Statistical Analysis Plan

Study Code C3591004 (D4280C00015)

Edition Number 2.0

Date 24th August 2017

A single blind, randomised, multi-centre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
AEoSI	adverse event of special interest
ALT	alanine aminotransaminase
AST	aspartate aminotransaminase
BDR	blinded data review
BMI	body mass index
CAZ-AVI	ceftazidime-avibactam
CE	clinically evaluable
CFB	change from baseline
CFU	colony forming unit
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
CrCl	creatinine clearance
CRP	c-reactive protein
CSP	clinical study protocol
CSR	clinical study report
CV	coefficient of variation
DSMB	data safety monitoring board
DOB	date of birth
ECG	electrocardiogram
EOIV	end of intravenous treatment
EOT	end of treatment
HR	heart rate
β-hCG	ß-human chorionic gonadotropin
IAI	Intra-abdominal infection
ITT	intent-to-treat
IV	intravenous
LFU	late follow-up

Abbreviation or special term	Explanation
LLN	lower limit of the normal range
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
Micro-ITT	microbiological intent-to-treat
N	number of patients or counts
NQ	not quantifiable
NR	not recorded
PCS	potentially clinical significant
PK	Pharmacokinetic
QT_m	QT measured
QT_cB	QT interval corrected using Bazett's formula
QT_cF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SMQ	standardised MedDRA search query
SOC	system organ class
TOC	test of cure
ULN	upper limit of the normal range
WBC	white blood cells

AMENDMENT HISTORY

Date	Brief description of change
17Apr2015	PPD, first version
05May2015	PPD, updates made based upon first round of sponsor review
12Jun2015	PPD, updates made based upon second round of sponsor review
24Aug2017	PPD, updates based upon protocol amendment edition 2 March 7 2017 Incorporated changes from blind data review for CAZAVI-CAZ016 study Incorporated changes from blind data review for CAZAVI-CAZ015 Major changes include: • Added ITT and Micro ITT analysis sets to the analysis in line with CCI; • Amended permissible visit windows for clinical and microbiological response; • Added in description to include total treatment statistics for table summaries; • Clarified approach with respect to microbiological definitions, including definition of response, selection of pathogen, determination of susceptibility, and grouping of pathogens; • Updated derivation of age for patients with missing date of birth; • Added description of oral medications table summary; • Amended AEs of SI to summarize by topic; • Represented change in sponsor from AstraZeneca to Pfizer; • Added clarification and appendix for ECMA process; • Amended approach for summarising laboratory abnormality criteria.

1. STUDY DETAILS

1.1. Study objectives

Primary objective (Safety)

- Evaluate the safety and tolerability of ceftazidime-avibactam (CAZ-AVI) plus metronidazole given at the selected dose regimen versus meropenem in paediatric patients aged ≥3 months to <18 years with complicated intra-abdominal infections (cIAI).

Secondary objectives

- Evaluate the descriptive efficacy of CAZ-AVI plus metronidazole versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI.
- Evaluate the pharmacokinetic (PK) of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cIAI.

Exploratory objectives

Not applicable.

1.2. Study design

This study is a single blind, randomised, multi-centre, active controlled trial. Patients aged from 3 months to less than 18 years with cIAI will be randomised to 1 of 2 groups (3:1 ratio): CAZ-AVI in combination with metronidazole versus meropenem.

Intravenous (IV) CAZ-AVI infusions will be given at the following doses per cohort:

- Cohorts 1 and 2: 2000 mg CAZ/500 mg AVI every 8 hours for patients ≥40 kg weight or 50 mg/kg CAZ/12.5 mg/kg AVI every 8 hours for patients <40kg weight, given as a 2-hour infusion.
- Cohorts 3 and 4a: 50 mg/kg CAZ/12.5 mg/kg AVI every 8 hours given as a 2-hour infusion.
- 4b: 50mg/kg CAZ/12.5mg/kg AVI every 8 hours for patients ≥6 months to <1 year, and 40mg/kg CAZ/10mg/kg AVI every 8 hours for patients ≥3 months to <6 months.

Patients whose creatinine clearance (CrCl) falls to ≤50 mL/min (adjusted to mL/min/1.73m^2 using Schwartz formula) while on treatment should have a CAZ-AVI dose reduction of 50% administered every 8 hours. Patients whose CrCl drops below 30 mL/min should be removed from study therapy. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl is approaching thresholds that would require intervention such as a dose change or discontinuation of therapy (ie CrCl approaching 50 or 30 mL/min), the Investigator should use his or her discretion in determining (ie confirming the value by repeat testing, if feasible) whether an immediate dose change, a short period of continued observation, or discontinuation of therapy is warranted.

Meropenem 20 mg/kg every 8 hours (±1 hour) given by IV infusion over approximately 15 to 30 minutes or up to 1 hour, or infusion duration as per local guidelines, with optional oral switch therapy as described above. For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours. For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours. Randomisation will be stratified as follows:

- Cohort 1: patients aged from 12 years to <18 years;
- Cohort 2: patients aged from 6 years to <12 years;
- Cohort 3: patients aged from 2 years to <6 years;
- Cohort 4: patients aged from 3 months to <2 years.

Patients will receive IV treatment for a minimum of 72 hours (3 full days, ie, 9 doses) before having the option to switch to an oral therapy, at the Investigator's discretion. The total period of treatment (ie, IV drug and oral switch treatment) is to be between 7 and 15 days. Patients may remain in the IV study treatment for the full 7 to 15 days.

Patients will be assessed for safety and efficacy throughout the study, and blood samples will be taken for PK assessment. The duration of each patient's participation in the study will be a minimum of 27 days to a maximum of 50 days after start of study treatment (defined as the time point at which first dose of study treatment is administered) at which time there will be a late follow-up (LFU) assessment visit. The LFU is to be performed 20 to 35 days after the last dose of any treatment.

1.3. Number of subjects

Patients will continue to be recruited into this study until 80 patients complete at least 72 hours (3 full days, ie, 9 doses) of study treatment (deemed to be evaluable patients).Patients will be randomised 3:1 to the CAZ-AVI plus metronidazole or meropenem study treatment groups. At least 60 and 20 evaluable patients, respectively, are required in the CAZ-AVI plus metronidazole and meropenem groups.

The proposed sample size is based on the probability of observing a 'rare' safety event. The 'rare' term used in this section is not based on the regulatory definition but is instead intended to reflect uncommon events. Safety data from this study and from Study D4280C00016 for complicated urinary tract infection will be combined for analysis. As a total of at least 120 patients will be treated with CAZ-AVI in both studies combined, when assuming an underlying incidence rate of 3% for a specific 'rare' event, this will ensure that the probability of observing such an event in at least 1 patient treated with CAZ-AVI exceeds 95%.

In addition, each of the 4 patient cohorts is required to have a minimum number of evaluable patients as follows:

- Cohort 1: At least 15:5 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 15:5 evaluable patients aged from 6 years to <12 years;
- Cohort 3: No required minimum of evaluable patients aged from 2 years to <6 years.
- Cohort 4: No required minimum of evaluable patients aged from 3 months to <2 years, comprising Cohorts 4a and 4b as follows:
    - Cohort 4a: Patients aged from 1 year to <2 years;
    - Cohort 4b: Patients aged from 3 months to <1 year.

Considering patients over all 4 cohorts combined, the maximum number of evaluable patients allowed to have been recruited having been diagnosed with complicated appendicitis is 90%.

Patients who are randomized and registered as having ended IV treatment with less than 9 doses do not meet the criteria for evaluable patients and will be eligible for enrolment replacement. Data from these replaced patients will be included in the safety analysis set (and not the safety evaluable analysis set). The process of replacement will ensure that the next patient randomized in the same stratum will be automatically assigned the same treatment group as the non-evaluable patient who needs to be replaced. The purpose of this is to minimise over-recruitment to reach the required number of evaluable patients in each treatment arm. Replacement subjects can themselves be replaced (up to a maximum of 5 replacements per allocated randomization code).

2. ANALYSIS SETS

2.1. Definition 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 final decision regarding eligibility of patients for all analysis sets will be finalised prior to declaring database lock. Specifically the manual aspect of the assessments for the clinically evaluable (CE) and microbiologically evaluable (ME) analysis sets will be undertaken by an evaluability review committee, including at a minimum: medical personnel, a microbiologist, and a statistician. The review will focus on data for which analysis set criteria cannot be determined programmatically, eg, protocol deviations and the use of prohibited concomitant medications. Preparation of data will be performed by unblinded study team members (protocol deviation data is potentially unblinding), and information will be presented in a blinded manner for decision making by the evaluability review committee. A more detailed outline of the criteria which will be determined by this review is included within Section 8.1.

2.1.1. Safety Analysis Set

The Safety analysis set will include all randomised patients who received any amount of IV study therapy (ie, CAZ-AVI plus metronidazole or meropenem). For the Safety analysis set, patients will be included in all outputs according to the study treatment they actually received.

2.1.2. Safety Evaluable Analysis Set

The safety evaluable analysis set will be a subset of the patients in the Safety analysis set that received at least 9 doses of study treatment. Each subject's dosing profile will be reviewed by unblinded medical personnel to confirm evaluability. Any cases that are not clear will be identified and presented in a blinded manner at a formal evaluability and clinical/microbiological assessment (ECMA) meeting to determine whether the subject is acceptable for inclusion in the safety evaluable analysis set.

2.1.3. PK Analysis Set

The PK analysis set will be a subset of the patients in the Safety analysis set who have at least 1 ceftazidime and/or avibactam plasma measurement available.

2.1.4. Efficacy analysis sets

The efficacy analysis of data in this study will be based on 4 subsets of patients (intent-to-treat (ITT), microbiological intent-to-treat (micro-ITT), CE and ME analysis sets) as defined below. The CE and ME analysis sets will be defined separately for each of the visits at which efficacy is assessed.

Patients who receive both study therapies will be excluded from these CE and ME analysis sets. Patients in the ITT, micro-ITT, CE and ME analysis sets will be summarized according to the randomized treatment assignment.

2.1.4.1. Intent-to-Treat Analysis Set

The ITT analysis set will include all patients who have been assigned a randomised treatment.

2.1.4.2. Microbiological intent-to-treat set

The micro-ITT set will include all randomised patients who have a baseline pathogen known to cause cIAI. All baseline pathogens isolated from the intraabdominal fluid or blood will be examined by a microbiologist prior to DBL and a list of those which cause cIAI will be identified in order to define this analysis set.

2.1.4.3. Clinically Evaluable Analysis Set

The CE analysis set is defined at the end of 72 hours of study treatment (determined by the 72 hour efficacy assessment visit), and at each of the End of Intravenous Treatment (EOIV), End of Treatment (EOT), Test of Cure (TOC) and Late Follow up (LFU) visits.

The CE analysis set will include all randomised patients who receive any amount of IV study drug and have a confirmed diagnosis of cIAI; patients must also meet the following specific conditions:

- Have received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;
- Have received at least 72 hours of IV study drug, defined as 9 doses, in order to be considered an evaluable clinical cure;
- Have been evaluated at the End of 72 hours assessment and at the specific visits of EOIV, EOT, and TOC with a clinical response of cure or failure (or have been assessed as a clinical failure at or after EOIV and before the planned assessment visit), or for LFU, have been evaluated with a clinical response of sustained cure or relapse;
- Had no important protocol deviations that would affect assessment of efficacy;
- Have not received concomitant antibiotics that would affect assessment of efficacy.

2.1.4.4. Microbiologically Evaluable Analysis Set

The ME analysis set will be defined at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC and LFU visits. It includes all patients meeting the following criteria:

- Randomised patients who have received any amount of IV study drug and have a confirmed diagnosis of cIAI;
- Have received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;
- Have received at least 72 hours of IV study drug, defined as 9 doses, in order to be considered an evaluable clinical cure;
- At the specific visit had a microbiological response which was not indeterminate (note; presumed eradication or presumed persistence is acceptable);
- Had no important protocol deviations that would affect assessment of efficacy;
- Have not received concomitant antibiotics that would affect assessment of efficacy;
- Have at least 1 typical intra-abdominal infection (IAI) bacterial pathogen which has been isolated from an adequate microbiological specimen at Baseline that is susceptible to both study agents (CAZ-AVI and meropenem).

2.1.4.4.1. Susceptibility to study drug for ME Analysis Set

Susceptibility to ceftazidime-avibactam for baseline pathogen species of *Enterobacteriaceae* and *P. aeruginosa* will be determined programmatically. A patient will be counted as having had at least 1 etiologic pathogen in the initial/pre-study culture that is susceptible to both treatment arms if;

For cases when a central microbiology reference laboratory result is present, a pathogen that satisfies the following interpretive criteria of susceptibility:

- Displays an MIC of ceftazidime-avibactam ≤ 8 mg/L for *Enterobacteriaceae* and/or *P. aeruginosa* (2017 FDA label, ceftazidime-avibactam highlights of prescribing information), categorizing it as susceptible to the combination;

- and displays an MIC of meropenem that categorizes it as susceptible by CLSI interpretive criteria, namely ≤ 1 mg/L for *Enterobacteriaceae*, ≤ 2 mg/L for *P. aeruginosa* (CLSI 2012).

For cases when the local lab result is used, a pathogen that satisfies the following interpretive criteria of susceptibility:

- displays a disk diffusion diameter for ceftazidime-avibactam (30 μg ceftazidime and 20 μg of avibactam) greater than or equal to the susceptible breakpoint, ie, ≥ 21 mm for *Enterobacteriaceae* and *P. aeruginosa* (2017 FDA label, ceftazidime-avibactam highlights of prescribing information);

- and disk diffusion diameters categorizing the isolate as susceptible to meropenem judged on the CLSI interpretive criteria of ≥ 23 mm for *Enterobacteriaceae* and ≥ 19 mm for *P. aeruginosa* (CLSI 2012).

Pathogen species not included in the definition above can not be confirmed to be susceptible and therefore would not meet the criteria to be included in ME analysis sets.

2.2. Violations and deviations

Protocol deviations are defined as any variations from the protocol, including enrolment of a patient who did not meet all inclusion and exclusion criteria and failed to perform the assessments and procedures within the required time frame. Protocol deviations will be summarized in two ways: a) a summary table will display counts of patients with important protocol deviations and b) the analysis sets table will display the counts of patients excluded from CE and ME analysis sets due to important protocol deviations that would affect the assessment of efficacy. All protocol deviations and their classification (i.e. whether or not it was important and whether or not it led to the exclusion from the CE and ME analysis sets) will be listed.

The review and assignment of deviations that affect patient-level analysis set statuses will be finalized as part of the final data review before database lock.

3. PRIMARY AND SECONDARY VARIABLES

3.1. Definitions and handling of missing data

Baseline

For all variables, the last assessment made prior to the first dose of study drug will be defined as the baseline.

For microbiological samples, if they come from a sterile source and are taken within 1 day of baseline and before any antibiotics are administered, it will also be considered for the derivation of baseline.

Change from Baseline (CFB)

Change from baseline will be calculated as the post-treatment value minus the baseline value.

Missing Data

No missing values will be imputed except age for some patients owing to the descriptive nature of the study.

3.1.1. Demographic and baseline characteristic variables

Demographic and baseline characteristics include the following:

- Age (in years for patients >=2 years of age, and in months for patients < 2 years of age);
- Sex (Male, Female);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Race category (White, Black/African American, Asian, Native Hawaiian/Pacific Islander, American Indian/Alaska Native, Other);
- Height (cm);
- Weight (kg);
- Body mass index (BMI) (kg/m^2);
- Medical and Surgical History;
- Renal status category (<30 mL/min/1.73m^2, ≥30 to <50 mL/min/1.73m^2, ≥50 to <80 mL/min/1.73m^2, ≥80 mL/min/1.73m^2).

- Study qualifying procedures summarized based on data entered in the following two CRF modules:
  - Procedures related to the infection;
  - Surgical history (subsetted for surgeries performed on study day -1 or 1).
- Appendicitis at screening.
- Diagnosis of intraabdominal infection.

Note that procedure type is recorded on either the procedures relating to infection or surgical history page depending on the patient. Prior to database lock, the entered values on each page will be mapped to the categories of laparotomy, laparoscopy, percutaneous drainage and appendectomy not otherwise specified (NOS). Patients can have more than one procedure type counted in this way.

Some countries will record date of birth (DOB) only partially, either year or month and year. For those patients DOB will be imputed, and age will be derived based on the imputed DOB. The following algorithm will be used for the imputation of DOB and derivation of age:

1. Use cohort to find the maximum and minimum possible age.
2. If age is recorded on the CRF, use this value to further narrow down the maximum and minimum possible age.
3. Use the date of informed consent alongside the maximum and minimum possible age to find the earliest and latest possible DOB.
4. Use any portions of the DOB which have been recorded to narrow down the earliest and latest possible DOB from step 3.
5. Find the midpoint of the earliest and latest possible DOB from step 4.
6. Use imputed DOB from step 5 to derive age at informed consent.

The following examples, all from Cohort 3 (2 to < 6 years), illustrate this algorithm:

Example	CRF_age	DOB (CRF) day/mo/yr	Informed Consent Date	Range of Possible DOBs		Midpoint of range of possible DOBs	Derived age
1	blank	xx/xx/2008	31-Aug-2014	1-Sep-2008	31-Dec-2008	31-Oct-2008	5y 9mo
2	3	xx/xx/2011	31-Aug-2014	1-Jan-2011	31-Aug-2011	2-May-2011	3y 3 mo
3	blank	xx/xx/2011	31-Aug-2014	1-Jan-2011	31-Dec-2011	2-Jul-2011	3y 1 mo
4	blank	xx/xx/2011	31-May-2014	1-Jan-2011	31-Dec-2011	2-Jul-2011	2y 10 mo
5	blank	xx/03/2011	10-Mar-2014	1-Mar-2011	31-Mar-2011	16-Mar-2011	2y 11 mo

A footnote will be added to the demography summary table to specify that imputation has been performed for age calculation and the number of patients within each cohort for which the imputation has been performed.

The demography listing will present DOB both as recorded in the CRF (eg, with missing month / date as applicable) and age as derived at the date of informed consent, and a footnote will also be put in place to describe that age imputation has been performed there.

3.1.2. Definition of prior and concomitant medication

A prior medication is defined as:

a. A medication that was taken any time in the 2 weeks prior to study entry up to the date of randomisation, regardless of whether this was stopped prior to the date of randomisation or not

A concomitant medication is defined as

a. Any medication taken at any time between the date of randomisation and up to the LFU visit.

Consequently, a medication could be counted as both prior and concomitant. Any medication prescribed at the LFU visit will not be deemed concomitant.

If any medications reported are not able to be determined as prior medications or concomitant medications due to missing or partial start dates and/or stop dates, the following imputation rules will be implemented:

- If the year is present but the month and day are missing, then 01JAN will be imputed for the start date and 31DEC for the stop date.

- If the year and month are present but the day is missing, then 01 will be imputed for the start date and the last day of the month for the stop date.

If the start date is missing, it is prior if the stop date is prior to the date of randomization. Otherwise, it is both prior and concomitant. If the stop date is missing, it is concomitant if start date is later than the date of randomization. If start date is prior to the date of randomization, it will be both prior and concomitant. If both stop/start years are missing or both stop/start dates otherwise cannot be imputed, then the date will be treated as missing and the medication will be treated as both prior and concomitant medications.

In case it appears that some of the medications are clearly 'prior' but classified as 'concomitant' and the imputation goes across the first dose day, such medications will be reviewed before the data base lock (BDRM) to make the final decision whether they should be classed as prior or concomitant.

An antibiotic is called "systemic" when it is classified as J01 (antibacterial for systemic use) code based on ATC classification.

3.1.3. Exposure and compliance variables

Exposure (in days) to the study therapy for CAZ-AVI alone, in combination with metronidazole, and for meropenem will be calculated as the difference between the last study therapy date and time and the first study therapy date and time converted to days plus 1 day. Total number of infusions for CAZ-AVI alone, in combination with metronidazole, and for meropenem will be calculated by summing all the number of infusions together. Average daily infusions will be calculated dividing total number of infusions by days of exposure. Treatment compliance over the entire treatment period will be defined as the number of infusions over all doses received, divided by the number of infusions over all doses expected during the treatment period, and then multiplied by 100. Any partial infusion will be considered as a complete infusion for the purpose of compliance, and the relevant details will be listed.

Exposure (in days) will also be calculated for patients who switch to oral therapy, using start and stop dates of oral therapy in the same way as described for study therapy above. In addition, the combined exposure (in days) of IV study treatment and oral therapy (if applicable) will be calculated.

3.2. Primary outcome (safety) variables

The primary outcome variables are for safety and tolerability as assessed by:

- Adverse events (AEs) and Serious adverse events (SAEs);
- Cephalosporin class effects and additional AEs (including, but not limited to seizures, *C. difficile*-associated diarrhoea, allergic reactions, hepatic abnormalities, haemolytic anaemia and changes in renal function);
- Vital signs (pulse, blood pressure, respiratory rate, temperature);

- Physical examination;
- Laboratory parameters, including CrCl;
- Electrocardiogram (ECG).

3.2.1. Definition of AEs

3.2.1.1. Adverse event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition, whether or not considered casually related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. All AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0.

The term AE is used to include both serious and non-serious AEs. Non-serious AEs and SAEs will be collected for each patient from the time when informed consent or ascent (whichever is earliest) is obtained at Screening through to the LFU visit. Any AEs that are unresolved at the patient's last AE assessment will be followed up by the investigator until the event is resolved or stabilized.

Each AE will be graded for severity. Each AE will be assessed for relationship to the study therapy as well. Where there is partial date information which does not clearly define whether an AE occurs post first infusion of IV therapy, the same imputation rules will be utilised as for the definition of prior or concomitant medications in Section 3.1.3, where assignment to post first infusion will be assumed where dates are in any way compatible for this to be true.

3.2.1.2. Serious AEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital abnormality or birth defect;
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

3.2.1.3. Cephalosporin class effects

Cephalosporin class effects (first time episode of hypersensitivity to class of cephalosporin drugs) and additional AEs will also be closely monitored (including, but not limited to seizures, *C. difficile*-associated diarrhoea, allergic reactions, hepatic abnormalities, haemolytic anaemia and changes in renal function).

3.2.1.4. AEs of Special Interest (AEoSI)

AEoSI will include the following safety topic groups for AEs:

- Liver disorder;
- Diarrhoea;
- Hypersensitivity/anaphylaxis;
- Haematological disorder;
- Renal disorder.

3.2.2. Laboratory parameters

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 1 of the clinical study protocol (CSP).

Table 1 presents the laboratory parameters that will be measured:

Table 1. Laboratory Parameters

Clinical Chemistry	Haematology	Urinalysis
Magnesium Bicarbonate Sodium Potassium Phosphorus Chloride Calcium Alkaline phosphatase Gamma glutamyltransferase Alanine Amino Transaminase (ALT) Aspartate Amino Transaminase (AST) Creatine kinase Lactate dehydrogenase Total bilirubin Indirect bilirubin Glucose, non-fasting	Haematocrit Haemoglobin Erythrocyte count Mean cell volume Leukocyte count (WBC) Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelets Coombs test (direct) Pregnancy testing Serum Beta-Human chorionic gonadotropin (β-hCG)	Urinalysis (routine and microscopy) will be performed according to the study centre's standard procedures

Table 1. Laboratory Parameters

Clinical Chemistry	Haematology	Urinalysis
Creatinine Blood urea nitrogen C-reactive protein (CRP) (optional)		

Creatinine clearance will be measured throughout the study until LFU using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula (Schwartz et al, 2009):

CrCl (mL/min/1.73m^2)=0.413×height (length) (cm)/serum creatinine (mg/dL)

3.2.3. Physical examinations

A complete physical examination will be performed and will include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, respiratory, cardiovascular, abdomen, musculoskeletal (including spine and extremities) and neurological systems, including height and weight. BMI (kg/m^2) will be calculated as the ratio of weight in kg/(height in cm/100)^2. BMI will only be calculated at Baseline (Day -1/Day 1). BMI will not be calculated for children <2 years of age (Cohorts 4a and 4b) as BMI is not considered a screening tool for healthy weight in children <2 years of age.

3.2.4. ECG

Each ECG will be interpreted as appropriate for the patient's age. ECG variables include ECG heart rate, QRS duration, QT interval, RR interval, PR interval, QTc (QTcB and QTcF).

Where QT_m=QT measured, RR = RR interval, and HR = Heart rate; QTcB (QT interval corrected by Bazett's formula) is calculated using the following formula:

$QT_c = QT_m / \sqrt{(RR)}$

Where RR = 60 / HR

QTcF (QT interval corrected by Fridericia's formula) is calculated dividing QT measured by the cube root of RR:

$QT_c = QT_m / 3\sqrt{(RR)}$

3.2.5. Vital signs

Vital signs include heart rate (beats per minute), body temperature (°C), respiratory rate (breaths per minute), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

3.3. Secondary outcome (efficacy) variables

- Plasma concentrations and PK parameters of CAZ and AVI;
- Clinical response at End of 72 hours' treatment, EOIV, EOT, and TOC;
- Microbiological response at EOIV, EOT, TOC, and LFU;
- Clinical relapse at LFU;
- Emergent infections.

3.3.1. Definition of clinical outcome

Clinical response outcomes at End of 72 hours and EOIV are clinical cure, clinical improvement, clinical failure and indeterminate, and at EOT, and TOC outcomes are clinical cure, clinical failure and indeterminate. Clinical response outcomes at LFU are sustained clinical cure, relapse or indeterminate. The derived analyses windows in Table 2 will be used to identify permissible values for the analysis for the CE and ME analysis sets:

Table 2: Visit Windows for End of 72 hours, EOIV, EOT, TOC, and LFU

Visit	Protocol-defined Window	Derived Analyses Window
End of 72 hours	After 72 hours of treatment, and up to 8 hours later	From completion of 9th study dose up to 80 hours after start of study drug.
End of IV therapy (EOIV)	Within 24 hours of completion of the last infusion of study drug	On day of last infusion of study drug (or +1 day), and no later than same day as start of oral therapy.
End of Treatment (EOT)	Within 48 hours of completion of the last dose of oral switch therapy for patients who switch, or within 24 hours of the last infusion of study drug for those who do not receive oral switch therapy	On day of last dose of oral therapy (or +2 days) for oral switch patients; on day of last infusion of study drug (or +1 day) for patients who do not switch
Test of cure (TOC)	8 to 15 days after the last dose of any study drug	7 to 19 days after the last dose of study drug
Late follow-up (LFU)	20 to 35 days after the last dose of any study drug	20 to 42 days after the last dose of study drug

The following tables present all the definitions for each visit.

3.3.1.1.1. Clinical Outcome at End of 72 hours

The clinical outcome categories at the End of 72 hours are defined in Table 3. Favourable clinical outcomes are clinical improvement and clinical cure.

Table 3: Clinical outcome assessments at End of 72 hours

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required.
Clinical Improvement	Patients who are improving but not enough to switch to oral therapy and are still on IV study drug at End of 72 hours and meet the following criterion: • Absence of new signs and symptoms, and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign.
Clinical Failure	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cIAI that requires alternative non-study antimicrobial therapy. • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cIAI. • Death in which cIAI is contributory. • 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 non-routine wound care. • Patients who are improving but not enough to switch to oral therapy and are still on IV study drug at End of 72 hours and who fail to meet the following criterion: Absence of new signs and symptoms, and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness,

Table 3: Clinical outcome assessments at End of 72 hours	
Outcome	**Definition**
	elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign.
Indeterminate[a]	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory. • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

3.3.1.1.2. Clinical Outcome at EOIV

The clinical outcome categories at EOIV are defined in Table 4.

Favourable clinical outcomes are clinical improvement and clinical cure. A clinical failure at EOIV will be carried forward to the EOT and TOC visits.

Table 4: Clinical outcome assessments at EOIV

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients who switch to oral therapy and meet all of the following criteria at EOIV: • Afebrile (temperature ≤38.0°C) for at least 24 hours • Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none
Clinical Failure[a]	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cIAI that requires alternative non-study antimicrobial therapy. • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cIAI. • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory. • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

[a] A clinical failure at EOIV will be carried forward to EOT and TOC.

3.3.1.1.3. Clinical Outcome at EOT

The clinical outcome categories at EOT are defined in Table 5. A favourable clinical outcome is clinical cure. A clinical failure at EOT will be carried forward to the TOC visit.

Table 5: Clinical outcome assessments at EOT

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required.
Clinical Failure[a]	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cIAI that requires alternative non-study antimicrobial therapy. • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cIAI. • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory. • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

[a] A clinical failure at EOT will be carried forward to TOC

3.3.1.1.4. Clinical Outcome at TOC

The clinical outcome categories at TOC are defined in Table 6. A favourable clinical outcome is clinical cure. Clinical response by pathogen at TOC will also be determined for each pathogen isolated at Baseline.

Table 6: Clinical outcome assessments at TOC	
Outcome	**Definition**
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required.
Clinical Failure	Patients who meet either of the following criteria: • Incomplete resolution or worsening of cIAI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy. • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory. • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

3.3.1.1.5. Clinical Outcome at LFU

Each patient who was considered clinically cured at TOC will be reassessed at LFU for evidence of clinical relapse of cIAI symptoms. The clinical outcome categories at LFU are defined in Table 7. A favourable clinical outcome at LFU is sustained clinical cure.

Table 7. Clinical outcome assessments at LFU

Outcome	Definition
Sustained Clinical Cure	Continued favourable response, defined as resolution of all acute signs and symptoms of cIAI and no further antimicrobial therapy is required.
Clinical Relapse	Patients who meet either of the following criteria: • Reappearance or worsening of signs and symptoms of cIAI that requires further antimicrobial therapy and/or surgery. • Death after TOC in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory. • Extenuating circumstances precluding classification as sustained clinical cure or clinical relapse (eg, patient lost to follow-up).

Note: Clinical outcome at LFU will only be assessed in patients who were considered clinically cured at TOC.

3.3.1.1.6. Microbiological response assessments

The per-pathogen microbiological outcome categories are defined in Table 8 using the same windows as defined for clinical outcome within Table 2. Favourable microbiological outcomes are eradication or presumed eradication. Baseline pathogens will be determined based on central laboratory data where available. In the absence of any baseline central laboratory data, then local laboratory data will be used to identify baseline pathogens.

Per-patient microbiological response is a consolidation of the per-pathogen microbiological response for each patient; in order for a patient to have a favourable per-patient microbiological response, the outcome for each baseline pathogen must be favourable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavourable (persistence or presumed persistence), the patient will be considered to have an unfavourable per-patient microbiological response.

In the cases that the overall microbiological responses are different in samples taken from the intra-abdominal infection site and blood, the per-patient microbiological response will be assessed based on the results from the intra-abdominal infection site.

Table 8: Per-pathogen microbiological outcome categories	
Outcome	**Definition**
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Presumed eradication	Source specimen was not available to culture, and the patient was assessed as a clinical cure or sustained clinical cure or (for EOIV only) clinical improvement
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MIC[a]	Source specimen demonstrates continued presence of the original baseline pathogen with a minimum inhibitory concentration value ≥4-fold larger than that observed for the baseline pathogen
Presumed persistence	Source specimen was not available to culture and the patient was assessed as a clinical failure or clinical relapse
Indeterminate	Source specimen was not available to culture and the patient's clinical outcome was assessed as indeterminate

[a] Persistence with increasing MIC is a subset of the Persistence outcome

For patients who have a microbiological outcome of persistence or presumed persistence at a particular visit, this outcome will be carried forward to subsequent visits.

3.3.1.1.7. Emergent infections

Pathogens first appearing after Baseline ("emergent infections") until the LFU are categorized in Table 9.

Table 9. Emergent infections

Infection category	Definition
Superinfection	An intra-abdominal culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy.
New infection	An intra-abdominal culture identified pathogen other than a baseline pathogen at any time after study treatment has finished along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy.

3.3.1.1.8. Per-pathogen microbiological response

Per-pathogen microbiological response is defined in Table 10.

Table 10: Per-Pathogen Microbiological Response

Outcome	Definition
Favourable	All baseline pathogens eradicated or presumed eradicated
Unfavourable	Any baseline pathogen with persistence or presumed persistence
Indeterminate	Any baseline pathogen indeterminate, and no baseline pathogen persistent

Note: For patients who have a microbiological outcome of persistence at a particular visit, this outcome will be carried forward to subsequent visits.

3.3.1.1.9. Pathogen group

Each pathogen will be assigned into one of the following groups to be used in summaries and listings, using a pre-defined list of groupings:

- Enterobacteriaceae;
- Gram-negative other than enterobacteriaceae;
- Gram-positive;
- Anaerobes.

4. ANALYSIS METHODS

4.1. General principles

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, summaries will be presented by cohort, treatment group and overall for treatment group across all cohorts. For disposition, demographics, medications, and data collected exclusively at baseline the total within each cohort will be presented as well. In this sense cohort is usually defined as cohorts 1 to 4, where cohort 4 is a combination of the cohorts 4a and 4b. For the following tables however, cohorts 4a and 4b will also be summarised in addition to cohorts 1 to 4:

- Plasma concentrations;
- Study drug administration and accountability;
- Overall summary of adverse events in any category;
- Overall summary of adverse events by system organ class (SOC) and preferred term;

- Summary of quantitative laboratory variable results and change from baseline results by visit;
- Summary of ECG variable results and change from baseline results by visit;
- Summary of physical examination results by visit.

Unless otherwise specified, demographics and baseline characteristics will be summarized for safety analysis set.

Continuous and quantitative variable summaries will include the number of patients (N), mean, standard deviation (SD), median, and ranges (minimum and maximum). Plasma concentrations will be summarized by the number of patients (N), mean, coefficient variation (CV), median, and ranges (minimum and maximum). Categorical and qualitative variable summaries will include the frequency and percentages of patients who are in the particular category. In general the denominator for the percent calculation will be based upon the total number of patients in the study population for each treatment group and cohort, unless otherwise specified.

For the reporting of descriptive statistics, the mean and median values will be presented to 1 or more decimal precision as the source data, SD values will be presented to 2 or more decimal precision, minimum and maximum values will be presented to the same precision as the source data, and percent will be presented with 1 decimal precision. In the event the SD or mean is at least 4 decimal places, the SD will be displayed to same number of decimal places as mean.

To determine upper limit of the normal range (ULN) and lower limit of the normal range (LLN) values, site-level ranges will be converted for laboratory data in this study. These ranges will then be used to define the potentially clinically significant (PCS) criteria in Table 12.

All analysis will be performed using SAS®, release 9.4 or higher.

A separate document will be produced containing the templates for table, listing, and figure.

4.2. Analysis methods

4.2.1. Baseline characteristic analysis

Baseline characteristics will be summarized for safety analysis set only.

4.2.1.1. Patient disposition

The number of patients who are randomized but never treated, who completed the study up to the TOC visit, and up to the LFU visit, and the number of patients withdrawing from the study therapy and study, including reason for withdrawal, will be summarized by cohort, treatment, overall within each cohort, and overall for each treatment for the ITT analysis set.

All data relevant to randomization and reasons for randomized but never treated as well as inclusion and exclusion criteria will be listed.

The number of patients in each of the analysis sets and the reasons for exclusion from analysis sets will be listed and summarized for the ITT analysis set.

A summary of important protocol deviations will be presented to display the number of patients with an important protocol deviation overall, and further broken down by deviation category for the safety analysis set.

A summary of the number of patients in each country and each centre will be produced for the ITT analysis set.

4.2.1.2. Demographics and baseline characteristics

Demographic and baseline characteristics included in Section 3.1.1 will be summarized by cohort, treatment group, overall within each cohort, and overall for each treatment. Age for cohort 4 will be summarized in months instead of years. For all other cohorts (1-3) age will be summarized in years.

Medical history data and current medical conditions (a medical history subset formed of conditions which are ongoing at screening) will be summarized by system organ class and preferred term for each cohort, treatment group overall within each cohort, and overall for each treatment. The surgical history data will also be summarized system organ class and preferred term for each cohort, treatment group, overall within each cohort, and overall for each treatment. Both the medical history and the surgical history will be coded with MedDRA Version 20.0.

All prior and concomitant medications will be coded using the AZDD Drug dictionary medication code (version: 17.1 or later) and systemic antibiotic medications will be summarized by ATC classification and preferred term (as well as cohort, treatment group, overall within each cohort, and overall for each treatment). Prior and concomitant medications that are not antibiotics will also be summarized by ATC classification and preferred term (as well as cohort, treatment group, overall within each cohort, and overall for each treatment).

4.2.1.3. Extent of Exposure and Compliance

Exposure

Exposure (in days) to CAZ-AVI alone and in combination with metronidazole, and to meropenem, will be summarized by cohort, treatment group and overall for each treatment. Average daily infusions and total number of IV infusions will also be summarized descriptively by cohort and overall for each treatment.

For patients who switch to oral therapy at the conclusion of their randomized treatment, a summary will be provided for the exposure (in days) to oral therapy by type of oral therapy,

cohort, treatment group, and overall for each treatment to which they were originally randomized. A table in the same format will also be presented for the combined exposure duration of IV and oral therapies.

Exposure of study and oral therapy will be presented in the study medication listings.

Treatment compliance

Treatment compliance will be summarized by cohort, treatment group and overall for each treatment. Compliance will be summarized descriptively (n, mean, standard deviation, median, minimum, maximum) and also with counts and percentages for the categories (<80%, 80%-120% and >120%). An additional summary of these statistics will be provided which summarizes the CAZ-AVI treatment group broken down into the individual components of CAZ-AVI and metronidazole, compared against meropenem.

4.2.2. Safety analysis

The primary variables are for safety and tolerability. No inferential statistical tests will be performed for any safety variables. Unless otherwise specified, the Safety analysis set will be used for summaries and listings. In addition the Safety evaluable analysis set will be used to assess key safety data such as adverse events, laboratory, vital signs and ECG data.

Safety assessments will be based on AE reports and the results of vital sign measurements, physical examinations, ECGs and clinical laboratory tests.

4.2.2.1. Adverse events

The incidence of AEs will be summarized and reviewed for potential significance and clinical importance. AEs occurring from the start of the first infusion of IV study therapy will be summarized by preferred term and SOC. AEs occurring before the start of study treatment will only be listed and not included in tables.

Adverse events will be grouped in tables by SOC and preferred term for each cohort, treatment group and overall for each treatment. All recorded AEs will be listed.

Summaries and listings of AEs leading to death, SAEs and AEs leading to discontinuation of study treatment will also be presented. Summaries will also be presented by blinded observer's causality assessment and by AE intensity.

AEoSI will be pre-defined using specific AE preferred terms from the MedDRA vocabulary for the following safety topic groups:

- Liver disorder;
- Diarrhoea;
- Hypersensitivity/anaphylaxis;

- Haematological disorder;
- Renal disorder.

The number and percentage of patients with at least 1 AE within each AEoSI topic group will be presented by study cohort, treatment and overall together with a further presentation of the AE incidence rates for each PT within each AEoSI topic group.

Cephalosporin class effects and additional AEs (including, but not limited to seizures, *C. difficile*-associated diarrhoea, allergic reactions, hepatic abnormalities, haemolytic anaemia and changes in renal function) will be detailed in clinical study report (CSR) by reviewing the AEoSI.

4.2.2.2. Laboratory assessments

Local laboratory data for chemistry and haematology parameters will be summarized and plotted (box plots) by cohort, treatment group, overall for each treatment, and visit for the observed values and for the corresponding change from baseline (CFB) values using descriptive statistics. If a patient has multiple results for a particular test at a particular visit, the first non-missing value will be used for the summary. Système International units will be reported for all analyses, but listings will reflect the original unit that was provided by the local laboratory with the test result. If a particular combination of treatment and cohort for a given parameter has fewer than five patients with data, then that combination will not be included in the boxplot.

The urinalysis parameters glucose, ketones, protein, nitrite, urobilinogen, and leukocyte esterase will be summarised using a shift table showing the number of patients with each combination of baseline value compared to maximum post-baseline value observed during treatment.

In addition, the following summaries at each applicable visit will also be provided:

- The number and percentage of patients with normal values, low values, and high values according to local laboratory reference ranges;
- Shift tables (from baseline) showing the number of patients with low, normal, or high values according to local laboratory reference ranges;
- The numbers and percentage of patients with abnormal or out of range values based on PCS criteria (Table 12) at any time during the study up to EOT visit, and separately at any time up to LFU visit.

The criteria for PCS results for laboratory tests are described in Table 12. For relationship to normal reference range, shift table summaries, and PCS summaries, if a patient has multiple values for a particular test at a particular visit the first non-missing value will used. Shift plots (ie, Scatter plot) of baseline and EOT with reference ranges for the lab tests with

continuous values will also be provided by cohort, treatment group and overall for each treatment.

The number and percentage of patients who meet potential Hy's law criteria: AST or ALT ≥3 × ULN and total bilirubin ≥2 × ULN at any point during the study will be summarized by cohort, treatment group and overall. The number of patients with ALP<=2 x ULN (alone and in addition to meeting potential Hy's law criteria) will also be summarised. The number of patients with maximum on-treatment ALT, AST and ALP will be cross-tabulated with the maximum on-treatment total bilirubin classified into the groups: <3 x ULN, ≥3 -<5 x ULN, ≥5 - <10 x ULN and ≥10 x ULN for ALT and AST, <=2 x ULN for ALP, and <2 x ULN and >= 2 x ULN for total bilirubin. A listing of PCS values for liver function tests will be presented.

Listings of all laboratory values for each patient will be presented, and abnormal or out-of-range PCS values will be flagged alongside these results.

The number and percentage of patients with CrCl in the following ranges: <30mL/min/1.73m^2, ≥30 to <50 mL/min/1.73m^2, ≥50mL/min/1.73m^2 to <80mL/min/1.73m^2, and ≥80mL/min/1.73m^2 will be tabulated at each of the Baseline, Day 7, EOIV, TOC and LFU visits for each cohort, treatment group, and overall.

4.2.2.3. Physical examinations

The numbers and percentage of patients with normal or abnormal assessment for each body system will be summarized by cohort, treatment group and overall for each treatment.

All physical examination data will be listed.

4.2.2.4. ECGs

Descriptive statistics for ECG at each applicable visit and for the corresponding change from baseline values at each applicable post-baseline visit will be summarized and plotted (box-plot) by cohort, treatment group and overall for each treatment. Shift plots from baseline to TOC will also be provided by cohort, treatment group and overall for each treatment.

The number and percentage of patients within overall ECG interpretation category (normal, abnormal) for baseline and post-baseline by cohort, treatment group and overall for each treatment, and visit will be summarized. The number of patients with normal, abnormal ECG interpretation shift results from baseline to the TOC visit will be provided.

Categorical summaries of absolute QT, QTcB, and QTcF values (≥450 msec, ≥480 msec, ≥500 msec) and CFB values in QT, QTcB, and QTcF values (≥30 msec, ≥60 msec) will be presented by treatment group, cohort and visit. The number and percentage of patients with post-baseline value of ≥500 msec and CFB value of ≥60 msec will also be presented by treatment group, cohort and visit.

Electrocardiogram results and the overall interpretations of these results will be listed respectively.

Listings of all ECG values for each patient will be presented with abnormal or out-of-range PCS ECG values flagged. These are defined in Table 13.

4.2.2.5. Vital signs

Vital signs will be summarized and plotted (box plots) for the observed values and for the corresponding CFB values at each applicable visit by cohort, treatment group and overall for each treatment.

Vital signs will be listed.

4.2.3. Analysis of secondary variables

4.2.3.1. Pharmacokinetic outcome variables

A listing of ceftazidime and avibactam concentrations at the nominal sampling windows by patient and cohort will be provided. For Cohorts 1 to 4, the plasma concentration will be summarized by nominal sampling time window using appropriate descriptive statistics (eg, number, mean, SD, minimum, median, maximum, geometric mean, lower and upper SD bounds [geometric mean ±SD], and coefficient of variation).

Plasma concentrations that are not quantifiable (NQ) or if there are missing values (e.g. no result [NR]) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time point where there is less than or equal to 50% of the values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are NQ, the mean, SD, geometric mean and CV% will be set to Not Calculated (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. Not calculated (NC) will be written in the field for standard deviation and CV% and NQ will be written in fields for mean, geometric mean, minimum, median and maximum.
- The number of NQ values (n below LLOQ) will be reported for each time point.
- Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics.

Geometric mean ±SD will be calculated as exp(u±s) where u and s are the mean and SD on a log scale.

Two figures showing plasma concentration (means ± SD) of ceftazidime and avibactam against time will also be presented by cohort.

Any PK modelling is not the scope of this document.

4.2.3.2. Clinical outcome, microbiological response and emergent infections

Clinical response outcome

Within each analysis set, the proportion of patients with a favourable outcome at End of 72 hours' treatment and EOIV is defined using the following formula:

$$\frac{\text{Number of patients with clinical cure or improvement}}{\text{(Number of patients in the analysis set)}}$$

Within each analysis set, the proportion of patients with a favourable outcome at EOT and TOC is defined using the following formula:

$$\frac{\text{Number of patients with clinical cure}}{\text{(Number of patients in the analysis set)}}$$

Within each analysis set, the proportion of patients with a favourable outcome at LFU is defined using the following formula:

$$\frac{\text{Number of patients with sustained clinical cure}}{\text{(Number of patients in the analysis set)}}$$

Where clinical response is summarized for the ITT and micro-ITT analysis sets, the nominal visit (i.e. as recorded on the CRF) throughout, whereas for summaries for the CE and ME analysis sets, visit windows will be used as defined in Table 2.

Clinical response outcomes will be summarized by cohort, treatment group and overall for each treatment in the ITT, micro-ITT, CE and ME analysis sets at End of 72 hours' treatment, EOIV, EOT, TOC, and LFU.

The number and percentage of patients with each clinical response outcome at each time point will be summarized by cohort, treatment group and overall for each treatment. For each time point the number, percentage and proportion of patients with clinically favourable outcome will also be summarized. A two-sided 95% CI for the percentage of subjects with a favourable outcome will be presented within each cohort and treatment group, and treatment group overall (computed using Jeffreys method). The rate of favourable clinical response at TOC will also be presented for each baseline pathogen in the ME at TOC and micro-ITT analysis sets.

The analysis for clinical response outcome described above will be repeated and split by patients with/without diagnosis of appendicitis at screening in the CE, ME, micro-ITT and ITT analysis sets. Additionally the analysis will be repeated again for the CE analysis set

only at the end of 72 hour visit window, where the eligibility for this window is amended from that in Table 2 to be from 72 hours until 80 hours after first dose of study IV treatment.

Microbiological response

Where microbiological response is summarized for the ITT and micro-ITT analysis set, the nominal visit (i.e. as recorded on the CRF) will be used throughout, whereas for summaries for the ME analysis set, visit windows will be used as defined in Table 2.

The number and percentage of patients with a favourable microbiological response outcome at each end point will be summarized by cohort, treatment group and overall for each treatment in the micro-ITT and ME analysis set at the EOIV, EOT, TOC and LFU visits.

Emergent infections

The proportion of patients with any emergent infection, and further subsetted into super infections and/or new infections, will be summarized by cohort, treatment group and overall for each treatment for the micro-ITT and ME at TOC analysis sets.

Per-pathogen microbiological response

The number and percentage of patients with per-pathogen microbiological favourable response will be summarized within pathogen group by cohort, treatment group and overall for each treatment for the ME analysis set at the EOIV, EOT, TOC and LFU visits. This summary will be repeated to display the favourable response in the same manner, with additional subsetting by baseline CAZ-AVI MIC and by baseline meropenem MIC. All pre-pathogen analysis will also be presented for the ITT and micro-ITT analysis sets.

Baseline pathogen susceptibility and MIC

The number and percentage of patients with each pathogen at baseline will be presented within pathogen group by cohort, treatment, overall for each treatment group for the micro-ITT and ME at TOC analysis sets.

The number and percentage of patients with baseline aerobic Gram-negative pathogens classed as susceptible, non-susceptible, intermediate, and resistant to each of CAZ-AVI, ceftazidime and meropenem will be summarized for the micro-ITT analysis set alongside the number of patients with a pathogen, the number of isolates, and the number of isolates tested.

Culture results and susceptibility testing results will be based upon the CLSI assessments and listed by cohort and treatment group. The results of the in vitro susceptibility tests of each baseline aerobic, Gram-negative pathogen (‘Susceptible’ and ‘Non-susceptible’) in all isolates, site of infection isolates, and blood isolates will be summarized by cohort, treatment group and overall for each treatment for the micro ITT analysis set.

MIC frequencies for each infecting species within pathogen group will be reported separately. Descriptive statistics for MICs will be reported for each infecting species and MIC range. Additionally, for infecting species for which the number is 10 or more, the MIC to inhibit the growth of 50% (MIC_{50}), and for which the number is 10 or more the MIC to inhibit the growth of 90% of organisms (MIC_{90}) will be reported.

5. INTERIM ANALYSES

As this study is descriptive in nature, no interim or final inferential analyses will be performed for either efficacy or safety.

5.1. Data Safety Monitoring Board (DSMB)

An data safety monitoring board (DSMB) is deemed necessary since the trial has a long period of enrolment, is multi-centre and multi-national.

The DSMB is charged with reviewing and evaluating the study safety (AEs, SAEs, and PCS laboratory results) at periodic intervals. The DSMB members will be familiarised with AEs and SAEs likely to occur in this patient population, based on experience in adults and adolescents, as well as with this class of drugs (cephalosporins). The DSMB will conduct pre-planned and possibly ad hoc reviews of accumulating data.

Based on the findings of these reviews, the DSMB may make recommendations to the sponsor regarding the study, including, but not limited to: continue the study without modification, modify the protocol or informed consent/assent document(s), or temporarily stop enrolment in all or some of the study centres. The sponsor will be responsible for discussing and, if considered appropriate, implementing the DSMB recommendations. Further details can be found in the DSMB charter.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Although protocol section 8.5.2.3 states that “Baseline pathogens will be determined based on central laboratory data”, section 5.2.1 of the protocol gives the option for the sample to be analyzed by central or local lab. Therefore, in case central lab is not available for the determination of baseline pathogens, local lab will be used if available (SAP Section 3.3.1 under subsection “Microbiological response assessments”).

An additional criterion was added for the CE and ME analysis sets (Sections 2.1.4.3 and 2.1.4.4) whereby a patient should not have received concomitant antibiotics that would affect the assessment of efficacy. This extra constraint was implemented as a result of discussions held during formal ECMA review meetings.

Categories of CrCl used for analysis purposes were given in protocol section 8.5.1.2 as mL/min, however since the Schwartz formula used to derive CrCl was based on $mL/min/1.73m^2$, this was the unit used for CrCl categories.

7. REFERENCES

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8. APPENDIX

8.1. Evaluability Review Process

Assessment of patient's evaluability for each analysis set will be determined by the criteria described in Section 2.1. Where possible, assignments will be made using programming algorithms. In some cases manual review of data may be necessary in order to determine assignment (see Table 11).

Data will be reviewed, and cases identified for presentation and discussion at the blinded evaluability and clinical/microbiological assessment (ECMA) meeting. Potentially unblinding data (e.g. protocol deviations, concomitant medication and study drug dosing) will only be reviewed by team members who are unblinded, and case summaries will be presented for discussion at the blinded ECMA meeting for determination of evaluability.

The output of the each ECMA meeting will be a spreadsheet of analysis set assignments of the cases that were discussed and decided to be excluded from any analysis set. This spreadsheet will be provided to the programming group and incorporated into the database. Result of assessment and rationale for any manual updates to analysis set assignments will be documented in the form of ECMA minutes.

Evaluability of each patient to each analysis set will be finalized prior to database lock.

Table 11: Evaluability assessments

Analysis set	Description	Analysis set criterion	Assessment performed
Safety Analysis Set (SAS)	*randomised patients who received any amount of IV study therapy*	a) randomised	Programmed
		b) any amount of IV drug * any dose of CAZ-AVI, or * any dose of meropenem	
Safety Evaluable Analysis Set (SES)	*subset of the patients in the SAS that received at least 9 doses of study treatment.*	a) in SAS	Programmed
		b) at least * 9 doses of CAZ-AVI or * 9 doses of meropenem	Manual confirmation by unblinded team, with blinded discussion of selected cases during ECMA meeting, if required

Analysis set	Description	Analysis set criterion	Assessment performed
PK Analysis Set	*subset of the patients in the SAS who have at least 1 ceftazidime and/or avibactam plasma measurement available*	a) in SAS	Programmed
		b) at least 1 ceftazidime and/or avibactam plasma measurement	
ITT Analysis Set	*all patients who have been assigned a randomised treatment.*	a) randomized	Programmed
Micro-ITT Analysis Set	*randomised patients who have a baseline pathogen known to cause cIAI*	a) randomised	Programmed
		b) at least 1 baseline pathogen in intra-abdominal fluid or in blood known to cause cIAI	Programmed and manual: A list of all baseline pathogens in this study will be manually classified by microbiologist as *always*, or *never* known to cause cIAI.  20170707A cIAI ISOLATE CODING-CLA Patients who have at least one baseline pathogen classified as "always" are automatically eligible for the micro-ITT. The remaining patients will be excluded from the micro-ITT.

Analysis set	Description	Analysis set criterion	Assessment performed
CE at 72h, CE at EOIV CE at EOT CE at TOC CE at LFU	*Patients who receive both study therapies will be excluded from CE and ME analysis sets*	a) Subject did not receive both study therapies	Programmed
	randomised patients who receive any amount of IV study drug and have a confirmed diagnosis of cIAI	b) randomised	Programmed
		c) any amount of study drug	Programmed
		d) confirmed diagnosis of cIAI	Programmed (based on inclusion criteria)
	received at least 48 h of IV study drug in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE	e) Clinical failure (or relapse at LFU) and ≥ 48h treatment OR e) Clinical failure (or relapse at LFU) and treatment-limiting AE with < 48h treatment	A manual review of IV study drug will be performed by unblinded personnel. These flags will be incorporated into the database, and the remaining criteria of clinical response will be assessed programmatically. The determination of 'treatment-limiting AEs' will be made programmatically based on a field from the CRF: "DISCONTINUATION OF STUDY DRUG DUE TO AN AE AND REQUIREMENT FOR ALTERNATIVE NON STUDY ANTIMICROBIAL THERAPY FOR CIAI".
	Have received at least 72 hours of IV study drug in order to be considered an evaluable clinical cure	f) Cure (or improvement or sustained cure) and ≥72h treatment	
	Have been evaluated at the End of 72h and at the specific visits of EOIV, EOT, and TOC with a clinical response of cure or failure (or have been assessed as a clinical failure before the planned assessment visit), or for LFU, have been evaluated with a clinical response of sustained cure or relapse	g) Outcome of cure (or improvement) OR failure at relevant visit (OR failure carried forward from previous visit) [OR sustained cure or relapse at LFU]	

Analysis set	Description	Analysis set criterion	Assessment performed
	Had no important protocol deviations that would affect assessment of efficacy	h) No protocol deviations affecting efficacy	Manual review of protocol deviations by unblinded personnel to select cases for discussion at ECMA meeting, during which a blinded assessment will be made of the evaluability of these cases.
	Have not received concomitant antibiotics that would impact assessment of efficacy	i) No concomitant antibiotics affecting efficacy	Manual review of reasons for concomitant antibiotic medications to select cases for discussion at ECMA meeting, during which a blinded assessment will be made of evaluability for these cases.
ME at 72h **ME at EOIV** **ME at EOT** **ME at TOC** **ME at LFU**	*Patients who receive both study therapies will be excluded from CE and ME analysis sets*	As per CE	
	randomised patients who have received any amount of IV study drug and have a confirmed diagnosis of cIAI	As per CE	
		As per CE	
		As per CE	
	Have received at least 48 hours of IV study drug in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE	As per CE	
	Have received at least 72 hours of IV study drug in order to be considered an	As per CE	

Analysis set	Description	Analysis set criterion	Assessment performed
	evaluable clinical cure		
	At the specific visit had a microbiological response which was not indeterminate	j) Micro response not indeterminate (presumed eradication or presumed persistence is acceptable)	Programmed.
	Had no important protocol deviations that would affect assessment of efficacy	As per CE	
	Have not received concomitant antibiotics that would impact assessment of efficacy	As per CE	
	Have at least 1 typical IAI bacterial pathogen which has been isolated from an adequate microbiological specimen at Baseline that is susceptible to both study agents (CAZ-AVI and meropenem)	k) ≥1 typical cIAI bacterial pathogen isolated from an adequate microbiological specimen at baseline	As per micro-ITT
		l) susceptible to both study agents (CAZ-AVI and meropenem)	Programmed, see Section 2.1.4.4.1for definition of susceptibility

8.2. Potentially clinically significant criteria

Table 12. Criteria for potentially clinically significant clinical laboratory tests

Category	Parameter	Lower limit	Upper limit	Percent decrease from baseline	Percent increase from baseline
Haematology	Haemoglobin	<0.6 x LLN	>1.3 x ULN	>25%	>30%
	Haematocrit	<0.6 x LLN	>1.3 x ULN	>25%	>30%
	RBC	<0.8 x LLN	>1.3 x ULN	>20%	>30%
	WBC	<0.5 x LLN	>2.0 x ULN	>60%	>100%
	Neutrophils	<0.5 x LLN	>2.2 x ULN	>70%	>100%
	Lymphocytes	<0.2 x LLN	>2.2 x ULN	>70%	>100%
	Eosinophils	N/A	>4.0 x ULN	N/A	>400%
	Platelets	<0.4 x LLN	>2.0 x ULN	>40%	>100%
Chemistry	ALT	N/A	>3.0 x ULN	N/A	>300%
	Albumin	<0.6 x LLN	N/A	>60%	N/A
	Alkaline phosphatase	<0.5 x LLN	>3.0 x ULN	>80%	>300%
	AST	N/A	>3.0 x ULN	N/A	>300%
	Bicarbonate	<0.7 x LLN	>1.3 x ULN	>50%	>30%
	BUN	N/A	>3.0 x ULN	N/A	>300%
	Calcium	<0.7 x LLN	>1.3 x ULN	>30%	>30%
	Chloride	<0.8 x LLN	>1.2 x ULN	>20%	>20%
	Creatinine	N/A	>2.0 × ULN	N/A	>100%
	Direct bilirubin	N/A	>2.5 x ULN	N/A	>150%
	Glucose, non-fasting	<0.6 x LLN	>4.0 x ULN	>40%	>200%
	Potassium	<0.8 x LLN	>1.2 x ULN	>15%	>20%
	Sodium	<0.85 x LLN	>1.1 x ULN	>10%	>10%
	Total bilirubin	N/A	>2.5 x ULN	N/A	>300%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; LLN, lower limit of normal; N/A, not applicable; RBC, red blood cell (erythrocytes); ULN, upper limit of normal; WBC, white blood cell (leukocytes).

Note that for PCS low flags, both the lower limit and percentage decrease criteria must be met.

Table 13: Criteria for potentially clinically significant electrocardiogram tests

Parameter	Age Range	Lower limit	Upper limit
Heart Rate	< 12 years >=12 years	< 50 bpm and decrease >=15 bpm from baseline < 50 bpm and decrease >=15 bpm from baseline	> 120 bpm and increase >= 15 bpm from baseline > 110 bpm and increase >= 15 bpm from baseline
PR Interval	< 12 years >=12 years	<= 90 ms <= 100 ms	>= 170 ms >= 180 ms
QRS Duration	<12 years >=12 years	<= 55 ms <= 70 ms	>= 90 ms >= 100 ms
QT		<= 200 ms	>= 500 msec and increase of >=60 msec from baseline
QTcB			>= 450 msec >= 500 msec Increase of >= 30 msec from baseline Increase of >= 60 msec from baseline >= 450 msec and increase of >= 30 msec from baseline >= 500 msec and increase of >= 60 msec from baseline
QTcF			>= 450 msec >= 500 msec Increase of >= 30 msec from baseline Increase of >= 60 msec from baseline >= 450 msec and increase of >= 30 msec from baseline >= 500 msec and increase of >= 60 msec from baseline