Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	Ceftazidime avibactam (CAZ-AVI)
Study Code	D4280C00002
Date	[redacted]
Protocol Dated	[redacted]

A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ-AVI, [redacted]) Versus Doripenem Followed by Appropriate Oral Therapy in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, With a Gram-Negative Pathogen in Hospitalized Adults

Sponsor:

AstraZeneca AB, S-151 85 Södertälje, Sweden

Centers affected by the Amendment:

This amendment affects all centers.

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

- Addition of statement that there is to be no delay in beginning antibiotic treatment once the patient has been randomly assigned to treatment
- Clarification of frequency of blood culture assessments
- Correction of the timing of pharmacogenetic sampling
- Clarification that suspicion of complete urinary tract obstruction meets exclusion criteria
- Specification that hypersensitivity to penicillin meets exclusion criteria

- Clarification surrounding general qualifications for switch to oral antibiotics
- Clarification of circumstances under which ciprofloxacin and sulfamethoxazole/trimethoprim are not appropriate for the switch to oral treatment
- Addition of definition of drug-drug interactions, contraindications, and the need for caution in adding or changing concomitant medications in elderly patients
- Specification that all study drug should be discontinued in the event a patient should become pregnant during the study.
- Administrative changes including correction of style and formatting errors

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

Section of protocol affected:

Synopsis and Section 3.1 (study design table)

Additional text added as footnote "a," with subsequent footnotes relettered accordingly:

[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.

Reason for Amendment:

To clarify that the study day terminology (Day −1, Day 0, Day 1) does not specify a 24-hour wait before starting antibiotic therapy, and there should be no delay in starting study treatment once the patient is assigned to treatment.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 3.1 (Figure 1, footnote "a")

Previous text:

[a] The Treatment Period includes the Baseline visit (Day 1),Visits 2 to 15 (Days 2 to 14), and the EOT (IV) visit. Visit 16 (EOT [IV]) must occur and urine specimen for culture must be obtained before the patient starts oral therapy.

Revised text:

[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. The Treatment Period includes the Baseline visit (Day 1), Visits 2 to 15 (Days 2 to 14), and the EOT (IV) visit. Visit 16 (EOT [IV]) must occur and urine specimen for culture must be obtained before the patient starts oral therapy.**

Reason for Amendment:

To clarify that the study day terminology (Day −1, Day 0, Day 1) does not specify a 24-hour wait before starting antibiotic therapy, and there should be no delay in starting study treatment once the patient is assigned to treatment.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 3.1 (Table 1, text in row entitled "Blood cultures")

Previous text:

As clinically indicated

Revised text:

If positive at Baseline, repeat at least every 3 days until negative. Blood cultures may also be obtained as clinically indicated

Reason for Amendment:

To clarify frequency of blood culture assessments

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 3.1 (Table 1)

Additional text added as footnote "a," with subsequent footnotes relettered accordingly:

[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.

Reason for Amendment:

To clarify that the study day terminology (Day −1, Day 0, Day 1) does not specify a 24-hour wait before starting antibiotic therapy, and there should be no delay in starting study treatment once the patient is assigned to treatment.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 3.1 (Table 1, footnote "p," previously footnote "o")

Previous text:

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

Revised text:

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

Reason for Amendment:

To clarify frequency of blood culture assessments

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 3.1 (Table 1, footnote "s," previously footnote "r")

Previous text:

[r] The pharmacogenetic sample should be taken from consented patients prior to commencement of study therapy. If this sample is not taken prior to the initiation of study therapy, it may be taken at Visit 3.

Revised text:

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

Reason for Amendment:

To correct the timing of pharmacogenetic sampling

Persons who initiated the Amendment:

[redacted] CAZ-AVI Clinical Project Team

Section of protocol affected:

Exclusion criterion #8

Previous text:

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

Revised text:

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

Reason for Amendment:

To clarify that suspicion of complete obstruction meets exclusion criterion

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Exclusion criterion #11

Previous text:

11. Patient has a history of hypersensitivity (eg, anaphylaxis), serious allergy, or any serious reaction to carbapenem or cephalosporin or other β-lactam antibiotics.

Revised text:

11. Patient has a history of hypersensitivity (eg, anaphylaxis), serious allergy, or any serious reaction to carbapenem, cephalosporin, penicillin, or other β-lactam antibiotics.

Reason for Amendment:

To add hypersensitivity to penicillin as reason for exclusion

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 5.5.3 (first paragraph)

Previous text:

If all of the following criteria for clinical improvement are met, patients may be switched to oral ciprofloxacin (or oral sulfamethoxazole/trimethoprim) after receiving a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy administered in the hospital.

Revised text:

If all of the following criteria for clinical improvement are met, patients may be switched to oral antibiotics after receiving a minimum of 5 full days (ie, 15 doses for patients whose estimated CrCl remains >50 mL/min) of IV study therapy administered in the hospital.

Reason for Amendment:

To increase clarity surrounding general qualifications of switch to oral antibiotics

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 5.5.3 (2nd paragraph below numbered list)

Previous text:

The choice of oral antimicrobials allowed per protocol is limited to 1 preferred oral option and 1 alternative oral option to decrease confounding factors when analyzing the study efficacy data. The oral option of choice is 500 mg ciprofloxacin taken orally twice daily. If the patient has a fluoroquinolone-resistant pathogen, the patient may receive oral sulfamethoxazole/trimethoprim (800 mg/160 mg) taken twice daily as the alternative option.

Revised text:

The choice of oral antimicrobials allowed per protocol is limited to 1 preferred oral option and 1 alternative oral option to decrease confounding factors when analyzing the study efficacy data. The oral option of choice is 500 mg ciprofloxacin taken orally twice daily. If the patient has a fluoroquinolone-resistant pathogen or a contraindication to ciprofloxacin (ie, hypersensitivity to quinolones or ciprofloxacin or any of its product components; concomitant administration of tizanidine), the patient may receive oral sulfamethoxazole/trimethoprim (800 mg/160 mg) taken twice daily as the alternative option.
Sulfamethoxazole/trimethoprim should not be used if the patient has a sulfamethoxazole/trimethoprim-resistant pathogen or a contraindication to sulfamethoxazole/trimethoprim (ie, hypersensitivity to sulfamethoxazole or trimethoprim, a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides, documented megaloblastic anemia secondary to folate deficiency, marked hepatic damage, or severe renal insufficiency when renal function status cannot be monitored).

Reason for Amendment:

To specify circumstances under which ciprofloxacin and sulfamethoxazole/trimethoprim are not appropriate for the switch to oral treatment

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 5.5.3 (3rd paragraph below numbered list)

Previous text:

If there is a valid reason that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are an appropriate choice, (eg, patient is hypersensitive to either ciprofloxacin or sulfamethoxazole/trimethoprim) the investigator will be required to discuss patient

management with the medical monitor and provide additional documentation as per directives in the study center manual. The uropathogen(s) must be susceptible to the switched oral medication.

Revised text:

If there is a valid reason that neither ciprofloxacin nor sulfamethoxazole/trimethoprim are an appropriate choice, the investigator will be required to discuss patient management with the medical monitor and provide additional documentation as per directives in the study center manual. The uropathogen(s) must be susceptible to the switched oral medication.

Reason for Amendment:

To broaden the statement so as to include all circumstances under which neither ciprofloxacin nor sulfamethoxazole/trimethoprim is an appropriate choice

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 5.6 (new subsection 5.6.1)

Previous text:

There is significant drug-drug interaction between doripenem and valproic acid or sodium valproate; therefore, coadministration of study drug and valproic acid or sodium valproate should be avoided.

Revised text:

5.6.1 Drug-drug interactions

A number of unfavorable reactions with other drugs are known for ceftazidime, doripenem, ciprofloxacin, and sulfamethoxazole/trimethoprim. Contraindications for these agents and known drug interactions are summarized in **Error! Reference source not found.**.

Drug-antibiotic interactions occur with many medications commonly prescribed in older adults, particularly those drugs with a narrow therapeutic index. Therefore, extra caution is advised in the event that concomitant medications need to be changed or added for elderly patients.

Reason for Amendment:

To more clearly define drug-drug interactions, contraindications, and the need for caution in adding or changing concomitant medications in elderly patients

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 5.6 (new Table 5)

Added table:

Table 5 Contraindications and drug-drug interactions

Study drug	Drug-drug interaction
Ceftazidime	Concurrent administration with chloramphenicol should be avoided. Chloramphenicol has been shown to be antagonistic to β-lactam antibiotics, including ceftazidime. Concurrent administration with aminoglycoside antibiotics or potent diuretics such as furosemide may result in nephrotoxicity. Because of potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics, renal function should be carefully monitored, especially if higher dosages of aminoglycosides are to be administered or if therapy is prolonged. Concurrent administration with combined oral estrogen/progesterone contraceptives may result in lower estrogen reabsorption and reduced efficacy of these contraceptives secondary to the effects of ceftazidime on gut flora.
Doripenem	Concurrent administration with probenecid is not recommended. Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. Concurrent administration with valproic acid increases the risk for breakthrough seizures through decreased plasma concentrations of valproic acid below the therapeutic range. Supplemental anti-convulsant therapy should be considered if administration of doripenem is necessary.
Ciprofloxacin	Administration in pregnant or lactating women is contraindicated.

Table 5 Contraindications and drug-drug interactions

Study drug	Drug-drug interaction
	Concurrent administration with tizanidine is contraindicated.
	Concurrent administration with methotrexate is not recommended; methotrexate may inhibit renal tubular transport of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions.
Ciprofloxacin	Concurrent administration with theophylline decreases theophylline clearance, resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions.
	Concurrent administration with caffeine or pentoxifylline (oxpentifylline) may raise serum concentrations of these xanthine derivatives.
	Concurrent administration with antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%.
	Concurrent administration with probenecid interferes with renal secretion of ciprofloxacin and increases ciprofloxacin serum concentrations.
	Concurrent administration with phenytoin may result in increased or reduced serum levels of phenytoin; monitoring of drug levels is recommended.
	Concurrent administration with warfarin may augment its anticoagulant effects. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of a fluoroquinolone to an increased international normalized ratio (INR) is difficult to assess. It is recommended that INR be monitored frequently during and shortly after coadministration of ciprofloxacin with an oral anticoagulant agent.

Table 5 Contraindications and drug-drug interactions

Study drug	Drug-drug interaction
	Concurrent administration with ropinirole increases the maximum plasma concentration (Cmax) of ropinirole by as much as 60%. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after coadministration with ciprofloxacin. Concurrent administration with clozapine increases serum concentrations of clozapine and N-desmethylclozapine, a metabolite, by as much as 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are recommended.
Sulfamethoxazole/ trimethoprim	Administration in pregnant or lactating women is contraindicated. Concurrent administration in elderly patients along with certain diuretics, primarily thiazides, may result in thrombocytopenia with purpura. Concurrent administration with digoxin may result in increased digoxin blood levels, especially in elderly patients. Serum digoxin levels should be monitored. Concurrent administration with warfarin may prolong prothrombin time; coagulation time should be reassessed. Concurrent administration with phenytoin may inhibit hepatic metabolism of phenytoin; possible excessive phenytoin effect should be monitored. Concurrent administration of sulfonamides with methotrexate can result in competition for renal transport of methotrexate, resulting in increased free methotrexate concentrations. A folate supplement should be considered in patients receiving anti-folate drugs such as methotrexate.

Table 5 Contraindications and drug-drug interactions

Study drug	Drug-drug interaction
	Concurrent administration with cyclosporine in renal transplant recipients may result in marked but reversible nephrotoxicity.
	Concurrent administration with indomethacin may result in increased sulfamethoxazole blood levels.
	Concurrent administration with pyrimethamine in doses exceeding 25 mg weekly may result in development of megaloblastic anemia.
	Concurrent administration with tricyclic antidepressants can decrease the efficacy of these agents.
Sulfamethoxazole/ trimethoprim	Concurrent administration with oral hypoglycemic agents potentiates their effects. Potentiation of sulfonylurea hypoglycemic agents is uncommon but has been reported.
	Concurrent administration with amantadine has resulted in a rare case of toxic delirium.
	Concurrent administration with drugs that form cations at physiological pH and are also partly excreted by active renal secretion (eg, procainamide, amantadine), may increase the possibility of competitive inhibition of this process, which may lead to an increase in plasma concentration of one or both of the drugs.
	Concurrent administration with any drugs that may cause hyperkalemia (eg, angiotensin-converting enzyme inhibitors) may increase the possibility of developing hyperkalemia
	Concurrent administration with zidovudine may increase the risk of hematological adverse reactions. If concomitant treatment is necessary, consideration should be given to monitoring of hematological parameters.
	Concurrent administration of trimethoprim with lamivudine may result in increased lamivudine exposure.

Reason for Amendment:

To add a detailed list of contraindications and drug-drug interactions relevant to treatment with ceftazidime, doripenem, ciprofloxacin, and sulfamethoxazole/trimethoprim

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 6.2.3 (Item #11)

Previous text:

11. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated (repeat daily if initial culture is positive or as clinically indicated)

Revised text:

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

Reason for Amendment:

To clarify frequency of blood culture assessments

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 6.2.4 (Item #13)

Previous text:

13. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated

Revised text:

13. If repeat cultures have not been finalized negative by the time of the EOT visit, a set of repeat blood cultures should be obtained

Reason for Amendment:

To clarify frequency of blood culture assessments

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 6.2.5 (Item #12)

Previous text:

12. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated

Revised text:

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

Reason for Amendment:

To clarify frequency of blood culture assessments

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 6.2.6 (Item #12)

Previous text:

12. Obtaining a blood sample for blood culture if previous blood culture was positive and also as clinically indicated

Revised text:

12. If repeat cultures have not been finalized negative by the time of the LFU visit, a set of repeat blood cultures should be obtained

Reason for Amendment:

To clarify frequency of blood culture assessments

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team

Section of protocol affected:

Section 13.3

Previous text:

If a patient becomes pregnant during the course of the study, CAZ-AVI should be discontinued immediately.

Revised text:

If a patient becomes pregnant during the course of the study, study drug (both IV and oral) should be discontinued immediately.

Reason for Amendment:

To specify that all study drug should be discontinued in the event a patient should become pregnant during the study.

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team