See Appendix F.

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

[h] See Section 6.4.8 for components of the complete physical examination.

[i] Infection-related signs and symptoms should be assessed daily while the patient is receiving study therapy at all visits. For cUTI patients, clinical signs and symptoms include fever or chills, flank pain, suprapubic and costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, and nausea or vomiting. For cIAI patients, clinical signs and symptoms include abdominal signs and symptoms plus abdominal and wound examinations. Surgical wound examination should occur daily even if inspection is limited by presence of the operative dressing (in the first 24-48 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 24-48 hours after surgery or earlier if the surgeon considers it is safe to remove the dressing. For patients with negative pressure wound therapy devices, a thorough wound examination should occur when a full dressing change

Table 1 Study plan

	Visit 1	Visit 2[a]	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
	Eligibility/ Screening Assessment (Days –1 to 0)	Baseline assessments plus Day 1[b] of study therapy	On therapy assessments (Days 2 to 21)[b]	EOT assessments (Within 24 hrs after completion of dose of IV therapy)	TOC assessments (7 to 10 days after completion of last dose of IV therapy)	cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization	cUTI 28 calendar days from randomization cIAI N/A

is performed.

j **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**

k **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 3-22 [Day 2 through to end of IV treatment, EOT, TOC and FU visit(s)]).**

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

m **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 FU visits. Should a patient experience significant diarrhea during or after study therapy, the investigator should consider obtaining a stool sample and testing for *C. difficile* toxin.**

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

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

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

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

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

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

t **Safety laboratory results should be collected at Screening, Baseline, every 3 days while on IV therapy (starting on day 2), EOT, TOC and FU**

Table 1 Study plan

	Visit 1	Visit 2[a]	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**

visit(s)). See Section 6.4.6. Starting local laboratory test results will be used to qualify patients for randomization. Laboratory specimens will be obtained prior to dosing and sent to the central microbiology laboratory. For any clinically significant abnormal laboratory results at FU visits, additional laboratory tests should be performed and results followed until resolution or stabilization. Abnormal laboratory results at TOC should be followed up as clinically indicated. Local laboratory test results will be used to qualify patients for eligibility and randomization.

u **Coombs test is to be performed locally where possible.**

v **Study center personnel will calculate the estimated creatinine clearance at Screening and when clinically indicated using serum creatinine results from the local laboratory. Calculate estimated creatinine clearance using Cockcroft-Gault formula (See Appendix E). For details regarding CAZ-AVI dosing in renal impairment see Section 5.5.2.2.**

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

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

y **Randomization will occur before dosing but after BAT is documented in the eCRF as noted in footnote "x."**

z **Plasma samples for pharmacokinetic assessments will be collected on Day 3 following a dose administration that is convenient for plasma sample collection at the following time points: anytime from 15 minutes prior to stopping until 15 minutes after stopping any infusion, anytime between 30 minutes and 90 minutes after stopping any infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping any infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient. See Section 6.5.1**

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

bb **For cIAI patients only, radiological examinations are not required for the study but the results should be recorded if assessed as part of the**

Table 1 Study plan

	Visit 1	Visit 2[a]	Visits 3 to 22	EOT[c]	TOC[d]	FU1[d]	FU2[d]
	Eligibility/ Screening Assessment (Days –1 to 0)	**Baseline assessments plus Day 1[b] of study therapy**	**On therapy assessments (Days 2 to 21)[b]**	**EOT assessments (Within 24 hrs after completion of dose of IV therapy)**	**TOC assessments (7 to 10 days after completion of last dose of IV therapy)**	**cUTI 21 calendar days from randomization cIAI 28 calendar days from randomization**	**cUTI 28 calendar days from randomization cIAI N/A**

diagnosis. Radiological examinations include plain abdominal radiographs, computed tomography scans, ultrasound, and/or magnetic resonance image scans with or without contrast.

[cc] **All documentation including surgical reports and imaging study results for any surgical intervention performed during the study must be submitted as soon as it becomes available. For those patients whose surgical intervention was percutaneous abscess drainage, the interventional radiology report serves as the operative note. Any follow-up 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: APACHE II, Acute Physiology and Chronic Health Evaluation II; β-hCG, β-human chorionic gonadotropin; BAT, Best Available Therapy; cIAI, complicated intra-abdominal infection; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; ECG, electrocardiogram; eCRF, electronic case report form; EOT, End of Treatment; FU1, Follow-up 1; FU2, Follow-up 2; N/A, not applicable; PK, pharmacokinetic; QTcF, corrected QT interval by Fridericia; TOC, Test of Cure.

Reason for the Amendment:

Clarification of visit structure, timing of visits and assessment requirements for each visit and laboratory results to be used for calculating the APACHE II score.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.1 Visit 1 Eligibility/Screening (Days –1 to 0) assessment procedure #11:

11. Determining APACHE II score (see Appendix F) using the most recent parameters available

Revised text, Section 6.2.1 Visit 1 Eligibility/Screening (Days –1 to 0) assessment procedure #11:

11. Determining APACHE II score (see Appendix F) using the most recent **local laboratory results** (**for cIAI patients only**)

Reason for the Amendment:

APACHE II score only required for cIAI patients in line with the pivotal cIAI study

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Addition of text, Section 6.2.1 Visit 1 Eligibility/Screening (Days –1 to 0) assessment procedure #14

14. Obtaining a blood sample for blood culture

Reason for the Amendment:

Clarify visit structure, timing of visits and assessment requirements for each visit (this change was implemented in global amendment 2 and is highlighted here for further clarity.)

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.4 EOT visit assessment procedures #15:

15. Determining clinical response assessment

Note: If a patient fails or relapses between scheduled visits, assessment should be recorded as an unscheduled visit.

Revised text, Section 6.2.4 EOT visit assessment procedures #15:

15. Determining clinical response assessment

Note: If a patient fails or relapses between scheduled visits**, the clinical response** assessment should be recorded as an unscheduled visit.

Reason for the Amendment:

Clarification visit structure, timing of visits and assessment requirements for each visit (this change was implemented in global amendment 2 and is highlighted here for further clarity).

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 3.1.2 Microbiological Assessments

It is important that the microbiology laboratory be instructed to retain all pathogens for at least 5 days from patients where a ceftazidime resistant pathogen (the study-qualifying pathogen as described below) is isolated for possible inclusion in this trial.

Revised text, Section 3.1.2 Microbiological Assessments

It is important that the microbiology laboratory be instructed to retain all pathogens **isolated from patients who are being considered for possible inclusion in this trial for at least 5 days (ie, the ceftazidime-resistant pathogen study-qualifying pathogen as described below, plus all other pathogens)**.

Reason for the Amendment

Clarification of microbiological assessment requirements.

Persons who initiated Amendment

AstraZeneca CAZ-AVI Clinical Project Team

Previous section title, Section 6.2.2:

Visit 2 (Day 1 [Baseline]) assessment procedures

Revised section title, Section 6.2.2:

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

Reason for the Amendment:

Clarify visit structure and timing of visits

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.6 FU1 visit assessment procedures:

The FU1 visit dates are calculated from the date of randomization and are different for each diagnosis. For patients entering the study with a diagnosis of cUTI, the FU1 visit should be conducted on Day 21 with a visit window of Day 21 to Day 25. For patients entering with a diagnosis of cIAI the FU1 visit should be conducted on Day 28 with a visit window of Day 28 to Day 35. Depending on the number of days of study therapy, it is possible for the FU1 visit window to overlap with the TOC (7 to 10 days after last study therapy) visit window. In those instances where the TOC and FU1 windows overlap, the 2 visits may be combined into 1 visit. All assessments for the TOC and FU1 visit must be completed, but any duplicate assessments only need to be completed 1 time.

Revised text, Section 6.2.6 FU1 visit assessment procedures:

The FU1 visit dates are calculated from the date of randomization and are different for each diagnosis. For patients entering the study with a diagnosis of cUTI, the FU1 visit should be conducted **21 calendar days from randomization** with a visit window of 21 to 25 calendar days from randomization. For patients entering with a diagnosis of cIAI the FU1 visit should be conducted **28 calendar days from randomization** with a visit window of **28 to 35 calendar days from randomization**. Depending on the number of days of study therapy, it is possible for the FU1 visit window to overlap with the TOC (7 to 10 days after last study therapy) visit window. In those instances where the TOC and FU1 windows overlap, the 2 visits may be combined into 1 visit. All assessments for the TOC and FU1 visit must be completed, but any duplicate assessments only need to be completed 1 time.

Reason for the Amendment:

Clarify visit structure and timing of visits

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.2.7 FU2 visit assessment procedures (cUTI patients only)

The FU2 visit is only required for the cUTI patients; the dates are calculated from the date of randomization. The FU2 visit should be conducted on Day 28. If it is not possible to conduct the visit on Day 28, the FU2 visit window is Day 28 to Day 32. Depending on the number of

days of study therapy, it is possible for the FU2 visit window to overlap with the TOC (7 to 10 days after last study therapy) visit window. In those instances where the TOC and FU2 windows overlap, the 2 visits may be combined into 1 visit. All assessments for the TOC and FU2 visit must be completed, but any duplicate assessments only need to be completed 1 time.

Revised text, Section 6.2.7 FU2 visit assessment procedures (cUTI patients only)

The FU2 visit is only required for the cUTI patients; the dates are calculated from the date of randomization. The FU2 visit should be conducted **28 calendar days from randomization**. If it is not possible to conduct the visit **on this day**, the FU2 visit window is **28 to 32 calendar days from randomization**. Depending on the number of days of study therapy, it is possible for the FU2 visit window to overlap with the TOC (7 to 10 days after last study therapy) visit window. In those instances where the TOC and FU2 windows overlap, the 2 visits may be combined into 1 visit. All assessments for the TOC and FU2 visit must be completed, but any duplicate assessments only need to be completed 1 time.

Reason for the Amendment:

Clarification of visit structure and timing of visits.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.3 Recording of adverse events- Adverse events based on examinations and tests:

The results from protocol-mandated laboratory tests and vital sign measurements will be summarized in the CSR. Deterioration as compared with Day 1 (Baseline) in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study therapy.

Revised text, Section 6.4.3 Recording of adverse events- Adverse events based on examinations and tests:

The results from protocol-mandated laboratory tests and vital sign measurements will be summarized in the CSR. Deterioration as compared with **Baseline** in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study therapy.

Reason for the Amendment:

Clarify visit structure and timing of visits

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.8 Physical examination:

- The cIAI-focused physical examination will include an assessment of the abdominal wound. A detailed abdominal assessment will be performed at Screening, Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, FU1, and FU2 visits. 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.

Revised text, Section 6.4.8 Physical examination:

- The cIAI-focused physical examination will include an assessment of the abdominal wound. A detailed abdominal assessment will be performed at **all** visits. 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. **In the first 24-48 hours post-operatively only, if it is considered unsafe to remove the original wound dressing, a limited examination around the dressing should be performed**.

Reason for the Amendment:

Clarify visit structure and timing of visits; clarification regarding the timing of wound assessments for patients with cIAI.

Persons who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.9 Resting ECG:

Triplicate digital 12-lead ECGs will be recorded within 1 to 2 minutes of each other, at the time points specified in Table 1 using equipment provided by the central ECG laboratory [redacted]. The reports for the triplicate repeat ECGs will consist of the mean data from 3 beats (heartbeats or intervals) reported during each separate ECG. Patients must relax in a recumbent position for at least 10 minutes prior to the ECG reading being recorded. Central processing of ECGs and data storage will be provided by [redacted]. Each ECG will define heart rate, RR, QRS interval, QTc interval, QTcF and QTcB, T-wave morphology (normal versus abnormal), and overall interpretation.

If any significant increase of QTcF (ie, increase from Baseline of ≥30 ms or QTcF >460 ms) is observed, then additional ECG assessments must be performed. Electrocardiograms should be performed after the next dose of study therapy then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to Baseline (Day 1) prior to receiving any study therapy). Assessments should be performed after the completion of study therapy administration and be recorded as unscheduled assessments.

Revised text, Section 6.4.9 Resting ECG:

Triplicate digital 12-lead ECGs will be recorded within 1 to 2 minutes of each other, at the time points specified in Table 1 using equipment provided by the central ECG laboratory [redacted]. The reports for the triplicate repeat ECGs will consist of the mean data from 3 beats (heartbeats or intervals) reported during each separate ECG. Patients must relax in a recumbent position for at least 10 minutes prior to the ECG reading being recorded. Central processing of ECGs and data storage will be provided by [redacted]. Each ECG will define heart rate, RR, QRS interval, QTc interval, QTcF and QTcB, T wave morphology (normal versus abnormal), and overall interpretation.

If any significant increase of QTcF (ie, increase from Baseline of ≥30 ms or QTcF >460 ms) is observed, then additional ECG assessments must be performed. Electrocardiograms should be performed after the next dose of study therapy then daily until 2 consecutive assessments demonstrate the QTcF has returned to normal or to **Baseline** (prior to receiving any study therapy). Assessments should be performed after the completion of study therapy administration and be recorded as unscheduled assessments. **If at least 2 ECGs have been obtained after completion of study drug and the QTcF has not returned to baseline, ECGs may be discontinued if all of the following apply: the QTcF has not worsened over the previous 3 days, the investigator considers that the QTcF is not due to study therapy, and the investigator feels it is safe to discontinue daily ECGs. In the event that daily ECGs are discontinued under these circumstances, an ECG should be obtained at the TOC visit (and if still meeting significant QTcF criteria at TOC, at the follow-up visit(s) as well).**

Reason for the Amendment:

Clarification of visit structure and timing of visits; clarification of the ECG assessments required following completion of study drug, respectively.

Persons who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 6.4.10.2 Body temperature:

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

study therapy (suggested at least 8 hours apart), and the actual time of body temperature collection will be recorded. Fever will be defined as a body temperature >38°C. For each individual patient, the method of temperature measurement ideally should be consistent for the duration of the study. If any medication with antipyretic properties has been taken by the patient, temperature readings should be taken at the end of the dosing interval (eg, 6 hours after the most recent dose for medications that are taken every 6 hours and 8 hours after the most recent dose for medications that are taken every 8 hours), and prior to administering the next dose of antipyretic-containing medication.

Revised text, Section 6.4.10.2 Body temperature:

Body temperature will be measured using an automated thermometer at the times indicated in Table 1. The patient's body temperature will be evaluated **at all visits**. **During study therapy, temperature should be evaluated** at least twice a day (suggested at least 8 hours apart). The actual time of body temperature collection will be recorded. Fever will be defined as a body temperature >38°C. For each individual patient, the method of temperature measurement ideally should be consistent for the duration of the study. If any medication with antipyretic properties has been taken by the patient, temperature readings should be taken at the end of the dosing interval (eg, 6 hours after the most recent dose for medications that are taken every 6 hours and 8 hours after the most recent dose for medications that are taken every 8 hours), and prior to administering the next dose of antipyretic-containing medication.

Reason for the Amendment:

Clarification of the timing of temperature assessments during the study.

Persons who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, 6.5.1 Collection of samples (Pharmacokinetics):

Blood samples will be taken from all patients in the CAZ-AVI group on Day 3 following dose administration that is convenient for collection of the plasma samples at the times presented in the study plan (see Table 1) and summarized as follows:

- Anytime within the 15 minutes prior to or after stopping CAZ-AVI infusion

Revised text, 6.5.1 Collection of samples (Pharmacokinetics):

Blood samples will be taken from all patients in the CAZ-AVI group on Day 3 following a dose administration that is convenient for collection of the plasma samples at the times presented in the study plan (see Table 1) and summarized as follows:

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

Reason for the Amendment:

Clarification of the timing of plasma samples for pharmacokinetic assessments.

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 12.2.3 Safety and tolerability:

For ECG variables, the QT correction factor will be based on the Bazett and Fridericia formulas. Categorical summaries of absolute QT and QTcF values (≥450 ms, ≥480 ms, ≥500 ms) and change from Day 1 (Baseline) values in QT and QTcF values (≥30 ms, ≥60 ms) will also be presented. All other ECG variables will be listed.

Revised text, Section 12.2.3 Safety and tolerability:

For ECG variables, the QT correction factor will be based on the Bazett and Fridericia formulas. Categorical summaries of absolute QT and QTcF values (≥450 ms, ≥480 ms, ≥500 ms) and change from **Baseline** values in QT and QTcF values (≥30 ms, ≥60 ms) will also be presented. All other ECG variables will be listed.

Reason for the Amendment:

Clarification of visit structure and timing of visits

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 11 Calculation of variables:

For the calculation of the variables in this section, with the exception of microbiological cultures, Baseline will be defined as the last nonmissing assessment before the start of study therapy. For microbiological cultures, the study-qualifying culture is the culture that documented the ceftazidime resistance, which made the patient eligible for the trial and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit. Refer to Section 3.1 for definitions of EOT, TOC, FU1, and FU2. Study randomization will be defined as the Day 1 (Baseline) visit.

Revised text, Section 11 Calculation of variables:

For the calculation of the variables in this section, with the exception of microbiological cultures, Baseline will be defined as the last nonmissing assessment before the start of study therapy. For microbiological cultures, the study-qualifying culture is the culture that documented the ceftazidime resistance, which made the patient eligible for the trial and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit. Refer to Section 3.1 for definitions of EOT, TOC, FU1, and FU2. **Randomization will occur at Visit 2 following the Baseline assessments.**

Reason for the Amendment:

Clarification of visit structure and timing of visits

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

3. CLARIFICATION OF PHARMACOKINETIC PARAMETERS

Sections of the protocol affected:

Synopsis, Section 6.3.7

Previous text, Synopsis and Section 6.3.7 Pharmacokinetic outcome variables:

Avibactam and ceftazidime compartmental PK parameters derived from population PK analysis, and potential PK/PD relationships will be reported separately. Summary statistics of ceftazidime and avibactam plasma concentrations at specified sampling windows will be reported in the CSR.

Revised text, Synopsis and Section 6.3.7 Pharmacokinetic outcome variables:

Avibactam and ceftazidime PK parameters derived from population PK analysis, and potential PK/PD relationships will be reported separately. Summary statistics of ceftazidime and avibactam plasma concentrations at specified sampling windows will be reported in the CSR.

Reason for the Amendment:

Reason being that a population analysis is based on a PK model that consists of one or several compartments.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

4. CLARIFICATION REGARDING cIAI PATIENTS WHO WILL BE REVIEWED BY THE SURGICAL REVIEW PANEL

Sections of the protocol affected:

Section 3.1.1

Previous text Section 3.1.1 Surgical Review Panel (cIAI patients only):

An independent expert surgical review panel (SRP) consisting of surgeons and 1 or more interventional radiologists will be convened at regular intervals throughout the study. There will be a charter for the SRP and the SRP will perform the review while blinded to study therapy. For all patients classified as a clinical failure (after study randomization and receipt of study therapy or BAT) and all patients classified as cure at TOC who undergo another procedure subsequent to randomization, the SRP will review

Revised text Section 3.1.1 Surgical Review Panel (cIAI patients only):

An independent expert surgical review panel (SRP) consisting of surgeons and 1 or more interventional radiologists will be convened at regular intervals throughout the study. There will be a charter for the SRP and the SRP will perform the review while blinded to study therapy. For all patients classified as a clinical failure (after study randomization and receipt of study therapy or BAT) and all patients classified as cure at TOC **or at FU1** who undergo another procedure subsequent to randomization, the SRP will review

Reason for the Amendment:

Clarification regarding the cIAI patients who will be reviewed by the Surgical Review Panel

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 3.1.2.2 Isolate collection:

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

(preferably at –70°C) until the end of the study or when contacted by the central microbiology laboratory.

Revised text, Section 3.1.2.2 Isolate collection:

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

Reason for the Amendment:

Clarification regarding abdominal culture isolate collection for patients with cIAI

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

5. CLARIFICATION OF ANALYSIS OF ISOLATES

Section of the protocol affected:

Section 3.1.2.4

Previous text, Section 3.1.2.4 Analysis of isolates

Susceptibility testing for CAZ-AVI will be performed by the disk diffusion method at the local laboratory using recommended CLSI methodology on all pathogens being submitted to the central microbiology laboratory, as outlined in the microbiology laboratory manual. Susceptibility disks will be provided by the sponsor.

Revised text, Section 3.1.2.4 Analysis of isolates:

Susceptibility testing for CAZ-AVI will be performed by the disk diffusion method at the local laboratory using recommended CLSI methodology on all pathogens being submitted to the central microbiology laboratory, as outlined in the microbiology laboratory manual (**unless sites are unable to perform these tests**). Susceptibility disks will be provided by the sponsor.

Reason for the Amendment:

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

Person who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

6. AMENDMENT OF INCLUSION CRITERIA

Section of the protocol affected:

Section 4.1

Previous text, Section 4.1 Inclusion criterion #4:

4. Patient has a ceftazidime resistant Gram-negative pathogen that was isolated from an appropriate culture within 5 days prior to study entry (ie, the study-qualifying culture), which was determined to be the causative agent of the entry infection and there is an isolate available to be sent to the central microbiology laboratory. For this study, ceftazidime resistance is defined as those bacterial isolates whose susceptibility results are intermediate or resistant using CLSI methodology and isolates that are resistant using EUCAST methodology.

Revised text, Section 4.1 Inclusion criterion #4:

4. Patient has a ceftazidime resistant Gram-negative pathogen that was isolated from an appropriate culture within 5 days prior to study entry (ie, **within 5 days prior to Screening**; the study-qualifying culture), which was determined to be the causative agent of the entry infection and there is an isolate available to be sent to the central microbiology laboratory. For this study, ceftazidime resistance is defined as those bacterial isolates whose susceptibility results are intermediate or resistant using CLSI methodology and isolates that are resistant using EUCAST methodology.

Reason for the Amendment:

Clarification that prior to study entry means prior to Screening.

Person who initiated the amendment:

AstraZeneca CAZ-AVI Clinical Project Team

7. AMENDMENT OF EXCLUSION CRITERIA

Section of protocol affected:

Section 4.2

Previous text, Section 4.2 Exclusion Criterion #1:

1. Patient has an APACHE II score >30

Revised text, Section 4.2 Exclusion Criterion #1:

1. Patient has an APACHE II score >30 **(cIAI patients only)**

Reason for the Amendment:

APACHE II score only required for cIAI patients in line with the pivotal cIAI study

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 4.2 Exclusion Criterion #3:

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

Revised text, Section 4.2 Exclusion Criterion #3:

3. Patient has a rapidly progressive or terminal illness with a high risk of mortality due to any cause, including acute hepatic failure, respiratory failure or severe septic shock **such that they are unlikely to survive the 4- to 5-week study period.**

Reason for the Amendment:

Clarification that patients who are unlikely to survive the study period are not suitable for enrollment in the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 4.2 Exclusion Criterion #24:

24. Patient has infections limited to the hollow viscous, such as simple cholecystitis, gangrenous cholecystitis without rupture, and simple appendicitis

Revised text, Section 4.2 Exclusion Criterion #24, and Additional exclusion criteria-cIAI patients:

Note: Exclusion Criterion #1 also only applies to cIAI patients (as per Global Amendment 3)

24. Patient has infections limited to the hollow **viscus**, such as simple cholecystitis, gangrenous cholecystitis without rupture, and simple appendicitis

Reason for the Amendment:

Clarification that exclusion criterion #1 applies to cIAI patients, and correction of typographical error.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

8. AMENDED CAZ-AVI DOSING REGIMEN FOR PATIENTS WHO NEED TO START INTERMITTENT HAEMODIALYSIS

Section of protocol affected:

Section 1.1.7, Section 5.5.2.2 title, text and Table 3

Previous text, Section 1.1.7 Human experience – Phase I:

The Phase I studies completed to date have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly male and female subjects. The [14C] avibactam study D4280C00008 showed that an average of 97% (range 95% to 98%) of administered radioactivity was recovered from the urine, over 95% within 12 hours of dosing. Avibactam is predominantly renally cleared with little contribution from metabolism. An average of 85% (range 67% to 101%) of administered avibactam was recovered from the urine during the study, with >50% being recovered within 2 hours of the start of the infusion. Renal clearance was 158 mL/min suggesting active tubular secretion. The PK and tolerability of avibactam have also been determined in patients with different degrees of renal impairment (Study NXL104/1003). The relationship between avibactam renal clearance and calculated creatinine clearance (CrCl) was found to be linear, consistent with the predominantly renal excretion of avibactam. Based on the data from Study NXL104/1003, dosage adjustments will be required in patients with moderate to severe renal impairment. Population PK and PK/pharmacodynamic (PD) modeling support adjustments in the dose amount and frequency of administration for ceftazidime avibactam (CAZ AVI, formerly [redacted]) that are consistent with those already recommended for ceftazidime (see Section 5.5.2.2).

Revised text, Section 1.1.7 Human experience – Phase I:

The Phase I studies completed to date have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly male and female subjects. The [14C] avibactam study D4280C00008 showed that an average of 97% (range 95% to 98%) of administered radioactivity was recovered from the urine, over 95% within 12 hours of dosing. Avibactam is predominantly renally cleared with little contribution from metabolism. An average of 85% (range 67% to 101%) of administered avibactam was recovered from the urine during the study, with >50% being recovered within 2 hours of the start of the infusion. Renal clearance was 158 mL/min suggesting active tubular secretion. The PK and tolerability of avibactam have also been determined in patients with different degrees of renal impairment (Study NXL104/1003). The relationship between avibactam renal clearance and calculated creatinine clearance (CrCl) was found to be linear, consistent with the predominantly renal excretion of avibactam. Based on the data from Study NXL104/1003, dosage adjustments will be required in patients with moderate to **end-stage** renal impairment. Population PK and PK/pharmacodynamic (PD) modeling support adjustments in the dose amount and frequency of administration for ceftazidime avibactam (CAZ AVI, formerly [redacted] that are consistent with those already recommended for ceftazidime (see Section 5.5.2.2).

Reason for the Amendment:

Clarification of the patient population for those with renal impairment.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous section title and text, Section 5.5.2.2 CAZ-AVI dose regimen adjustments for patients with moderate to severe renal impairment (creatinine clearance 50 to 6 mL/min):

Dose adjustments for CAZ-AVI for patients with an estimated CrCl between 50 and 6 mL/min are outlined in Table 3. Since decreased renal function does not alter the PK of metronidazole, dosing adjustments for metronidazole are not needed for patients with cIAI as the entry diagnosis.

Revised section title and text, Section 5.5.2.2 CAZ-AVI dose regimen adjustments for patients with moderate to end-stage renal impairment (creatinine clearance ≤50 mL/min):

Dose adjustments for CAZ-AVI for patients with an estimated CrCl ≤**50 mL/min** are outlined in Table 3. **If subsequent to study entry and while still on IV study therapy, the patient's CrCl decreases to <6 mL/min and there is a requirement to start intermittent haemodialysis, recommended dosing information for CAZ-AVI is also provided in Table 3 which is based on the dosing recommendations for ceftazidime (Fortum® SmPC). Should the investigator consider that either peritoneal dialysis or continuous**

renal replacement therapy is required to be started during IV study therapy, the patient should be discontinued from CAZ-AVI and alternative antibacterial therapy initiated. This is because there are currently no dosing recommendations for CAZ-AVI in these circumstances. Since decreased renal function does not alter the PK of metronidazole, dosing adjustments for metronidazole are not needed for patients with cIAI as the entry diagnosis.

Reason for the Amendment:

Added recommended dosing information for CAZ-AVI should a patient require intermittent haemodialysis during the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Previous text, Section 5.5.2.2 Table 3:

Table3 CAZ-AVI dose, regimens, and infusion times for patients with moderate to severe renal impairment (creatinine clearance 50 to 6 mL/min)

Estimated creatinine clearance (mL/min)[a]	Ceftazidime and avibactam dose, interval, duration
50 to 31	1000 mg ceftazidime and 250 mg avibactam every 12 hours ±30 minutes over 120 minutes at a constant rate of infusion
30 – 16	1000 mg ceftazidime and 250 mg avibactam every 24 hours ±30 minutes over 120 minutes at a constant rate of infusion
15 – 6	500 mg ceftazidime and 125 mg avibactam every 24 hours ±30 minutes over 120 minutes at a constant rate of infusion

[a] Estimated creatinine clearance using Cockcroft-Gault formula (Appendix E).

Note: Metronidazole infusion time = 60 min (for cIAI patients). Dosing adjustments for metronidazole are not needed.

Revised text, Section 5.5.2.2 Table 3 (table name and contents):

Table3 CAZ-AVI dose, regimens, and infusion times for patients with moderate to end-stage renal impairment (creatinine clearance ≤ 50 mL/min)

Estimated creatinine clearance (mL/min)[a]	Ceftazidime and avibactam dose, interval, duration
50 – 31	1000 mg ceftazidime and 250 mg avibactam every 12 hours ±30 minutes over 120 minutes at a constant rate of infusion
30 – 16	1000 mg ceftazidime and 250 mg avibactam every 24 hours ±30 minutes over 120 minutes at a constant rate of infusion
15 – 6	500 mg ceftazidime and 125 mg avibactam every 24 hours ±30 minutes over 120 minutes at a constant rate of infusion
Additional CAZ-AVI dosing information, should a patient's CrCl decrease to <6ml/min while on study therapy:	
< 6[b]	**500 mg ceftazidime and 125 mg avibactam every 48 hours ±30 minutes over 120 minutes at a constant rate of infusion. If on intermittent haemodialysis, a supplemental dose should be given following each dialysis session**

[a] Estimated creatinine clearance using Cockcroft-Gault formula (Appendix E).

[b] **CrCl< 6ml/min is an exclusion criterion for the study. Additional dosing information for CAZ-AVI is provided should a patient's CrCl decrease to <6mL/min whilst receiving study therapy**

Note: Metronidazole infusion time = 60 min (for cIAI patients). Dosing adjustments for metronidazole are not needed.

Reason for the Amendment:

Added recommended CAZ-AVI dosing information should a patient require intermittent haemodialysis during the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

9. CLARIFICATION OF TREATMENT COMPLIANCE PROCEDURES:

Section affected:

Section 5.7

Previous text, Section 5.7 Treatment compliance:

The qualified study center personnel at the investigative study center will administer study therapy and treatment compliance will be assured. The dose, date, and exact start and stop

time of administration of the study therapy will be recorded and checked by the monitor at monitoring visits.

Revised text, **Section 5.7 Treatment compliance:**

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

Reason for the Amendment:

Update of text to reflect route of study drug administration.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

10. AMENDMENT OF CONCOMITANT AND POST STUDY TREATMENT(S)

Section of the protocol affected:

Section 5.6

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

Patients with concurrent fungal infections may receive antifungal therapy.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. If analgesic medications are needed for pain, the use of analgesic medication without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after being randomized to study therapy, the investigator should contact the AstraZeneca physician or [redacted] physician (as an AstraZeneca delegate) before initiating therapy. Continued patient study participation will be determined based upon assessment of the safety risk to the patient if he or she were to continue in the study. Patients who have completed study therapy and are in the FU period should remain in the study as they are not actively on study therapy but being followed for outcomes.

For those receiving BAT, the investigator should refer to the local label(s) to assess and understand pertinent drug-to-drug interactions for the BAT option(s) selected.

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

Patients with concurrent fungal infections may receive antifungal therapy. **In addition, if a new infection develops at a remote site (ie, outside of the cIAI or cUTI) between the date and time of randomization and the last follow-up visit, and the investigator considers**

addition of non-study antibiotics essential to the safety and well-being of the patient, additional antibiotics (outside of the antimicrobials specified in the protocol) may be added to study therapy. If possible, the investigator should attempt to choose antibiotics that would not have antibacterial activity against the patient's cIAI/cUTI baseline pathogen(s) to avoid confounding the assessment of the effect of study therapy.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. If analgesic medications are needed for pain, the use of analgesic medication without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after being randomized to study therapy, the investigator should contact the AstraZeneca physician or [redacted] physician (as an AstraZeneca delegate) before initiating therapy. Continued patient study participation will be determined based upon assessment of the safety risk to the patient if he or she were to continue in the study. Patients who have completed study therapy and are in the FU period should remain in the study as they are not actively on study therapy but being followed for outcomes.

The uptake of avibactam by Organic Anion Transporters (OATs) was inhibited by probenecid *in vitro* and hence, has potential to alter the elimination of avibactam when co-dosed. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-dosing of CAZ-AVI with probenecid is not recommended.

For those receiving BAT, the investigator should refer to the local label(s) to assess and understand pertinent drug-to-drug interactions for the BAT option(s) selected.

Reason for the Amendment:

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

In vitro data suggests that the uptake of avibactam by OATs is inhibited by probenecid and hence, co-administration of CAZ-AVI with probenecid is not recommended.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

11. CLARIFICATION OF RESPONSIBILITIES FOR STUDY DRUG DESTRUCTION PROCEDURES

Section of protocol affected:

Section 5.7.1

Previous text, Section 5.7.1 Accountability:

At the end of the study, study center personnel account for all unused study therapy and for appropriate destruction or return of all unused study therapy to a designated facility or AstraZeneca for destruction. Destruction procedures must be approved by AstraZeneca. It

must be possible to reconcile delivery records with records of study therapy use and destroyed/returned stock. The investigator or pharmacist should sign certificates of delivery and return.

Revised text, Section 5.7.1 Accountability:

At the end of the study, study center personnel account for all unused study therapy and for appropriate destruction or return of all unused study therapy to a designated facility or AstraZeneca for destruction. **Destruction procedures can be approved by AstraZeneca or [redacted] (on AstraZeneca's behalf), provided that the site has documented procedure for destruction in place**. It must be possible to reconcile delivery records with records of study therapy use and destroyed/returned stock. **The investigator or pharmacist should document drug accountability; delivery and return of study therapy should be signed and dated.**

Reason for the Amendment:

Clarification of responsibilities for checking study drug destruction procedures.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

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

Section of protocol affected:

Section 5.8.1, 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 TOC visit. Adverse events and SAEs will be followed up (see Sections 6.4.3 and Section 6.4.5).

If a patient is withdrawn from the study, see Section 5.9.

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

A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of discontinuation from the IP and at the TOC **and follow-up visit(s)**. Adverse events and SAEs will be followed up (see Sections 6.4.3 and Section 6.4.5).

If a patient is withdrawn from the study, see Section 5.9.

Reason for the Amendment:

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

Person who initiated Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

13. AMENDMENT OF FAILURE CRITERIA FOR cIAI PATIENTS

Section of protocol affected:

Section 6.3.1

Previous text, Section 6.3.1 Table 4:

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

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

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

Revised text, Section 6.3.1 Table 4:

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

Clinical response	Definition

Cure	Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) **is necessary**; **for cIAI patients no** drainage or surgical intervention **after 96 hours from randomization** is necessary **(ie. drainage or surgical intervention up to 96 hours from randomization is permissible).**
Failure	Patients who meet any 1 of the following criteria will be considered a treatment failure: • Death related to the index infection • Patient who received treatment with additional antibiotics (other than those allowed per protocol) for ongoing symptoms of index infection (including patients prematurely discontinued from study therapy due to an adverse event who require additional antibiotics for the index infection) • Patient previously met criteria for failure (not applicable for EOT). In addition, patients with cIAI will be considered a treatment failure in the following conditions: • Persisting or recurrent infection within the abdomen documented by the findings at re‑intervention either percutaneously or operatively **(after 96 hours from randomization)** • Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or nonroutine wound care
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response cannot be made • Death where index infection is clearly noncontributory • Circumstances that preclude classification as a cure or failure.

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

Reason for the Amendment:

Amended the failure criteria for cIAI patients so that a re-intervention up to 96 hours from randomization should not be classed as a treatment failure. This is considered to be part of the initial surgical procedure conducted prior to randomization.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

14. AMENDMENT OF THE METHOD OF CALCULATING THE CONFIDENCE INTERVAL

Section of the protocol affected:

Synopsis, Section 12.2.2

Previous text, Synopsis Analyses:

Two-sided 95% Wilson confidence intervals (CIs) for the proportion of patients with clinical cure within each treatment group (CAZ-AVI and BAT) at TOC will be calculated (Wilson 1927).

The primary efficacy objective of this study is to estimate the per-patient clinical response to CAZ-AVI and BAT at the TOC visit, in the mMITT analysis set. This will be achieved by assessing the 2-sided 95% Wilson CIs for the proportion of patients with clinical cure at TOC for CAZ-AVI in the mMITT analysis set. Results will be presented for the entire study population and separately by entry diagnosis. Corresponding CIs for the efficacy of the BAT will provide a context for these estimates of the efficacy of CAZ-AVI. Due to the infeasibility of recruiting larger numbers of patients infected with Gram negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Secondary efficacy outcome variables considering proportions will be analyzed by determining 2 sided 95% Wilson CIs for the outcome proportion within each treatment group (CAZ-AVI and BAT). Analyses of other secondary efficacy variables, baseline characteristics, and health utilization variables will be summarized using descriptive statistics or frequency counts in tables, listings, and figures as appropriate. With the exception of microbiological cultures, Baseline will be defined as the last nonmissing assessment before the start of study therapy. For microbiological cultures, the study qualifying culture is the culture that documented the ceftazidime resistance that made the patient eligible for the trial and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit.

Revised text, Synopsis Analyses:

Two-sided 95% **Jeffreys** confidence intervals (CIs) for the proportion of patients with clinical cure within each treatment group (CAZ-AVI and BAT) at TOC will be calculated (**Brown LD et al. 2001**, **Cai 2005**).

The primary efficacy objective of this study is to estimate the per-patient clinical response to CAZ-AVI and BAT at the TOC visit, in the mMITT analysis set. This will be achieved by assessing the 2-sided 95% **Jeffreys** CIs for the proportion of patients with clinical cure at TOC for CAZ-AVI in the mMITT analysis set. Results will be presented for the entire study

population and separately by entry diagnosis. Corresponding CIs for the efficacy of the BAT will provide a context for these estimates of the efficacy of CAZ-AVI. Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Secondary efficacy outcome variables considering proportions will be analyzed by determining 2-sided 95% **Jeffreys** CIs for the outcome proportion within each treatment group (CAZ-AVI and BAT). Analyses of other secondary efficacy variables, baseline characteristics, and health utilization variables will be summarized using descriptive statistics or frequency counts in tables, listings, and figures as appropriate. With the exception of microbiological cultures, Baseline will be defined as the last nonmissing assessment before the start of study therapy. For microbiological cultures, the study-qualifying culture is the culture that documented the ceftazidime resistance that made the patient eligible for the trial and the supplementary culture is defined as the culture obtained at the Baseline visit prior to receipt of first dose of study therapy. A supplementary culture is required for all patients entering with a cUTI diagnosis. For cIAI patients, a supplementary culture is only required if the patient is undergoing a surgical procedure on or after the date of the Baseline/Randomization visit.

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

General considerations: Refer to Section 12.2.1 for descriptions of summarizations by treatment group. The analysis of the proportion of patients with clinical cure at TOC in the mMITT analysis set is the primary analysis.

Primary efficacy outcome variable: The primary efficacy outcome variable is the proportion of patients with clinical cure at the TOC visit in the mMITT analysis set. For derivation of the efficacy outcome variable refer to Section 11. The number and percentage in each treatment group and entry diagnosis will be tabulated. Indeterminates will be included in the denominator for calculating the percentages for only the mMITT analysis set, but they will be excluded from the denominator for the extended ME analysis set. Two-sided 95% CIs for the proportion of clinical cure at TOC for CAZ-AVI and BAT will be computed using the Wilson method (Wilson 1927). Due to the infeasibility of recruiting larger numbers of patients infected with Gram-negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Forest plots will be used to present the point estimate and the associated 2-sided 95% CI using Wilson's method for the clinical cure rate within each treatment group.

Secondary efficacy outcome variables:

The secondary variables assessing the outcomes are:

- Proportion of patients with clinical cure at the EOT, FU1, and FU2 visits in the mMITT analysis set and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set

- Proportion of patients with clinical cure at the TOC visit by pathogen (eg, *E. coli*, *Klebsiella spp*., *P. aeruginosa*), by resistance mechanism (eg, KPC producer, ESBL producer), and by entry diagnosis (cIAI/cUTI) in the mMITT and extended ME analysis sets

- Proportion of patients with clinical cure by previously failed treatment class (eg, quinolone, β lactam/β lactamase inhibitor, third- or fourth-generation cephalosporin, carbapenem), at the TOC visit in the mMITT analysis set, and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set

- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits in the mMITT and extended ME analysis sets

- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, FU1, and FU2 visits in the mMITT and extended ME analysis sets

- Proportion of patients with a favorable microbiological response at the TOC visit by resistance mechanism (eg, KPC producer, ESBL producer) in the mMITT and extended ME analysis sets

- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits, by MIC categories in the mMITT and extended ME analysis sets

The definitions for the outcomes are presented in Section 6.3. The clinical cure analyses will be presented for the mMITT and extended ME analysis sets. The microbiological response analyses will be presented for the mMITT and extended ME analysis sets. Clinical response rates per-pathogen will also be presented for the mMITT and extended ME analysis sets. If a patient has more than 1 unique causative pathogen identified and has a response of clinical cure, then the patient's clinical response will be a clinical cure for all of the causative pathogens. Conversely, if the patient is a clinical failure, the patient's clinical response will be clinical failure for all of the causative pathogens.

The numbers and percentages in each treatment group, with corresponding 2-sided 95% Wilson CIs in each treatment group, will be presented for all the secondary efficacy variables listed above. The clinical and microbiological secondary efficacy variables will also be presented graphically as Forest plots.

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

General considerations: Refer to Section 12.2.1 for descriptions of summarizations by treatment group. The analysis of the proportion of patients with clinical cure at TOC in the mMITT analysis set is the primary analysis.

Primary efficacy outcome variable: The primary efficacy outcome variable is the proportion of patients with clinical cure at the TOC visit in the mMITT analysis set. For derivation of the

efficacy outcome variable refer to Section 11. The number and percentage in each treatment group and entry diagnosis will be tabulated. Indeterminates will be included in the denominator for calculating the percentages for only the mMITT analysis set, but they will be excluded from the denominator for the extended ME analysis set. Two-sided 95% CIs for the proportion of clinical cure at TOC for CAZ-AVI and BAT will be computed using the **Jeffreys** method (**Brown LD et al. 2001**, **Cai 2005**). Due to the infeasibility of recruiting larger numbers of patients infected with Gram negative resistant pathogens, no formal statistical comparisons between treatment groups will be performed.

Forest plots will be used to present the point estimate and the associated 2-sided 95% CI using **Jeffrey's** method for the clinical cure rate within each treatment group.

Secondary efficacy outcome variables:

The secondary variables assessing the outcomes are:

- Proportion of patients with clinical cure at the EOT, FU1, and FU2 visits in the mMITT analysis set and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set
- Proportion of patients with clinical cure at the TOC visit by pathogen (eg, E. coli, *Klebsiella spp.*, *P. aeruginosa*), by resistance mechanism (eg, KPC producer, ESBL producer), and by entry diagnosis (cIAI/cUTI) in the mMITT and extended ME analysis sets
- Proportion of patients with clinical cure by previously failed treatment class (eg, quinolone, β lactam/β lactamase inhibitor, third- or fourth-generation cephalosporin, carbapenem), at the TOC visit in the mMITT analysis set, and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis set
- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits in the mMITT and extended ME analysis sets
- Proportion of patients with a favorable per-patient microbiological response at the EOT, TOC, FU1, and FU2 visits in the mMITT and extended ME analysis sets
- Proportion of patients with a favorable microbiological response at the TOC visit by resistance mechanism (eg, KPC producer, ESBL producer) in the mMITT and extended ME analysis sets
- Proportion of favorable per-pathogen microbiological response at the EOT, TOC, FU1, and FU2 visits, by MIC categories in the mMITT and extended ME analysis sets

The definitions for the outcomes are presented in Section 6.3. The clinical cure analyses will be presented for the mMITT and extended ME analysis sets. The microbiological response

analyses will be presented for the mMITT and extended ME analysis sets. Clinical response rates per pathogen will also be presented for the mMITT and extended ME analysis sets. If a patient has more than 1 unique causative pathogen identified and has a response of clinical cure, then the patient's clinical response will be a clinical cure for all of the causative pathogens. Conversely, if the patient is a clinical failure, the patient's clinical response will be clinical failure for all of the causative pathogens.

The numbers and percentages in each treatment group, with corresponding 2-sided 95% **Jeffreys** CIs in each treatment group, will be presented for all the secondary efficacy variables listed above. The clinical and microbiological secondary efficacy variables will also be presented graphically as Forest plots.

Reason for the Amendment:

The method for calculating the confidence interval has been changed from that of Wilson to Jeffreys, as the Jeffreys calculation has better properties.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

15. ADMINISTRATIVE CHANGES

Sections of the protocol affected:

Section 6.3.2.3, Section 12.1, Section 14

Previous text, Section 12.1 Description of analysis sets:

The analysis of data will be based on different analysis sets according to the purpose of analysis, ie, for safety and efficacy. The decision regarding validity of data for each of the analysis sets will be based on a review of data, which will occur prior to database lock.

Revised text, Section 12.1 Description of analysis sets:

The analysis of data will be based on different analysis sets according to the purpose of analysis, ie, for safety and efficacy. The decision regarding validity of data for each of the analysis sets will be based on a review of **blinded** data, which will occur prior to database lock.

Reason for the Amendment:

Clarification that blinded data will be reviewed prior to database lock (this change was implemented in global amendment 2 and is highlighted here for further clarity).

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

References added:

Section of protocol affected:

Synopsis, Section 5.5.2.2, Section 12.2.2, and Section 14

Brown 2001
Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical Science 2001; 16:101-133.

Cai 2005
Cai, TT. One-sided confidence intervals in discrete distributions. Journal of Statistical Planning and Inference. 2005; 131:63-68.

FORTAZ® Prescribing information
FORTAZ® (ceftazidime for injection) Prescribing Information. Glaxosmithkline Research Triangle Park NC, USA. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050578s053,050634s020lbl.pdf. Accessed 18 June 2013.

FORTUM® Summary of Product Characteristics
FORTUM® 1g injection Summary of Product Characteristics (SmPC). GlaxoSmithKline UK. Available at http://www.medicines.org.uk/emc/. Accessed 22 April 2013.

Reason for the Amendment:

References added in Synopsis, Section 12.2.2, and Section 5.5.2.2, Section 14.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

References removed:

Previous text, Section 14 List of references:

Murray et al. 2007

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

Wilson 1927

Wilson EB. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc. 1927;22:209-12.

Revised text, Section 14 List of references:

References deleted

Reason for the Amendment:

Reference is no longer cited in the protocol

References updated:

Previous text, Section 14 List of references:

Go et al

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

Revised text, Section 14 List of references:

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

Previous text, Section 14 List of references:

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

Revised text, Section 14 List of references

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

Reason for the Amendment:

Update of references

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team