Clinical Study Protocol Amendment	
Amendment Number	3
Drug Substance	Ceftazidime-Avibactam
Study Code	D4280C00018
Date	[redacted]
Protocol Dated	[redacted]

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

Sponsor:

AstraZeneca AB, S-151 85 Södertälje, Sweden

Centres affected by the Amendment:

This amendment affects all centers in the study

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

1. Amendment of exclusion criteria on estimated creatinine clearance.

2. Clarification of the doses and treatment regimens for patients whose estimated creatinine clearance drops to ≤50 mL/min while on IV study therapy.

3. Amendment of medical emergencies and SAE contacts information

1. AMENDMENT OF EXCLUSION CRITERIA ON ESTIMATED CREATININE CLEARANCE.

Section of protocol affected:

Section 4.2

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

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

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

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

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

(a) Estimated creatinine clearance ≤ **50 mL/min** calculated by Cockcroft Gault method (Cockcroft et al 1976). Refer to Appendix D for calculation information. (**For patients enrolled into the study whose creatinine clearance drops to ≤50 mL/min while on IV study therapy, the study drug dosing instructions are provided in sections 5.5.2.2 and 5.5.2.3 and should be closely followed.)**

Reason for Amendment:

In the RECLAIM Phase III studies [study codes: D4280C00001 and D4280C00005] in patients with complicated intra-abdominal infections (cIAI), CAZ-AVI met the primary objective of statistical non-inferiority compared to meropenem. However, subgroup analyses indicated that cIAI patients with moderate renal impairment at study baseline (MRIB; defined as estimated creatinine clearance [CrCl] ≤50 mL/min calculated by the Cockcroft-Gault method) who were treated with CAZ-AVI plus metronidazole had a lower cure rate compared to patients treated with meropenem. There was also a numerical imbalance between the treatment groups in terms of deaths in the MRIB subgroup (8 deaths in the CAZ-AVI MRIB subgroup compared to 3 deaths in the meropenem MRIB subgroup).

Although the treatment difference in clinical cure rate observed in the MRIB subgroup could be the result of small numbers in a subgroup analysis, the magnitude of the effect leads AstraZeneca to consider that at least part of the effect was due to a lack of timely dose adjustments in a subset of patients with rapidly improving renal function in the first few days of treatment. Since it would be challenging to determine which of the MRIB patients will undergo rapidly improving renal function vs. those whose renal function will remain stable in the first few days after study entry, AstraZeneca has decided to exclude from study entry all patients with moderate renal impairment at study baseline.

2. CLARIFICATION OF THE DOSES AND TREATMENT REGIMENS FOR PATIENTS WHOSE ESTIMATED CREATININE CLEARANCE DROPS TO ≤50 ML/MIN WHILE ON IV STUDY THERAPY.

Section of protocol affected:

Synopsis; Section 5.5.2; Section 5.5.2.2; Section 5.5.2.3

Previous text: Synopsis (text to be deleted underlined)

Investigational product (CAZ-AVI plus metronidazole), dosage, and mode of administration

Patients randomized to receive CAZ-AVI will receive meropenem placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 30 minutes, immediately followed by CAZ-AVI (500 mg of avibactam and 2000 mg of ceftazidime) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes, immediately followed by metronidazole (500 mg) administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes. In patients with normal renal function and patients with mild renal impairment, treatments will be repeated every 8 hours (±30 minutes); dose regimen adjustments for patients with moderately impaired renal function are described in Section 5.5.2.2. Details for administration of CAZ-AVI, metronidazole, and meropenem placebo can be found in the handling instructions document.

Comparator (meropenem), dosage, and mode of administration

Patients randomized to receive the comparator will receive meropenem (1000 mg) administered by IV infusion in a volume of 100 mL at a constant rate over 30 minutes, immediately followed by CAZ-AVI placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes, immediately followed by metronidazole placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes. In patients with normal renal function and patients with mild renal impairment, treatments will be repeated every 8 hours (±30 minutes); dose regimen adjustments for patients with moderately impaired renal function are described in Section 5.5.2.2. Details for administration of meropenem, CAZ-AVI placebo, and metronidazole placebo can be found in the handling instructions document.

Revised text: Synopsis (new text in bold and underlined)

Investigational product (CAZ-AVI plus metronidazole), dosage, and mode of administration

Patients randomized to receive CAZ-AVI will receive meropenem placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 30 minutes, immediately followed by CAZ-AVI (500 mg of avibactam and 2000 mg of ceftazidime) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes, immediately followed by metronidazole (500 mg) administered by IV infusion in a volume of.

100 mL at a constant rate over 60 minutes. In patients with normal renal function and patients with mild renal impairment, treatments will be repeated every 8 hours (±30 minutes); **dose regimen adjustments for patients whose CrCl drops to ≤ 50 mL/min while on IV study therapy are described in Section 5.5.2.2 and 5.5.2.3** Details for administration of CAZ-AVI, metronidazole, and meropenem placebo can be found in the handling instructions document.

Comparator (meropenem), dosage, and mode of administration

Patients randomized to receive the comparator will receive meropenem (1000 mg) administered by IV infusion in a volume of 100 mL at a constant rate over 30 minutes, immediately followed by CAZ-AVI placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 120 minutes, immediately followed by metronidazole placebo (0.9% saline) administered by IV infusion in a volume of 100 mL at a constant rate over 60 minutes. In patients with normal renal function and patients with mild renal impairment, treatments will be repeated every 8 hours (±30 minutes); **dose regimen adjustments for patients whose CrCl drops to ≤ 50 mL/min while on IV study therapy are described in Section 5.5.2.2 and 5.5.2.3**. Details for administration of meropenem, CAZ-AVI placebo, and metronidazole placebo can be found in the handling instructions document.

Previous text: Section 5.5.2 (text to be deleted underlined)

Patients randomized to receive CAZ-AVI will receive meropenem placebo (0.9% saline) intravenously immediately followed by CAZ-AVI (500 mg of avibactam and 2000 mg of ceftazidime) intravenously, immediately followed by metronidazole (500 mg) intravenously. Patients randomized to receive the comparator, meropenem, will receive meropenem intravenously, immediately followed by CAZ-AVI placebo (0.9% saline) intravenously, immediately followed by metronidazole placebo (0.9% saline) intravenously.

Meropenem (1000 mg) / meropenem placebo will be given in a 100-mL infusion bag at a constant IV rate over 30 minutes, CAZ-AVI/ CAZ-AVI placebo will be given in a 100 mL infusion bag at a constant IV rate over 120 minutes, and metronidazole (500 mg)/metronidazole placebo will be give in a 100 mL infusion bag at a constant IV rate over 60 minutes. Dosing intervals for patients with normal renal function and mild renal impairment are described in Section5.5.2.1; dose and dose interval adjustments for patients with moderate renal impairment are described in Section 5.5.2.2.Details for administration of meropenem / meropenem placebo, CAZ-AVI / CAZ-AVI placebo, and metronidazole / metronidazole placebo can be found in the handling instructions document.

Investigators should take into account the approximate 900 mL of normal saline (sodium chloride 0.9%USP) that patients will receive when assessing the patient's daily fluid intake.

Revised text: Section 5.5.2 (new text in bold and underlined)

Patients randomized to receive CAZ-AVI will receive meropenem placebo (0.9% saline) intravenously immediately followed by CAZ-AVI (500 mg of avibactam and 2000 mg of ceftazidime) intravenously, immediately followed by metronidazole (500 mg) intravenously.

Patients randomized to receive the comparator, meropenem, will receive meropenem intravenously, immediately followed by CAZ-AVI placebo (0.9% saline) intravenously, immediately followed by metronidazole placebo (0.9% saline) intravenously.

Meropenem (1000 mg) / meropenem placebo will be given in a 100-mL infusion bag at a constant IV rate over 30 minutes, CAZ-AVI/ CAZ-AVI placebo will be given in a 100 mL infusion bag at a constant IV rate over 120 minutes, and metronidazole (500 mg)/metronidazole placebo will be give in a 100 mL infusion bag at a constant IV rate over 60 minutes. Dosing intervals for patients with normal renal function and mild renal impairment are described in Section 5.5.2.1; **dose and dose interval adjustments for patients whose creatinine clearance drops to ≤ 50 mL/min while on IV study therapy are described in Section5.5.2.2 and 5.5.2.3.** Details for administration of meropenem / meropenem placebo, CAZ-AVI / CAZ-AVI placebo, and metronidazole / metronidazole placebo can be found in the handling instructions document.

Investigators should take into account the approximate 900 mL of normal saline (sodium chloride 0.9%USP) that patients will receive when assessing the patient's daily fluid intake.

For patients enrolled into the study whose creatinine clearance drops to ≤50 ml/min while on IV study therapy, follow the instructions in sections 5.5.2.2 and 5.5.2.3

Previous text: Section 5.5.2.2 (text to be deleted underlined)

5.5.2.2 Dose adjustments for patients with moderate renal impairment (CrCl 31 to 50 mL/min)

Serum creatinine levels must be measured at the local laboratory during Screening (Days 1 to 0) and as clinically indicated thereafter. In order to determine the need to adjust the dose and/or dosing interval of IV study therapy to be administered, the patient's estimated creatinine clearance must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the patient's most recent actual (not ideal) body weight, and the Cockcroft Gault formula provided in Appendix D. The results must be recorded in the eCRF.

Dose adjustments for CAZ-AVI or meropenem for patients with an estimated creatinine clearance between 31 and 50 mL/minute (moderate renal impairment) are outlined in Table 3 and Table 4. A schematic of the dosing intervals for patients with moderate renal impairment is displayed in Figure 4. Since decreased renal function does not alter the pharmacokinetics of metronidazole, dosing adjustments for metronidazole are not needed.

If necessary, a 1-time dosing interval adjustment can be made after the first dose of IV study therapy to create a suitable dosing schedule. The dosing interval adjustment must be such that the second dose is given a minimum of 8 hours and a maximum of 12 hours after the first dose (ie, a –4 hour window is allowed for the second dose). If a 1-time dose interval adjustment is made for the second dose, all further dosing times will be calculated based on the time of the

second dose. If a dose adjustment is made, the end of the first dose day should be modified to be consistent with the dose adjustment.

Revised text: Section 5.5.2.2 (new text in bold and underlined)

5.5.2.2 **Dose regimen adjustments for patients whose CrCl drops between 31 to 50 mL/min while on IV study therapy**

Serum creatinine levels must be measured at the local laboratory during Screening (Days 1 to 0) and as clinically indicated thereafter. In order to determine the need to adjust the dose and/or dosing interval of IV study therapy to be administered, the patient's estimated creatinine clearance must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the patient's most recent actual (not ideal) body weight, and the Cockcroft Gault formula provided in Appendix D. The results must be recorded in the eCRF.

Dose adjustments for CAZ-AVI or meropenem **for patients whose estimated creatinine clearance drops between 31 and 50 mL/minute while on IV study therapy are outlined in Table 3 and Table 4**. A schematic of the dosing intervals for patients with moderate renal impairment is displayed in Figure 4.Since decreased renal function does not alter the pharmacokinetics of metronidazole, dosing adjustments for metronidazole are not needed.

Section 5.5.2.3, first paragraph

Previous text: (text to be deleted underlined)

If subsequent to study entry and while still on IV study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (ie, estimated CrCl falls below 31mL/min), retesting should be performed promptly. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl is below 31 mL/min, the investigator should use his or her discretion in determining whether an immediate dose change, a short period of continued observation, or discontinuation of therapy is warranted. Once a dose change is decided upon, the investigator should inform the dispensing pharmacist immediately. The pharmacist should then provide the appropriate dose adjustments as outlined in Table 5, to allow the patient to continue blinded study therapy.

Revised text:

If subsequent to study entry and while still on IV study therapy, a patient's estimated CrCl falls below the threshold for study inclusion, retesting should be performed promptly. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl is below 31 mL/min, the investigator should use his or her discretion in determining whether an immediate dose change, a short period of continued observation, or discontinuation of therapy is warranted. Once a dose change is decided upon, the investigatorshould inform the dispensing pharmacist immediately. The pharmacist should then provide the appropriate dose adjustments as outlined in Table 5, to allow the patient to continue blinded study therapy.

Reason for Amendment:

To provide additional clarity for dosing patients enrolled into the study whose creatinine clearance drops to ≤50 ml/min after study entry.

3. AMENDMENT OF MEDICAL EMERGENCIES AND SAE CONTACTS INFORMATION

Section of protocol affected:

Section 13.1

Previous text: (text to be deleted underlined)

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

Revised text: (new text in bold and underlined)

Name	Role in the study	Address and telephone number
[redacted]	Study Physician	[redacted]
[redacted]	**Clinical Development Manager**	AstraZeneca [redacted]

Reason for Amendment

Change of personal

Persons who initiated the Amendment:

AstraZeneca CAZ-AVI Clinical Project Team