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Global Revised Clinical Study Protocol	
Drug Substance	Ceftazidime-avibactam
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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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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	22 September 2015		
2	07 March 2017		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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PROTOCOL SYNOPSIS

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)

International Co-ordinating Investigator

PPD
PPD, MD

United States

Study site(s) and number of patients planned

A sufficient number of patients are to be randomised 3:1 for 80 patients to complete at least 72 hours (3 full days, ie, 9 doses) of study treatment (ie, evaluable patients; at least 60 patients in the ceftazidime and avibactam [CAZ-AVI] plus metronidazole group and at least 20 patients in the meropenem group).

Patient recruitment will ensure that no more than 90% of evaluable patients will have diagnosed complicated appendicitis in all cohorts combined. Patients will be allocated to 1 of 4 cohorts based on age. Randomisation will be stratified 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

Approximately 70 study centres are planned.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2015	2
Estimated date of last patient completed	Q3 2017	

Study design

This study will be a single blind, randomised, multi-centre, active controlled trial. Patients aged from 3 months to less than 18 years with complicated intra-abdominal infections (cIAIs) will be randomised to 1 of 2 treatment groups (3:1 ratio): CAZ-AVI in combination with metronidazole versus meropenem. Randomisation will be stratified appropriately. Patients aged from 3 months to <1 year (Cohort 4b) must have been born at term (defined as gestational age ≥37 weeks).

Patients will receive intravenous (IV) treatment for a minimum of 72 hours (3 full days, ie, 9 doses) before having the option to switch to an oral therapy as specified below. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food.

Patients will be assessed for safety and efficacy throughout the study, and blood samples will be taken for pharmacokinetic (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.

Objectives

Primary (Safety) Objective:	Outcome Measure:
Evaluate the safety and tolerability of CAZ-AVI plus metronidazole given at the selected dose regimen versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI	• Adverse events (AEs) and serious adverse events (SAEs) from the signing of the Informed Consent/Assent Form to the LFU visit (27 to 50 days after start of study treatment) • Cephalosporin class effects and additional AEs (including, but not limited to seizures, *Clostridium difficile*-associated diarrhoea, allergic reactions, hepatic abnormalities, haemolytic anaemia and changes in renal function) • Clinical: vital signs (pulse, blood pressure, respiratory rate, temperature), electrocardiogram (ECG), and physical examinations • Laboratory: complete blood count with differential and comprehensive metabolic panel • Creatinine clearance (CrCl)

Secondary Objective:	Outcome Measure:
Evaluate the descriptive efficacy of CAZ-AVI plus metronidazole versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI	• Clinical Outcomes at End of 72 hours' Treatment, End of Intravenous Treatment (EOIV), End of Treatment (EOT) and Test of Cure (TOC) • Microbiological response at EOIV, EOT, TOC and LFU • Clinical relapse at LFU • Emergent infections
Evaluate the PK of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cIAI	• PK data of ceftazidime and avibactam will be analysed separately • Plasma concentration will be listed and summarised by nominal sampling time window using appropriate descriptive statistics • PK parameters derived from population PK analysis and potential PK/pharmacodynamic (PD) relationships will be reported separately

Target patient population

Patients aged from 3 months to less than 18 years with cIAI.

Duration of treatment

The IV study treatment is to be given for a minimum of 72 hours (3 full days, ie, 9 doses). At any time after a minimum of 72 hours of IV study treatment has been received, there is an option to switch to an oral therapy, as specified below. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food. The total period of treatment (ie, IV drug or oral switch therapy) is to be between 7 and 15 days. Patients may remain on the IV study treatment for the full 7 to 15 days.

Investigational product, dosage and mode of administration

The study is single blind, ie, a Blinded Observer will not know the patient's treatment assignment and will conduct clinical assessments (including efficacy and safety). There is no use of placebo to act as a treatment blind.

Intravenous CAZ-AVI infusions will be given at doses based on the age and weight of the patient with adjustment according to renal function:

Cohort	Age range	Body weight	CAZ-AVI dose CrCl ≥50 mL/min	CAZ-AVI dose CrCl ≥30 to <50 mL/min
			CAZ-AVI must be administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes)	
1[1]	12 years to <18 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
1[1]	12 years to <18 years	<40 kg	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
2[1]	6 years to <12 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
2[1]	6 years to <12 years	<40 kg	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
3[1]	2 years to <6 years	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4a[2]	1 year to <2 years	All	50 mg/kg ceftazidime /12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b[2]	6 months to <1 year	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b[2]	3 months to <6 months	All	40 mg/kg ceftazidime/10 mg/kg avibactam	20 mg/kg ceftazidime/5 mg/kg avibactam

[1] Patients considered for entry into the study will be within the normal range of body mass index (BMI) for their age, (2 to <18). A healthy weight BMI for this age group falls between the 5th percentile and ≤95th percentile according to height, weight, and age.

[2] BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

The Investigator should follow the package insert for meropenem for dose modifications associated with renal impairment.

Patients whose CrCl drops below 30 mL/min should be withdrawn from study therapy. Patients withdrawing from study therapy can be administered alternative therapies at the Investigator's choice, which should be recorded in the Case Report Form. If possible, patients should still be followed for safety. 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. If in the opinion of the Investigator there is a clinically significant reduction in a patient's estimated CrCl during the treatment period, then the Investigator should contact the Medical Monitor to discuss the above mentioned options (immediate dose change, a short period of continued observation, or discontinuation of therapy). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and Investigator's clinical evaluation.

The suggested dosing regimen of metronidazole is 10 mg/kg IV over 20 to 30 minutes every 8 hours (±30 minutes), but it can also be prescribed/adjusted by the Investigator according to local labels. The metronidazole infusion will be started no later than 30 minutes after completion of the CAZ-AVI infusion.

An optional switch to oral therapy is permitted on or after Study Day 4 (ie, after 72 hours of IV study drug). The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food:

- Oral amoxicillin/clavulanic acid (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or

- Oral ciprofloxacin (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care) plus metronidazole (administered at a dose and formulation per standard of care), or

- Pathogen-based therapy (in discussion with the Medical Monitor). The choice of oral antibacterial agent for pathogen-based therapy will be driven by the results of a susceptibility test, which will be provided to the Investigator by either the local or central laboratory. Initiation of pathogen-based therapy is at the Investigator's discretion. Before administering pathogen-based therapy, the Investigator will discuss the results of the susceptibility test and the selected antibacterial drug (which should be approved for use in children) with the Medical Monitor.

The patient may continue on IV study drug for the entire duration of the study therapy (7 to 15 days), at the discretion of the Investigator.

Comparator

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.

Statistical methods

Block randomisation using an interactive voice/web response system will be used to assign patients in a ratio of 3:1 to the study treatment groups of CAZ-AVI plus metronidazole or meropenem, respectively, in each of the cohorts for the age groups. All study data will be summarised within each age cohort separately and also overall (regardless of age cohort).

Safety data

The primary objective will be to assess the safety and tolerability of CAZ-AVI plus metronidazole compared with comparator (meropenem). Safety data include AEs, clinical laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety variable, the last assessment made prior to the first dose of study drug will be defined as the baseline. All safety data collected from this study will be summarised by the received treatment group (ie, for CAZ-AVI plus metronidazole versus meropenem irrespective of switching to oral therapy) for all patients who received any amount of study treatment (termed the 'Safety analysis set'), and key data will also be summarised for those patients who received at least 72 hours of study treatment (termed the 'Safety evaluable analysis set') by received treatment group. Descriptive statistics will be produced to summarise the safety data. Safety data from this study will be combined with those from another CAZ-AVI paediatric study for complicated urinary tract infections (D4280C00016) and will be presented in the same way.

The incidence of AEs and SAEs will be summarised by system organ class and preferred term, according to the Medical Dictionary for Regulatory Activities vocabulary, by treatment group. The summaries will also be produced by relationship to study drug, and by AE intensity. AEs leading to discontinuation from study treatment will also be summarised. Summary tables for clinical laboratory tests, vital signs, ECGs, and physical examination findings will be produced.

Descriptive efficacy data and patient characteristic/Baseline data

Efficacy will be assessed descriptively in the intent-to-treat (ITT) set (all randomised patients), the microbiological ITT (micro-ITT) set (all randomised patients who have a baseline pathogen known to cause cIAI), the clinically evaluable (CE) analysis set (patients who meet minimal disease criteria for cIAI and all evaluability criteria, including patients who received at least 72 hours of the intended dose and duration of IV study drug, and for whom sufficient information regarding the infection is available to determine the patient's outcome),

and the microbiologically evaluable (ME) analysis set (patients who meet minimal disease criteria for cIAI and all evaluability criteria similar to the CE analysis set, and have at least 1 typical IAI bacterial pathogen at Baseline that is susceptible to both study agents, ie, CAZ-AVI and meropenem).

Efficacy will be assessed in the ITT, micro-ITT, CE, and ME analysis sets with respect to the proportion of patients with clinical response outcome of cure (at the end of 72 hours' treatment, EOIV, the EOT, and the TOC visit) and clinical response outcome of relapse (at the LFU visit). Favourable microbiological response will be assessed in the ME and the micro-ITT analysis sets, and the number of patients with emergent infections (up to LFU) will be assessed in the ME analysis set. Patients in the ITT, micro-ITT, CE, and ME analysis sets will be summarised according to the randomised treatment assignment.

Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. All summaries will be presented by treatment group. Demographic data and other baseline characteristic data will also be summarised.

Pharmacokinetic data

Pharmacokinetic assessment will be conducted for the PK analysis data set. The data set will consist of all patients who will receive CAZ-AVI treatment, and have at least 1 ceftazidime and/or avibactam plasma measurement available.

A listing of ceftazidime and avibactam concentrations at the nominal sampling windows by patient and cohort will be provided. For Cohorts 1 to 4b, the plasma concentration will be summarised 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).

In addition, the avibactam and ceftazidime concentration, paediatric patient demographics, and disease status data from Cohorts 1 to 4b will be combined with the data from appropriate previous clinical studies in paediatric patients and/or adults for a population PK analysis. The actual dosing and plasma sampling times will be used for the analysis. The developed population PK model may be used to conduct simulations to determine probability of PK/PD target attainment to help to justify the CAZ-AVI dose regimens for paediatric patients with cIAI. A stand-alone population PK modelling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report outside of the clinical study report.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AEoSI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAT	Best Available Therapy
BMI	Body mass index
CAZ-AVI	Ceftazidime and avibactam
CE	Clinically evaluable
cIAI	Complicated intra-abdominal infection
CrCl	Creatinine clearance
CRF	Case Report Form (electronic/paper)
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
cUTI	Complicated urinary tract infection
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EOIV	End of Intravenous Treatment
EOT	End of Treatment
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
β-hCG	ß-human chorionic gonadotropin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalised ratio

Abbreviation or special term	Explanation
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive voice/web response system
KPC	*Klebsiella pneumoniae carbapenemase*
LFU	Late Follow-up
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
micro-ITT	Microbiological intent-to-treat
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant staphylococcus aureus
OAT	Organic anion transporter
PD	Pharmacodynamic
PK	Pharmacokinetic
QT_cB	QT interval corrected using Bazett's formula
QT_cF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TOC	Test of Cure
ULN	Upper limit of normal
WBC	White blood cells

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Avibactam is a novel, non β-lactam, β-lactamase inhibitor. Although avibactam itself possesses no intrinsic antibacterial activity, it has been shown to restore in vitro activity of ceftazidime against Class A, Class C and some Class D β lactamase-producing pathogens including those commonly associated with complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs). Avibactam, when combined with ceftazidime, has also been shown to be active against strains that express a combination of β-lactamase types, as well as strains that are concomitantly resistant to other antibacterial classes such as fluoroquinolones.

Beta-lactamase inhibition by avibactam is effected through the formation of a stable covalent carbamoyl linkage to the enzyme complex. It inhibited Class A and Class C β-lactamases by 50% at lower concentrations than other currently marketed β-lactamase inhibitors such as clavulanic acid, tazobactam, and sulbactam. In addition, avibactam is a potent inhibitor of Class C enzymes whereas clavulanic acid, tazobactam, and sulbactam lack any activity against this class of enzymes. Unlike currently available β-lactamase inhibitors, avibactam does not induce β-lactamase production.

Avibactam inhibited *Klebsiella pneumoniae carbapenemase* (KPC)-2 β-lactamase in vitro and restored ceftazidime susceptibility to *Enterobacteriaceae*-harboring KPC-2 or KPC-3 β-lactamase (Stachyra et al 2009). The potent in vitro activity of the ceftazidime and avibactam (CAZ-AVI) combination against *Enterobacteriaceae*-producing Class A, and Class C, β-lactamases has been confirmed in vivo in murine pneumonia, septicaemia, and pyelonephritis models.

Currently the options for the treatment of Gram-negative infections, especially multi-drug resistant strains including extended-spectrum β-lactamase producers, are extremely limited. Until recently, there have been no new investigational compounds under early or late development specifically targeted to combat these organisms. Hence, the availability and development of new agents to treat these infections will be a welcome addition to the existing treatments.

Details of the CAZ-AVI clinical development programme to date can be found in Section 5.2.2 of the CAZ-AVI Investigator's Brochure.

The purpose of this study is to assess the safety, tolerability and descriptive efficacy of CAZ-AVI plus metronidazole versus meropenem in patients aged from 3 months to less than 18 years with cIAI. Data from this study will be compared to similar data generated in adult patients so as to be able to extrapolate efficacy and tolerability to children. The dosing regimen(s) has been chosen based on the paediatric pharmacokinetic (PK) study and PK/pharmacodynamic (PD) modelling of the exposure, required for the successful treatment of infections used in Phase 3 adult studies.

1.2 Rationale for study design, doses and control groups

This study will be a single blind, randomised, multi-centre, active controlled trial.

Single blind study observer is a well-accepted study design in a paediatric population. Children are a vulnerable population and need close clinical monitoring by unblinded observers to interject when needed whilst the Blinded Observer will assess the safety and the clinical cure without bias. Given the risk to patients and severity of disease, a placebo-controlled trial would not be ethically appropriate.

The study is designed to include patients <1 year of age who are born at term only (defined as a gestational age ≥37 weeks). Maturation during foetal life and after birth is a process involving all organs and functions of the growing human. As such, all the main steps of drug disposition (absorption, distribution, metabolism, catabolism, elimination/excretion) may be under the influence of still incomplete morphological stages. An incompletely absorbed compound may be less effective whereas a poorly metabolized and/or excreted compound may result in an increased risk of toxicity. Both risks will have to be evaluated. Better understanding of the maturing kidney should help to anticipate possible early and late adverse effects of drugs in neonatal populations. Nephrogenesis is completed by the end of 34th week of gestation and the kidney of a full-term neonate (ie, between 37 and 41 weeks of gestation) possesses a full set of nephrons and adult levels of glomerular filtration rate are reached between 1 and 2 years of age. Therefore, patients <1 year of age who were born pre-term are excluded from this study.

This study will be conducted in hospitalised patients with cIAI requiring surgical intervention and treatment with intravenous (IV) antibiotics. The CAZ-AVI doses in this trial have been selected to achieve similar exposures reached in the Phase 3 studies in adults (D4280C00001 and D4280C00005), with the intention of reaching the same level of efficacy (for further details regarding the dose selection rationale, please refer to the CAZ-AVI Investigator's Brochure).

Complicated intra-abdominal infections are typically polymicrobial, potentially involving anaerobes such as the *Bacteroides fragilis* group. Metronidazole will be added to CAZ-AVI to provide coverage for anaerobic organisms. The spectrum of activity of CAZ-AVI when combined with metronidazole is well suited to treatment of pathogens commonly responsible for cIAIs.

Meropenem is approved and widely used for the safe treatment of cIAIs, and carbapenems are considered the drugs of choice for treating infections due to extended spectrum β-lactamase-producing Gram-negative bacilli. The dose/regimen of meropenem to be used in this trial is described in Section 7.

1.3 Benefit/risk and ethical assessment

This study is the first study with therapeutic intent for CAZ-AVI in children with cIAIs; however, the doses of CAZ-AVI have previously shown to achieve similar exposures in adults and children, so efficacy of CAZ-AVI in children is likely.

Cohort 4 (≥3 months to <2 years) includes very young patients (aged from 3 months to <6 months) who are particularly vulnerable in terms of lack of a physiological reserve and rapid maturation of organs. Therefore, in order to ensure that exposure (maximum concentration and area under the curve) was minimised in this group, while also still assuring robust predictions of sufficient exposure above the PK/PD target, Cohort 4 was divided into 2 parts for further analysis for dose selection: Cohort 4a (from 1 year to <2 years) and Cohort 4b (≥3 to <1 year). This analysis indicated that a lower dose of 40 mg/kg ceftazidime/10 mg/kg avibactam reduces exposure in Cohort 4b, while still providing very high predictions of sufficient exposure above the PK/PD target (≥98% probability of target attainment) in patients with normal renal function and patients with mild renal impairment. Thus, for the purposes of dosing in this study, Cohort 4 is split into Cohort 4a, who will receive the same dose as Cohort 2 (50 mg/kg ceftazidime/12.5 mg/kg avibactam, every 8 hours), and Cohort 4b, who will receive 50 mg/kg ceftazidime/12.5 mg/kg avibactam, every 8 hours for patients from 6 months to <1 year of age, and 40 mg/kg ceftazidime/10 mg/kg avibactam for patients from 3 months to <6 months of age.

The doses for use in patients with renal impairment have been chosen on the basis of modelling and simulation to achieve similar exposures of both ceftazidime and avibactam to those in adults with normal or mild renal impairment and predictions of sufficient exposure above the PK/PD target.

Patients enrolled into this clinical study will have cIAIs that are of sufficient severity to require hospitalisation and treatment with IV antibiotics. The potential benefit to patients participating in this study is that they will receive effective antibiotic therapy for their infection. The potential benefit of this study, in general, is the identification of a novel antibiotic combination product that is a safe and effective treatment for cIAIs in the paediatric population, in the face of the changing pattern of antibiotic resistance. The safety and tolerability of CAZ-AVI was established in a Phase 1 study in children from 3 months to <18 years, during which the exposures were similar to those observed in adults.

It is possible that CAZ-AVI may not be as effective a treatment as the comparator for treatment of cIAIs. Although this risk is mitigated partly by the addition of metronidazole to provide coverage for anaerobic infections and in that the study patients will be closely monitored and managed with appropriate therapies as determined by the Investigator providing treatment. Furthermore, drug-drug interaction studies conducted between CAZ-AVI and metronidazole did not demonstrate any drug interaction or adverse safety impact.

A Phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group, comparative study to determine the efficacy, safety, and tolerability of CAZ-AVI plus metronidazole versus meropenem was conducted in the treatment of cIAIs in hospitalised adults, aged 18 to 90 years. The treatment duration was 5 to 15 days (RECLAIM study). The doses administered were IV CAZ-AVI (500 mg avibactam and 2000 mg ceftazidime), immediately followed by 500 mg IV metronidazole, or 1000 mg IV meropenem, and 529 patients in each treatment arm received study treatment. Study treatments were administered every 8 hours. CAZ-AVI was non-inferior compared with meropenem.

CAZ-AVI plus metronidazole was effective in treating infections due to Gram-negative pathogens resistant to ceftazidime with response rates similar to that seen with ceftazidime-susceptible isolates. The adverse events (AEs) were generally mild or moderate in severity and the overall frequency and pattern of AEs were comparable between the treatment groups. Analysis of the safety topics of interest did not reveal any new safety concerns.

Another Phase 3 study was an open-label, randomised, multicentre, study of CAZ-AVI and Best Available Therapy (BAT) for the treatment of infections due to ceftazidime-resistant Gram-negative pathogens, which was conducted in 333 adults aged 18 to 90 years diagnosed with cIAI or cUTI. The dose administered was 2000 mg ceftazidime/500 mg avibactam IV over 2 hours. Those patients diagnosed with cIAI received an additional dose of 500 mg metronidazole IV. Study treatments were repeated every 8 hours and the treatment duration was 5 to 21 days. In terms of the primary objective to estimate the per-patient clinical response to CAZ-AVI and BAT at the Test of Cure (TOC) visit, the estimated clinical cure rate at the TOC visit was 90.9% for CAZ-AVI and 91.2% for BAT. In the mMITT analysis set, the per-patient favourable microbiological response rate for patients with cUTI at the TOC visit was higher in the CAZ-AVI group than in the BAT group (81.9% versus 64.2%, respectively).

There were no definitive conclusions of any treatment-related trends in patients with cIAI, and there were no obvious safety concerns identified from the data available. In the patients with cUTI, the proportion who experienced an AE up to the Late Follow-up (LFU) visit was 28.3% in the CAZ-AVI group and 35.3% in the BAT group. For patients with cUTI and cIAI, the majority of AEs were mild or moderate in intensity. Up to the LFU visit, the incidence of serious adverse events (SAEs) was low and balanced across treatment groups (5.5% in the CAZ-AVI group and 6.0% in the BAT group). All SAEs were assessed as not causally related to the study treatment by the Investigator. The number of patients with AEs of special interest (AEoSI) was generally low and balanced across treatment groups, with the exception of diarrhoea in patients with cUTI, which was higher in the BAT group (5.9% and 2.0%, for BAT and CAZ-AVI, respectively). No new safety concerns were identified from the safety topics of interest. The frequency of potentially clinically significant changes in clinical laboratory tests was also low and balanced across treatment groups. There were no Hy's Law cases.

A Phase 2 study (NXL104/2001) examining the safety of CAZ-AVI versus imipenem cilastatin followed by appropriate oral therapy as a comparator was conducted in 137 patients aged 18 to 90 years with cUTIs. In this study patients were randomised 1:1 and given 500 mg ceftazidime and 125 mg avibactam IV every 8 hours or 500 mg imipenem cilastatin IV every 6 hours. Approximately 35% of patients in the CAZ-AVI group and 42% of patients in the imipenem cilastin group experienced a local reaction at the IV infusion site. The majority of the infusion site reactions were mild or moderate in intensity. One patient in the imipenem cilastatin group experienced a severe local reaction (induration, swelling). The most common infusion-related events across the treatment arms were erythema, pain and tenderness. Of note, patients in the CAZ-AVI group received 3 infusions per day, while patients in the imipenem cilastatin group received 4 infusions per day.

In the Phase 2 study (NXL104/2002) examining CAZ-AVI plus metronidazole versus meropenem as a comparator in patients with cIAIs, approximately 30% of participants in both the CAZ-AVI and meropenem comparator treatment groups experienced at least 1 symptom of local intolerability, with pain, erythema, swelling and tenderness reported most frequently across both groups. The majority of infusion site events were mild. There was a somewhat greater percentage of patients with infusion site events of moderate/severe intensity in the CAZ-AVI group, who also received IV metronidazole (17/101 patients [16.8%]) versus the meropenem group (11/102 patients [10.8%]). Of note, patients in the CAZ-AVI plus metronidazole group received an infusion of 3 different agents per dose, whilst patients in the meropenem group received an infusion with 1 study drug per dose.

A Phase 1, open-label, single-dose study to characterise the pharmacokinetics (PK) of CAZ-AVI and assess its safety and tolerability following a single IV dose was conducted in hospitalised paediatric patients aged 3 months to <18 years, receiving systemic antibiotic therapy for suspected or confirmed infection. The patients in this study were stratified by age and patients were enrolled in each cohort as follows: Cohort 1, patients aged ≥12 to <18 years; Cohort 2, patients aged ≥6 to <12 years; Cohort 3, patients aged ≥2 to <6 years; and Cohort 4, patients aged ≥3 months to <2 years (split into 2 groups of at least 4 patients each, ≥3 months to <1 year and ≥1 year to <2 years).

Patients in Cohort 1 and any patients in Cohort 2 weighing ≥40 kg received a single IV dose of CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) administered as a single infusion over a 2-hour period on Day 1. Patients in Cohort 2 weighing <40 kg received a single IV dose of CAZ-AVI (50 mg/kg ceftazidime and 12.5 mg/kg avibactam) administered as a single infusion over a 2-hour period on Day 1. These doses were applicable for patients with normal renal function and mild renal insufficiency (creatinine clearance [CrCl] >50 to ≤80 mL/min).

In Cohorts 3 and 4, patients with normal renal function or mild renal insufficiency received a single IV dose of CAZ-AVI (50 mg/kg ceftazidime and 12.5 mg/kg avibactam) on Day 1. Each patient in the study received a single IV dose of CAZ-AVI administered as a continuous infusion over a 2-hour period. There were 32 patients in the safety analysis set and 32 patients in the PK analysis set.

Concentration versus time overlay plots suggest that the plasma ceftazidime and avibactam concentration profiles were similar in all 4 cohorts across sampling time points.

Review of the haematology, coagulation, clinical chemistry, and urinalysis laboratory values did not reveal any unexpected findings within patients or any trends across patients; there were no potentially clinically significant haematology, clinical chemistry, or liver function test values reported. No patients met Potential Hy's Law criteria. Review of vital signs values and physical examination findings did not identify any new safety concerns. There were no clinically significant changes in electrocardiograms (ECGs) reported. The single IV dose of CAZ-AVI was well tolerated, with no new safety concerns identified in hospitalised paediatric patients.

The risk considerations for this study encompass the known and potential risks for CAZ-AVI and its component products avibactam and ceftazidime, as well as those risks associated with other treatments that may be administered as described in this protocol. Other possible treatments include the marketed products metronidazole and meropenem. As the risks for these marketed products are widely available in their respective prescribing information, these risks will not be discussed within this section.

The risks for CAZ-AVI have not been fully elucidated; however it is assumed that known or potential risks for CAZ-AVI should include those identified in the clinical studies with CAZ-AVI, avibactam alone, and also for ceftazidime alone. Additional risk information for avibactam and CAZ-AVI is located in the CAZ-AVI Investigator's Brochure.

The full risk profile for ceftazidime is described in the prescribing information for the product (refer to local ceftazidime product labelling). Important risks as laid out in the warnings and precautions in product labelling for ceftazidime include:

- Hypersensitivity reactions. Though patients with hypersensitivity and serious allergic reactions to cephalosporins, carbapenem or other β-lactam antibiotics are excluded from the trial, first-time episodes of such reactions could occur.
- Antibiotic-associated diarrhoea, *Clostridium difficile* diarrhoea, colitis, and pseudomembranous colitis
- Bacterial overgrowth with non-susceptible organisms
- Distal necrosis as a result of inadvertent intra-arterial administration of ceftazidime
- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae such as tremors, myoclonus, seizures, encephalopathy, and coma

Potential risks for CAZ-AVI include the occurrence of events seen with ceftazidime alone, but that go beyond the frequency and/or severity of those seen with ceftazidime. Local intolerance has been seen in the preclinical studies, and has been monitored in the clinical programme. In the Phase 1 studies, erythema and haematoma at the administration site were reported.

In regard to hypersensitivity reactions, there was 1 report in the CAZ-AVI clinical trials, where the clinical Investigator considered the events of skin rash and elevated liver function tests to be a possible hypersensitivity reaction because of the temporal relationship of the events to drug administration. In the CAZ-AVI development programme, rashes have been reported. Elevations of liver enzymes, independent of skin rashes or other potential signs of hypersensitivity, have also been reported.

In summary, the known and potential risks of receiving the developmental antibiotic combination CAZ-AVI are expected to be similar to those seen with ceftazidime and

cephalosporins in general. Thus far, no unique risks have been identified for the avibactam component or the combination of CAZ-AVI. The risks of the marketed antibiotics are considered acceptable. Whilst it is anticipated that CAZ-AVI will have similar efficacy for the treatment of cIAIs, it is possible that efficacy will not be demonstrated. For each patient in the trial, appropriate treatment of the cIAI is thus determined by the clinical Investigator based on the clinical response of the patient.

1.4 Study design

This study will be a single blind, randomised, multi-centre, active controlled trial. Patients aged from 3 months to less than 18 years with cIAIs will be randomised to 1 of 2 treatment groups (3:1 ratio): CAZ-AVI in combination with metronidazole versus meropenem. Patients aged from 3 months to <1 year (Cohort 4b) must have been born at term (defined as gestational age ≥37 weeks).

A sufficient number of patients are to be randomised 3:1 for 80 patients to complete at least 72 hours (3 full days, ie, 9 doses) of study treatment (ie, evaluable patients; at least 60 patients in the CAZ-AVI group and at least 20 patients in the meropenem group).

Patients will be allocated to 1 of 4 cohorts based on age. Randomisation will be stratified 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

Intravenous CAZ-AVI infusions will be given at doses based on age and weight with adjustment according to renal function as detailed in Table 5.

Patients whose CrCL drops below 30 mL/min should be withdrawn from study therapy. Patients withdrawing from study therapy can be administered alternative therapies at the Investigator's choice, which should be recorded in the Case Report Form (CRF). If possible, patients should still be followed for safety (see Section 3.9.1). 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. If

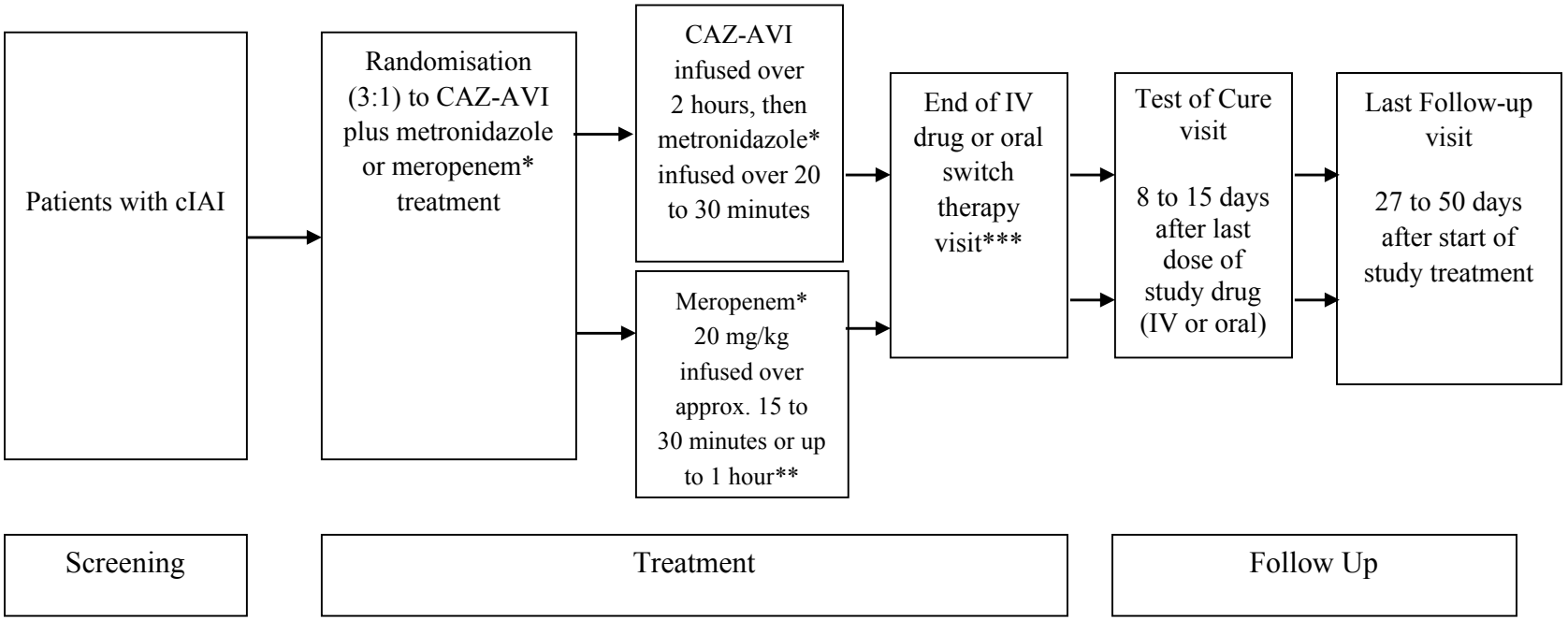
in the opinion of the Investigator there is a clinically significant reduction in a patient's estimated CrCl during the treatment period, then the Investigator should contact the Medical Monitor to discuss the above mentioned options (immediate dose change, a short period of continued observation, or discontinuation of therapy). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and Investigator's clinical evaluation.

The suggested dosing regimen of metronidazole is 10 mg/kg IV over 20 to 30 minutes every 8 hours (±30 minutes), but it can also be prescribed/adjusted by the Investigator according to local labels. The metronidazole infusion will be started no later than 30 minutes after completion of the CAZ-AVI infusion. The dose/regimen of meropenem will be 20 mg/kg every 8 hours (±1 hour) infused over approximately 15 to 30 minutes or up to 1 hour (or infusion duration as per local guidelines). For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours.

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, as specified in Section 7.7 below. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food. The total period of treatment (ie, IV drug and oral switch treatment) is to be between 7 and 15 days. Patients may remain on 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 at which time there will be a LFU assessment visit. The LFU is to be performed 20 to 35 days after the last dose of any treatment.

Figure 1 Study flow chart



*Optional switch to oral therapy permitted on or after Study Day 4 (ie, after 72 hours [3 full days, ie, 9 doses] of IV study drug. Assessment should be performed no later than 8 hours after the 72-hour time point. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food:
- Oral amoxicillin/clavulanic acid (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or
- Oral ciprofloxacin (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care) plus metronidazole (administered at a dose and formulation per standard of care), or
- Pathogen-based therapy (in discussion with the Medical Monitor), see Section 7.7.

The patient may continue on IV study drug for the entire duration of the study therapy (7 to 15 days), at the discretion of the Investigator.
** Or infusion duration as per local guidelines. For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours.
*** Visit performed within 24 hours of completion of last infusion or within 48 hours after the last dose of oral switch therapy.

2. STUDY OBJECTIVES

2.1 Primary objective (safety)

Primary Objective:	Outcome Measure:
Evaluate the safety and tolerability of CAZ-AVI plus metronidazole given at the selected dose regimen versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI	• AEs and SAEs from the signing of the Informed Consent Form (ICF)/Assent Form to the LFU visit (27 to 50 days after start of study treatment) • 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) • Clinical: vital signs (pulse, blood pressure, respiratory rate, temperature), ECG, and physical examinations • Laboratory: complete blood count with differential and comprehensive metabolic panel • CrCl

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
Evaluate the descriptive efficacy of CAZ-AVI plus metronidazole versus meropenem in paediatric patients aged ≥3 months to <18 years with cIAI	• Clinical outcomes at End of 72 hours' Treatment, End of Intravenous Treatment (EOIV), End of Treatment (EOT), and TOC • Microbiological response at EOIV, EOT, TOC and LFU • Clinical relapse at LFU • Emergent infections
Evaluate the PK of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cIAI	• PK data of ceftazidime and avibactam will be analysed separately • Plasma concentration will be listed and summarised by nominal sampling time window using appropriate descriptive statistics • PK parameters derived from population PK analysis and potential PK/PD relationships will be reported separately

2.3 Safety objectives

Safety is the primary objective.

2.4 Exploratory objectives not applicable

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Must be ≥3 calendar months to <18 years of age. Patients aged ≥3 calendar months to <1 year must have been born at term (defined as gestational age ≥37 weeks).

2. Written informed consent from parent(s) or other legally acceptable representative(s), and informed assent from patient (if age appropriate according to local regulations)

3. If female and has reached menarche, or has reached Tanner stage 3 development (even if not having reached menarche) (refer to Appendix E for further details on Tanner staging), the patient is authorised to participate in this clinical study if the following criteria are met:

At screening:

(i) (a) Patient reports sexual abstinence for the prior 3 months or reports use of at least 1 of the acceptable methods of contraception, including an intrauterine device (with copper banded coil), levonorgestrel intrauterine system (eg, Mirena®), or regular medroxyprogesterone injections (Depo-Provera®); or (b) Patient agrees to initiate sexual abstinence from the time of screening until 7 days after end of treatment with study drug; and

(ii) Patient is advised to avoid conception from the time of screening until 7 days after receipt of study drug and agrees not to attempt pregnancy from the time of screening until 7 days after end of treatment with study drug; and

(iii) Patient is provided guidelines regarding continuation of abstinence, initiation of abstinence, or about allowed contraception; and

(iv) Patient has a negative serum β-human chorionic gonadotropin (β-hCG) test just prior to study entry. Since serum tests may miss an early pregnancy, relevant menstrual history and sexual history, including methods of contraception, should be considered. Note: if the result of the serum β-hCG test cannot be obtained prior to dosing of investigational product, a patient may be enrolled on the basis of a

negative urine pregnancy test, though a serum β-hCG test result must still be obtained.

Note 1: Hormonal contraceptives delivered orally, as patches, or via vaginal devices should not be used as a method of birth control because the effect of CAZ-AVI on the efficacy of these types of contraceptives has not yet been established.

Note 2: Barrier methods (such as male condom) can be used as a means of preventing sexually transmitted disease but are not acceptable as a means of contraception for this clinical trial.

4. Must, based on the judgment of the Investigator, require hospitalisation initially and antibacterial therapy for 7 to 15 days in addition to surgical intervention for the treatment of the current cIAI

5. Require surgical intervention (eg, laparotomy, laparoscopic surgery or percutaneous drainage) to manage the cIAI

6. Must have clinical evidence of cIAI as follows:

(i) Pre-operative enrolment inclusion:

(a) Requires surgical intervention that is expected to be completed within 24 hours of enrolment

– Laparotomy, laparoscopy, or percutaneous drainage

(b) Evidence of a systemic inflammatory response (at least 1):

– Fever (defined as oral temperature >38.5°C, or equivalent to method used) or hypothermia (with a core body or rectal temperature <35°C, or equivalent to method used)

– Elevated white blood cells (WBC) (>15000 cells/mm^3)

– C-reactive protein (CRP) levels (>10 mg/L)

(c) Physical Findings consistent with intra-abdominal infection, such as:

– Abdominal pain and/or tenderness

– Localised or diffuse abdominal wall rigidity

– Abdominal mass

(d) Intention to send specimens from the surgical intervention for culture

(e) (Optional) Supportive radiologic findings of intra-abdominal infection, such as perforated intraperitoneal abscess detected on:

- Computed tomography (CT) scan or
- Magnetic resonance imaging (MRI) or
- Ultrasound

(ii) Intra-operative/postoperative enrolment inclusion (in cases of postoperative enrolment, must be within 24 hours after the time of incision):

Visual confirmation of intra-abdominal infection associated with peritonitis at laparotomy, laparoscopy or percutaneous drainage (to be confirmed pending feasibility); must have 1 of these diagnoses:

(a) Appendiceal perforation or peri-appendiceal abscess

(b) Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall

(c) Acute gastric or duodenal perforations, only if operated on >24 hours after singular perforation occurs

(d) Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs

(e) Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites)

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrolment or randomisation in the present study

3. Participation in another clinical study with an investigational product (IP) during the last 30 days before the first dose of IV study drug or have previously participated in the current study or in another study of CAZ-AVI (in which an active agent was received)

4. History of hypersensitivity reactions to carbapenems, cephalosporins, penicillin, other β-lactam antibiotics, metronidazole, or to nitroimidazole derivatives

5. Concurrent infection, that may interfere with the evaluation of response to the study antibiotics at the time of randomisation

6. Patient needs effective concomitant systemic antibacterials (oral, IV, or intramuscular) in addition to those designated in the 2 study groups (CAZ-AVI plus metronidazole group or meropenem group) (see Section 7.8)

7. Receipt of non-study systemic antibacterial drug therapy for cIAI, for a continuous duration of more than 24 hours during the 72 hours preceding the first dose of IV drug, except in proven resistant organisms and/or worsening of the clinical condition. More than 2 consecutive doses are not permitted if the individual doses are expected to give >12 hours' cover (ie, giving a total cover of >24 hours.) For patients enrolled after a surgical procedure, only 1 dose of non-study antibiotics is permitted postoperatively.

8. Patient is considered unlikely to survive the 6 to 8 week study period

9. Patient is unlikely to respond to 7 to 15 days of treatment with antibiotics

10. Patient is receiving haemodialysis or peritoneal dialysis

11. Diagnosis of abdominal wall abscess confined to musculature of the abdominal wall or ischaemic bowel disease without perforation, traumatic bowel perforation requiring surgery within 12 hours of perforation, or perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation (these are considered situations of peritoneal soiling before the infection has become established)

12. Simple (uncomplicated), non-perforated appendicitis or gangrenous appendicitis without rupture into the peritoneal cavity identified during a surgical procedure OR presence of primary peritonitis (ie, spontaneous bacterial peritonitis) or peritonitis associated with cirrhosis or chronic ascites

13. At the time of randomisation, patient is known to have a cIAI caused by pathogens resistant to the study antimicrobials planned to be used in the study

14. Presence of any of the following clinically significant laboratory abnormalities:

(a) Haematocrit <25% or haemoglobin <8 g/dL (<80g/L, <4.9 mmol/L)

(b) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3×the age-specific upper limit of normal (ULN), or total bilirubin >2×ULN (except known Gilbert's disease)

For a) and b): unless if these values are acute and directly related to the infectious process being treated.

15. Creatinine clearance <30 mL/min/1.73 m^2 calculated 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)

16. History of seizures, excluding well-documented febrile seizure of childhood

17. Any situation or condition that would make the patient, in the opinion of the Investigator, unsuitable for the study (eg, would place a patient at risk or compromise the quality of the data) or may interfere with optimal participation in the study

18. If female, currently pregnant or breast feeding

See Section 3.4 for procedures for withdrawal of incorrectly enrolled patients.

3.3 Subject enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening. Patients will be enrolled if they meet all the inclusion criteria, including informed consent and assent in writing from parent(s) or other legally-acceptable representative(s)/patient as applicable, and none of the exclusion criteria. The Blinded Observer may perform screening and enrolment; however, the Investigator must perform randomisation.

The Blinded Observer/Investigator will:

1. Obtain signed informed consent from the parent or guardian/legally acceptable representative(s) of the potential patient and informed assent from the potential patient (if age appropriate according to local regulations) before any study specific procedures are performed

2. Assign potential patient a unique enrolment number, beginning with 'E#'

3. Determine patient eligibility (see Sections 3.1 and 3.2)

4. Investigator only: Assign eligible patient unique randomisation code (via an interactive voice/web response system [IXRS] not available for access by the Blinded Observer)

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria, must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the Medical Monitor immediately, and a discussion should occur between the Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Medical Monitor must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Block randomisation using an IXRS will be used to assign patients in a ratio of 3:1 to the study treatment groups of CAZ-AVI plus metronidazole or meropenem, respectively, in each of the cohorts for the age groups (see Section 8.2 for a description of the sample size).

A representative of AstraZeneca, under the supervision of AstraZeneca statistical personnel, will perform this randomisation.

3.6 Methods for ensuring blinding

This study will be observer-blinded. Each investigational site will be required to have a site-specific Blinding Plan that describes site-specific precautions being taken to ensure that the study is observer-blinded, taking into account the specific patient care procedures, equipment, and information accessibility at that site.

At each investigational site, at least 1 blinded Investigator (referred to as "Blinded Observer" hereafter) will not know the patient's treatment assignment and will conduct clinical assessments related to safety and efficacy. The Blinded Observer may perform screening and enrolment activities but will not be responsible for randomising patients (the Blinded Observer will not have access to the IXRS). The Blinded Observer will not ask other members of the study team, the patient, or the patient's parent(s)/legally acceptable representative(s) which study treatment is being given, and will avoid all attempts to uncover treatment assignment. The Blinded Observer should arrange to see the patient during times when study drug is NOT being administered, and not when assessments are being performed that could possibly unblind the Blinded Observer, in order to maintain the blind. If possible, the same Blinded Observer should complete all clinical assessments for a patient. The Blinded Observer should perform all causality assessments for all AEs and SAEs.

At each investigational site, an unblinded Investigator (referred to as "Investigator" hereafter), Pharmacist or designee, study centre personnel, patient, and parent(s)/legally acceptable representative(s) may be aware of which IV study drug therapy is being administered and shall be instructed not to reveal to the Blinded Observer which drug the patient is receiving. Refer to Section 3.7 if the Blinded Observer learns of the treatment assignment.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists from the IXRS. Routines for this will be described in the IXRS user manual that will be provided to each centre.

This study has an observer-blinded design. During the study, the Blinded Observer(s) will not make any effort to determine which IV study drug is being administered. The details of blinding will be described in the Blinding Plan.

Only in the case of an emergency, when knowledge of the study drug is essential for the immediate clinical management or welfare of a specific patient and the Investigator or designee is not available to provide or cannot provide appropriate medical care to the patient, may the Blinded Observer be unblinded to the patient's treatment assignment.

Before any unblinding of the Blinded Observer, it is strongly advised to discuss options with the Medical Monitor or appropriate study personnel. As soon as possible, and without revealing the patient's study treatment assignment (unless important to the safety of patients remaining in the study), the Blinded Observer or designee must notify PRA if the observer blind is broken for any reason and the Blinded Observer was unable to contact PRA before unblinding. PRA will inform AstraZeneca of the incident.

3.8 Restrictions

Hormonal contraceptives which are potentially subject to drug-to-drug interaction, such as pills, patches, and intravaginal devices, are not acceptable methods of birth control during this study based on potential for antibiotics to alter gut flora, hormone absorption, and hormone effectiveness. If an adolescent female study participant was previously using hormonal contraceptives such as pills, patches, and intravaginal devices, she should follow her health care provider's specific recommendations for effective use of these methods after completing IV study therapy. Such recommendations may address the need for a second method of contraception until the hormonal method becomes fully effective.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient or patient's parent(s)/legally acceptable representative(s) decision. The patient or the patient's parent(s) or other legally acceptable representative(s) is at any time free to decide to discontinue treatment, without prejudice to further treatment

- AE (eg, risk to patients, as judged by the Investigator)

- Positive pregnancy test at any time during the study treatment period
- In the absence of any alternative explanation for an increase in the following abnormalities, individual patients should be withdrawn if the following hepatic/liver criteria are met:
  - ALT or AST >8×ULN
  - ALT or AST ≥3×ULN and either total bilirubin ≥2×ULN or evidence of coagulopathy. Evidence of coagulopathy should be discussed with the PRA physician where possible
  - ALT or AST ≥3×ULN and with appearance of symptoms suggestive of new or progressive liver disease. Symptoms suggestive of new or progressive liver disease should be discussed with the PRA physician where possible
- Significant reduction in CrCl measurements as judged by the Investigator
- CrCl value <30 mL/min
- Severe non-compliance with study protocol, as judged by the Investigator
- In the opinion of the Investigator, it is not in the best interest of the patient to continue study therapy and/or lack of efficacy

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients or the patient's parent(s) or other legally acceptable representative(s) are free to decide to discontinue the child's use of IP or withdraw from the study (ie, IP and assessments – see Section 3.10), without prejudice to further treatment. A patient or the patient's parent(s) or other legally acceptable representative(s) who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s).

Adverse events and SAEs will be followed up (See Section 6). For patients who discontinue IP early, their follow-up assessments should be collected (see Section 6.3.2 for follow-up of unresolved AEs). Liver CRF modules should be completed for patients discontinued after meeting hepatic/liver criteria. The patient should be scheduled for the EOIV visit within 24 hours after IV study therapy discontinuation, ideally before starting any new antibiotic treatment.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are patients who have provided informed consent/assent and subsequently who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Failed Eligibility Criteria' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients or the patient's parent(s) or other legally acceptable representative(s) are free to withdraw the child from the study at any time (IP and assessments), without prejudice to further treatment.

A patient or the patient's parent(s) or other legally acceptable representative(s) who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patients at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study plan detailing study procedures

	Assessment or Procedure	Baseline[1]	Treatment: Day 1[2]	Treatment: Days 2 and 3	Treatment: Days 4 to ≤15[3]	Treatment: EOIV[4]	Treatment: EOT[5] (Oral only)	Follow-up: TOC[6]	Follow-up: LFU[7]
Clinical	ICF (and Assent Form, if applicable)[8]	X							
	Verify inclusion/exclusion criteria	X							
	Medical and surgical history	X							
	Complete physical examination[9]	X		X After 72 hours' treatment only		X	X	X	X[10]
	Prior and concomitant medications (including lactating mother)[11]	X	X	X	X	X	X	X	X
	Vital signs[12]	X	X	X	X	X	X	X	X[10]
	ECG[13]	X	X					X	
	Record adjunctive therapeutic procedures (if performed)		X	X	X	X	X	X	X
	Record radiological examinations[14]	X							
	Clinical outcome			X[15] After 72 hours' treatment only		X[15]	X[15]	X[15]	X[16]
	AEs and SAEs[17]	X	X	X	X	X	X	X	X
Laboratory	Complete blood count with differential, chemistry panel, CrCl calculation, ESR, and optional CRP [18]	X	If clinically indicated		X[19]	X[20]	If clinically indicated	X[21]	If clinically indicated

	Assessment or Procedure	Baseline[1]	Treatment: Day 1[2]	Treatment: Days 2 and 3	Treatment: Days 4 to ≤15[3]	Treatment: EOIV[4]	Treatment: EOT[5] (Oral only)	Follow-up: TOC[6]	Follow-up: LFU[7]
Micro	Urine or serum pregnancy test[22]	X						X	
Micro	Urine sample routine analysis[23]	X	If clinically indicated						
Micro	Intra-abdominal fluid sample[24]	X	If clinically indicated						
Micro	Blood sample for culture[25]	Blood cultures should be performed as clinically indicated.							
PK	Blood for PK analyses[26]			X					
	Randomisation[27]	X							
	Study drug administration		X	X	X	X			
	Oral switch therapy administration (optional at Investigator's discretion)				X				

ESR=erythrocyte sedimentation rate

1. Perform baseline assessments within 24 hours before first dose of IV study drug.
2. Day 1 is the first day of IV study drug administration; subsequent study days are consecutive days. Perform Day 1 assessments after administration of at least 1 dose of IV study drug.
3. On Days 4 to ≤15, study drug administration applies to all patients and daily assessments are to be performed only for patients on IV study drug.
4. Perform EOIV assessments in person by the Blinded Observer within 24 hours after completion of the last infusion of study drug or at time of premature discontinuation of study drug or early withdrawal from study (if on IV study drug). Conduct the EOIV assessments in place of the regular study visit (eg, Days 4 to ≤15) assessments that would have been performed the day of that visit. A patient may be eligible to switch to oral therapy on or after Day 4 (Section 7.2); EOIV assessments must occur before starting oral switch therapy.
5. Perform EOT assessments in person within 48 hours after the last dose of oral switch therapy or at time of premature discontinuation of study drug or early withdrawal from study (if on oral switch therapy).
6. Perform TOC assessments in person 8 to 15 days after last dose of any study drug (IV or oral).
7. Perform LFU assessments 20 to 35 days after last dose of any study drug (IV or oral). Conduct LFU via telephone for any patient who has not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs are noted, or at the discretion of the Blinded Observer or Investigator, the patient should be immediately scheduled for an in-person visit.
8. Obtain informed consent from parent(s) (or other legally acceptable representative[s]) in writing and informed assent from patient (if age appropriate according to local requirements) before initiating any study assessments or procedures.

9. Height measured at Baseline only. Weight measured at Baseline only, but should be measured at subsequent time points if clinically indicated and feasible. Physical examination to be performed after completion of 72 hours' treatment (either Day 3 or Day 4, depending on timing of treatment administration). Assessment should be performed no later than 8 hours after the 72-hour time point.
10. Not applicable if visit conducted by telephone.
11. For patients who are breast fed, all medications taken by the lactating mother in the previous 2 weeks prior to the first dose of study therapy until LFU will also be recorded.
12. Temperature, respiratory rate, pulse and blood pressure, by the appropriate method for the patient's age. To be performed before ECG on days when both assessments are indicated.
13. Baseline ECG to be performed prior to obtaining blood samples for laboratory testing. Day 1 ECG to be performed within 30 minutes following the end of the first study treatment infusion. Electrocardiograms will be taken after the patient has been resting in a recumbent position for at least 10 minutes.
14. Radiological examinations are not required for the study, but the results should be recorded if done as part of the diagnosis. Radiological examinations include WBC scans, plain abdominal radiographs, CT scans, ultrasound and/or MRI scans with or without contrast.
15. Blinded Observer: Assess clinical outcome per protocol, assessment after 72 hours of treatment. Assessment should be performed no later than 8 hours after the 72-hour time point (no assessment required on Day 2).
16. Blinded Observer: Assess patients for clinical relapse per protocol. Emergent infections will be assessed up to LFU.
17. Investigator or Blinded Observer: Collect and report AEs and SAEs from signing of the ICF (and Assent Form if applicable) until at least 30 days after any dose of study drug (IV or oral) (or LFU, whichever is later); site staff are to follow unresolved AEs and SAEs at LFU until resolution or stabilisation. The causality assessment should be done by the Blinded Observer (not the Investigator) for all AEs and SAEs.
18. Laboratory tests indicated at Baseline do not need to be repeated if they were performed within 24 hours of the Baseline visit, unless clinically indicated. Perform local safety laboratory tests at additional time points as clinically indicated. Erythrocyte sedimentation rate to be performed if clinically indicated or if required per standard of care. C-reactive protein is an optional test and may be included if part of standard of care. C-reactive protein and CrCl calculation may be repeated at additional time points if clinically indicated. Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Direct Coombs test at Baseline and TOC only. Test results of any samples taken as standard of care should be recorded in the CRF.
19. Conduct on Day 7 if patient is still on IV study drug at that time.
20. If EOIV occurs within 48 hours after these assessments are performed on Study Day 7, do not repeat these assessments.
21. Perform at TOC only if patient had an abnormal (high/low flag) result on or after EOIV.
22. Perform test if patient is a female who has reached menarche or has reached Tanner stage 3 development (even if not having reached menarche). If a pregnancy test is positive post baseline, follow reporting requirements in Section 6.6. Note: if the result of the serum β-hCG test cannot be obtained prior to dosing of investigational product, a patient may be enrolled on the basis of a negative urine pregnancy test, though a serum β-hCG test result must still be obtained. At TOC, a serum pregnancy test is required.
23. At Baseline, before any antibiotics are administered. Subsequent additional time points if clinically indicated.
24. At Baseline, make every attempt to obtain intra-abdominal fluid sample preferably before any antibiotics administered. Subsequent time points if clinically indicated.
25. If clinically indicated and not already collected per standard of care.
26. Blood samples for PK (1 mL per sample for Cohorts 1 and 2, and 0.5 mL per sample for Cohorts 3, 4a, and 4b) will be collected from patients randomised to CAZ-AVI plus metronidazole treatment on Day 3 following a dose administration that is convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI infusion, anytime between 30 minutes and 90 minutes after

stopping CAZ-AVI infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient. Blood samples should be taken in a manner such that the Blinded Observer remains blinded.

27. Verify that the patient meets all study inclusion and no exclusion criteria before randomisation.

4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan (Table 1). Details of study assessments are provided in Section 5.

At screening, consenting/assenting patients will be assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study. Baseline assessments must be performed within 24 hours of administration of the first dose of IV study drug. The following assessments will be performed at Baseline:

- Provision of informed consent/assent and verification of inclusion and exclusion criteria. Informed consent should be obtained from the parent(s) (or other legally acceptable representative[s]) in writing and informed assent from the patient (if age appropriate according to local requirements) before initiating any study assessments or procedures.
- Medical and surgical history
- Complete physical examination, including height and weight
- Prior and concomitant medication recording, including medications taken by the mother if the infant is breast feeding. Prior medications include all prescription and over-the-counter medications being taken by the patient (and lactating mother, if patient is breast fed) for the 2 weeks prior to study entry.
- Vital signs (temperature, respiratory rate, pulse and blood pressure, by the appropriate method for the patient's age). To be performed before the ECG.
- ECG (to be performed prior to obtaining blood samples for laboratory testing)
- Record radiologic examinations
- AEs and SAEs to be collected from the time of provision of informed consent/assent
- Complete blood count with differential, Direct Coombs test, chemistry panel, ESR (if clinically indicated or if required per standard of care), CrCl calculation, and optional CRP. Note: Laboratory tests indicated at Baseline do not need to be repeated if they were performed within 24 hours of the Baseline visit, unless clinically indicated. C-reactive protein is an optional test and may be included if part of standard of care. C-reactive protein and CrCl calculation may be repeated at additional time points if clinically indicated. Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.

- Urine or serum pregnancy test applicable only to female patients who have reached menarche or have reached Tanner stage 3 development (even if not having reached menarche). If a pregnancy test is positive post-baseline, follow reporting requirements in Section 6.6. Note: if the result of the serum β-hCG test cannot be obtained prior to dosing of IP, a patient may be enrolled on the basis of a negative urine pregnancy test, though a serum β-hCG test result must still be obtained.

- Urine sample for routine analysis

- Intra-abdominal fluid sample collection (preferably before administration of any antibiotics)

- Blood sample for culture (if clinically indicated and not already collected per standard of care)

- Randomisation via IXRS only after verification of all inclusion and exclusion criteria

4.2 Treatment period

The procedures for this period are listed in the Study Plan (Table 1). Details of study assessments are provided in Section 5.

4.2.1 Day 1

Day 1 is the first day of IV study drug administration; subsequent study days are consecutive days. Day 1 assessments should be performed after administration of at least 1 dose of IV study drug. The following will be performed:

- IV study drug administration: CAZ-AVI plus metronidazole or meropenem; see Section 7.2 for dosing and treatment regimens

- Recording of concomitant medications, including mother if patient is breast fed

- Vital signs (to be performed before the ECG)

- ECG within 30 minutes following the end of the first study treatment infusion

- Recording of any adjunctive therapeutic procedures performed

- If clinically indicated: CrCl calculation, urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.

- Recording of any AEs/SAEs

4.2.2 Days 2 and 3

The following will be performed:

- IV study drug administration
- Complete physical examination after completion of 72 hours' treatment only. This assessment may be performed on Day 4, depending on the timing of treatment administration. Assessment should be performed no later than 8 hours after the 72-hour time point.
- Recording of concomitant medications, including mother if patient is breast fed
- Vital signs
- Recording of any adjunctive therapeutic procedures performed
- Assessment of clinical outcome after 72 hours' treatment. Assessment should be performed no later than 8 hours after the 72-hour time point (assessment is not required on Day 2). See Section 8.5.2.2 for definitions of clinical outcomes.
- Recording of any AEs/SAEs
- If clinically indicated: CrCl calculation, urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.
- Blood sampling for PK analysis from patients randomised to CAZ-AVI plus metronidazole treatment on Day 3 only. To be performed following a dose administration that is convenient for the plasma sample collections at the following time points: anytime within 15 minutes prior to or after stopping CAZ-AVI infusion, anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion. Every attempt should be made to obtain at least 1 sample from each of the 3 time windows for each patient.

4.2.3 Days 4 to ≤15

On Days 4 to ≤15, study drug administration applies to all patients and daily assessments are to be performed only for patients on IV study drug. 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 as specified in Section 7.7 below. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food. Patients can continue to take IV CAZ-AVI up to Day 15. The following will be performed:

- IV study drug or oral switch therapy administration
- Complete physical examination after completion of 72 hours' treatment only. This assessment may be performed on Day 3, depending on the timing of treatment administration. Assessment should be performed no later than 8 hours after the 72-hour time point.
- Recording of concomitant medications, including mother if patient is breast fed
- Vital signs
- Recording of any adjunctive therapeutic procedures performed
- Recording of any AEs/SAEs
- Complete blood count with differential, chemistry panel, and CrCl calculation to be conducted on Day 7 if the patient is still receiving IV study drug at that time
- If clinically indicated: urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.

4.2.4 End of IV treatment

EOIV assessments should be performed in person by the Blinded Observer within 24 hours after completion of the last infusion of study drug or at the time of premature discontinuation of study drug or early withdrawal from study (if on IV study drug). The EOIV assessments should be conducted in place of the regular study visit (eg, Days 4 to ≤15) assessments that would have been performed the day of that visit. A patient may be eligible to switch to oral therapy on or after Day 4 (Section 7); EOIV assessments must occur before starting oral switch therapy. The following will be performed:

- Complete physical examination
- Recording of concomitant medications, including mother if patient is breast fed
- Vital signs
- Recording of any adjunctive therapeutic procedures performed

- If clinically indicated: urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.

- Assessment of clinical outcome

- Recording of any AEs/SAEs

- Complete blood count with differential, chemistry panel, and CrCl calculation. If EOIV occurs within 48 hours after these assessments are performed on Study Day 7, these assessments should not be repeated.

- Oral switch therapy administration

4.2.5 End of Treatment (oral switch therapy)

The assessments at EOT should be performed in person within 48 hours after the last dose of oral switch therapy or at the time of premature discontinuation of oral switch therapy or early withdrawal from study (if on oral switch therapy). If a patient does not switch to oral therapy, the EOIV assessments should be conducted instead of the EOT assessments. For patients receiving oral switch therapy only, the following will be performed:

- Complete physical examination

- Recording of concomitant medications, including mother if patient is breast fed

- Vital signs

- Recording of any adjunctive therapeutic procedures performed

- If clinically indicated: CrCl calculation, urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.

- Assessment of clinical outcome

- Recording of any AEs/SAEs

4.3 Follow-up period

The procedures for this period are listed in the Study Plan (Table 1). Details of study assessments are provided in Section 5.

4.3.1 Test of Cure

The assessments at the TOC visit should be performed in person 8 to 15 days after last dose of any study drug (IV or oral). The following will be performed:

- Complete physical examination
- Recording of concomitant medications, including mother if patient is breast fed
- Vital signs
- ECG (to be performed after the vital signs)
- Recording of any adjunctive therapeutic procedures performed
- If clinically indicated: urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.
- Assessment of clinical outcome
- Recording of any AEs/SAEs
- Complete blood count with differential, chemistry panel, and CrCl calculation to be performed only if the patient had an abnormal (high or low) result at or after EOIV.
- Direct Coombs test
- Serum pregnancy test

4.3.2 Late Follow-up

Assessments at LFU should be performed 20 to 35 days after last dose of any study drug (IV or oral). The LFU visit may be conducted via telephone for any patient who has not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs are noted, or at the discretion of the Blinded Observer or Investigator, the patient should be immediately scheduled for an in-person visit. The following will be assessed at LFU:

- Complete physical examination (not applicable if visit conducted by telephone)

- Recording of concomitant medications, including mother if patient is breast fed
- Vital signs (not applicable if visit conducted by telephone)
- Recording of any adjunctive therapeutic procedures performed
- If clinically indicated: CrCl calculation, urine sample for routine analysis, intra-abdominal fluid sample for culture, blood sample for culture, ESR, CRP (optional), weight (if feasible). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and the Investigator's clinical evaluation. Test results of any samples taken as standard of care should be recorded in the CRF.
- Assessment of clinical relapse
- Recording of any AEs/SAEs

5. STUDY ASSESSMENTS

5.1 Efficacy assessments

Clinical outcome, relapse, and emergent infections will be assessed by the Blinded Observer at the time points specified in Table 1. The Blinded Observer will assess clinical outcome, (including at LFU, assessment of patients for clinical relapse) and collection and reporting of AEs and SAEs from signing of the ICF (and Assent Form if applicable) until at least 30 days after any dose of study drug (IV or oral) or LFU.

5.2 Microbiological assessments

Culture and organism identification should be performed at the local or regional laboratory, as applicable. Susceptibility testing should be done at the local or regional laboratory to support patient care. All isolates should be sent to the central laboratory for organism identification and susceptibility testing.

Refer to the study-specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of intra-abdominal fluid and blood culture samples or isolates.

5.2.1 Intra-abdominal fluid for microbiological culture

Intra-abdominal fluid samples (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) should be obtained for culture at Baseline (preferably before any antibiotics are administered) for all patients and at any time until LFU, if clinically indicated and performed as part of the patient's regular medical care. Baseline intra-abdominal fluid samples for culture must be obtained from the site of abdominal infection during surgical

intervention. Intra-abdominal fluid samples should be collected only when collection of a sample is medically feasible. If a sample is collected, isolation of bacteria and susceptibility testing on identified bacteria should be done by the local or regional laboratory per the laboratory's standard processes. In cases where the number of potential pathogens seen in the initial culture is numerous, the local or regional laboratory should follow standard processes in identifying pathogens causing the intra-abdominal infection. All pathogens prepared and evaluated should be sent to the central laboratory for reconfirmation.

5.2.2 Blood samples for microbiological culture

If clinically indicated, blood samples (1 mL) may be obtained for culture at Baseline (preferably before any antibiotics are administered) and at any time until LFU.

This protocol complies with European Union's recommendations for blood loss associated with paediatric research (European Commission 2008) and the World Health Organisation guidelines "Blood Sample Volumes in Child Health Research: Review of Safe Limits" (Howie 2011). To minimise risk from blood loss associated with this study, standard of care laboratory results will be used whenever possible. In addition, paediatric blood collection tubes will be used and capillary methods of blood draw will be implemented whenever feasible. PK samples will be collected from patients unless deemed unsafe due to the risk from additional blood loss (per the Investigator's judgment).

5.3 Safety assessments

5.3.1 Laboratory safety assessments

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

The following laboratory variables will be measured:

Table 2 Laboratory safety variables

Comprehensive Metabolic Panel	Haematology	Urinalysis
Magnesium	Haematocrit[a]	Urinalysis (routine and microscopy) will be performed according to the study centre's standard procedures
Bicarbonate	Haemoglobin	
Sodium	Erythrocyte count	
Potassium	Mean cell volume	
Phosphorus	Leukocyte count (WBC)	
Chloride	Neutrophils	
Calcium	Lymphocytes	
Alkaline phosphatase	Monocytes	
Gamma glutamyltransferase	Eosinophils	
ALT	Basophils	
AST	Platelets	
Creatine kinase	**Immunohaematology**	
Lactate dehydrogenase	Coombs test (direct)	
Total bilirubin	**Pregnancy testing**	
Indirect bilirubin	Serum β-hCG (females only)	
Glucose, non-fasting	**Inflammation index**	
Creatinine	CRP (optional)	
Blood urea nitrogen	Erythrocyte sedimentation rate[b]	

Note: any other laboratory parameter that is deemed to be important as per local practices can be assessed if considered necessary, but will not be part of the required laboratory parameters as per protocol. Assessment of any additional laboratory parameters should not impact the blood volume to be drawn.

[a] If a patient's haemoglobin or haematocrit decreases significantly (in the Investigator's judgment) after administration of the CAZ-AVI infusion, a workup for haemolytic anaemia should be performed per standard of care.

[b] To be collected if clinically indicated or if required per standard of care.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The Direct Coombs test is required at Baseline and TOC only.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. If a patient shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥2×ULN please refer to Appendix D for further instructions.

Creatinine clearance will be measured at Baseline and at each time that serum creatinine is being assessed as part of the clinical chemistry panel using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula (Schwartz et al 2009). It is recommended that serum creatinine, and therefore CrCl obtained using the Schwartz bedside formula, are assessed at additional time points if the Investigator deems that the test is required for the safety of the patient, based on previous results and the patient's clinical condition, and if the additional test(s) does not exceed the maximum volume of blood allowed per protocol. The Investigator should also consider the balance of the risk and benefit of taking additional samples when making the decision. If a biochemistry panel is requested and serum creatinine can be added and evaluated without increasing the volume of blood allowed per protocol, the site should record the result in the CRF. Note: measurement of height is not required at each point that CrCl is estimated:

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

If there is a significant reduction (according to the Investigator) in a patient's estimated CrCl during the treatment period, the Investigator should contact the Medical Monitor for discussion.

5.3.2 Physical examination

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. Height and weight will be measured at Baseline only. Weight may be measured at subsequent time points if clinically indicated and feasible. Body mass index (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. Tanner staging of development (refer to Appendix E for further details on Tanner staging) will be assessed at Baseline only (Day -1/Day 1) for females who have not reached menarche but may reasonably have the potential to become pregnant.

5.3.3 Electrocardiogram

A single 12-lead (or as appropriate per Investigator decision) ECG recording will be performed at the times indicated in Table 1. At Baseline, the ECG will be performed prior to obtaining blood samples for laboratory testing. The Day 1 ECG will be performed within 30 minutes following the end of the first study treatment infusion. Electrocardiograms will be taken after the patient has been resting in a recumbent position for at least 10 minutes. The results for the ECG will be paper reports provided locally for safety review by the Investigator.

Each ECG will be interpreted as appropriate for the patient's age.

5.3.4 Vital signs

Vital signs will be measured as required as well as at the time intervals indicated in Table 1 before the ECG on the days when both assessments are indicated. On days when more than 1 vital signs assessment is performed, the first set of vital sign measurements for the day and the highest temperature of the day should be recorded in the CRF.

5.3.4.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured. The patients will be required to rest in the supine position for at least 10 minutes prior to heart rate and blood pressure measurements. For timings of vital signs assessments refer to Table 1.

5.3.4.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in Table 1 and the actual time of body temperature collection will be recorded. For each individual patient, the method of temperature measurement (oral, rectal, temporal, axillary, or tympanic, as appropriate) ideally should be consistent for the duration of the study.

5.3.4.3 Respiratory rate

Respiratory rate will be measured in breaths per minute at the times indicated in Table 1.

5.3.5 Cephalosporin class effects

In addition to AE and SAE monitoring as described in Section 6, cephalosporin class effects 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).

5.4 Other assessments

Medical and surgical history and prior and concomitant medications will be recorded at Baseline and, if applicable, during the study according to Table 1. See Section 7.8 for further details on concomitant medications. Serum β-hCG pregnancy tests will be performed at Baseline and TOC in female patients who have reached menarche or have reached Tanner stage 3 development. If the result of the serum β-hCG test cannot be obtained prior to dosing

of investigational product, a urine pregnancy test may be done at Baseline though a serum β-hCG test result must still be obtained.

If performed, adjunctive therapeutic procedures will be recorded throughout the treatment period until TOC.

Radiological examinations are not required for the study, but the results should be recorded if done as part of the diagnosis. Radiological examinations include WBC scans, plain abdominal radiographs, CT scans, ultrasound and/or MRI scans with or without contrast.

5.5 Pharmacokinetics

5.5.1 Collection of samples

Blood samples (1 mL per sample for Cohorts 1 and 2, and 0.5 mL per sample for Cohorts 3, 4a, and 4b) for determination of ceftazidime and avibactam in plasma will be taken at the times presented in Table 1 in a manner such that the Blinded Observer remains blinded (ie, the Investigator should collect the samples). The date and time of sample collection will be recorded, as well as the date and time of the dose of IV study therapy immediately preceding the sample collection.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.5.2 Determination of drug concentration

Samples for determination of ceftazidime and avibactam concentration in plasma will be analysed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.5.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

5.6 Pharmacodynamics not applicable

5.7 Pharmacogenetics not applicable

5.8 Biomarker analysis not applicable

5.9 Volume of blood

The minimum total volume of blood that will be drawn from each patient in the study is displayed in Table 3 for Cohorts 1 and 2, Table 4 for Cohorts 3, 4a, and 4b. Assessments that are to be performed if clinically indicated and are not mandated by the protocol are not included in the tables below. The combined volume of all blood samples taken from a subject by the end of the study for investigational laboratory tests (ie, complete blood count with differential, chemistry panel, Direct Coombs test, pregnancy testing, and PK analyses) is to be no more than 2.4 cc/kg. Any deviation from this should be clinically justified.

Table 3 Volume of blood per patient – Cohorts 1 and 2

	Day	Baseline	Day 3	EOIV	TOC	Totals (minimum blood volume)
Blood Volume (mL)	Chemistry	2		2	2	6
	Haematology	0.75		0.75	0.75	2.25
	Direct Coombs	1.5			1.5	3
	Serum pregnancy	2			2	4
	PK		3			3
	Totals	**6.25**	**3**	**2.75**	**6.25**	**18.25**

Table 4 Volume of blood per patient – Cohorts 3, 4a, and 4b

	Day	Baseline	Day 3	EOIV	TOC	Totals (minimum blood volume)
Blood Volume (mL)	Chemistry	2		2	2	6
	Haematology	0.75		0.75	0.75	2.25
	Direct Coombs	1.5			1.5	3
	Serum pregnancy					0
	PK		1.5			1.5
	Totals	**4.25**	**1.5**	**2.75**	**4.25**	**12.75**

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally 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.

The term AE is used to include both serious and non-serious AEs.

6.2 Definition of serious adverse event

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 hospitalisation or prolongation of existing hospitalisation

- 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 jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Non-serious AEs and SAEs will be collected for each patient from the time of signature of informed consent/assent until the LFU visit (27 to 50 days after start of study treatment).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the study staff for as long as medically indicated. AstraZeneca and its representatives retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Blinded Observer causality rating against the IV study therapy (yes or no) and against metronidazole (yes or no)
- Action taken with regard to IV study therapy
- Outcome of AE

In addition, the following variables will be collected for SAEs:

- Onset Date (date AE met criteria for serious AE)
- Detection date (date Investigator became aware of serious AE)

- AE is serious due to:

(a) Death, if fatal outcome, the following will be collected:

  – Date of death

  – Autopsy performed

  – Primary/secondary cause of death

(b) Life threatening

(c) Inpatient hospitalisation or prolongation of existing hospitalisation (note: patients will be hospitalised at study entry. The initial hospitalisation that made the patient eligible for the study will not be considered an SAE but if the hospitalisation is prolonged due to an AE, the hospitalisation becomes an SAE)

  – Date of hospitalisation

  – Date of discharge

(d) Congenital abnormality or birth defect

(e) Important medical event

(f) Suspected transmission via a medicinal product of an infectious agent

- Blinded Observer causality assessment in relation to study procedures (yes/no)
- Blinded Observer causality assessment in relation to other medication (yes/no)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE. The Blinded Observer should provide an assessment of the severity of each AE/SAE.

6.3.4 Causality collection

The Blinded Observer will assess causal relationship between IP and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs, the Blinded Observer will also assess causal relationship for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *'Have you/the child had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

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

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE or SAE (see Section 6.3.8.2).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the screening assessment will be reported as an AE.

6.3.7 Actions required in cases of increases in liver chemistry values

The Investigator is responsible for, without delay, determining whether the patient meets potential Hy's law criteria; AST or ALT ≥3×ULN **and** total bilirubin ≥2×ULN irrespective of the value of the patient's alkaline phosphatase, at any point during the study following the start of study medication.

A Hy's Law case is defined as study patient with an increase in serum AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, or another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. Details regarding the actions required in the cases of increases in ALT, AST, and total bilirubin can be found in Appendix D.

If a patient reaches an ALT or AST=5×ULN, the patient may continue with the IP as planned unless discontinuation criteria as described in Section 3.10 are met. The patient should be seen within 48 hours to instigate enhanced follow-up and monitoring. Enhanced follow-up should include collection of clinical and historical information to determine the cause of ALT and/or AST elevations. Additional testing for liver laboratory test results must be done every 48 hours until the peak value has been reached as documented by a decline in the values and/or until the patient is feeling better. The frequency of retesting can decrease to once per week or less if abnormalities stabilise or study drug has been discontinued and the patient is asymptomatic. The patient should be followed until resolution (including laboratory testing).

6.3.8 Exceptions from standard adverse event collection

6.3.8.1 Lack of Effect

Where there is deterioration in the condition for which the IV study therapy is being used, there may be uncertainty as to whether this is lack of efficacy, disease progression, and whether it constitutes an AE. In such cases, unless the AstraZeneca or reporting physician considers that the IV study therapy contributed to the deterioration or local regulations state the contrary, the deterioration should be considered to be lack of efficacy and not an AE.

Insufficient therapeutic effect will be captured as an efficacy outcome. Instances of, or discontinuation due to insufficient therapeutic effect (ie, lack of efficacy) should not be collected as AEs. A clinical failure should not be recorded as an AE.

6.3.8.2 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which CAZ-AVI is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Expected progression of the disease under study and/or expected progression of signs and symptoms of the disease under study, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE. Any event or extended hospitalisation that is unequivocally due to disease progression must not be reported as an SAE unless it is believed that IV study therapy actively contributed to the progression of the disease (ie, not by way of insufficient therapeutic effect). Events that are unequivocally due to disease progression should not be reported as an AE during the study.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators will enter SAE information into the Electronic Data Capture system within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated PRA representative, on behalf of AstraZeneca, works with the Investigator to ensure that all the necessary information is provided to the PRA Drug Safety Department. PRA Drug Safety will forward all SAE information to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events (if received for instance during a weekend or a public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday) **and within 3 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform PRA representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the PRA Datalabs system, an automated email alert is sent to the PRA Drug Safety Department. Tata Consultancy Services will be responsible for processing all SAEs onto the AstraZeneca Patient Safety Database, and the information will be passed on to AstraZeneca.

If the PRA Datalabs system is not available, then the Investigator or other study site personnel reports the SAE to the PRA Drug Safety Department by telephone, fax, or email.

PRA contact information for SAE reporting:

FAX: +44 1792 525 720
E-mail: MHGsafety@prahs.com
Telephone: +49 621 8782 154

PRA, on behalf of AstraZeneca, is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, Ethics Committees, and participating Investigators, in accordance with International Conference on Harmonisation (ICH) Guidelines and/or local regulatory requirements. PRA may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit additional information requested by AstraZeneca or PRA as soon as it becomes available.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug CAZ-AVI and the EU Summary of Product Characteristics for the active comparator product (including any AstraZeneca comparator).

6.5 Overdose

Overdose is defined as a dose administered to a patient in excess of that specified in this protocol. Overdose does not automatically make an AE serious but if the consequences of the

overdose are serious for example death or hospitalisation, the event is serious and should be reported as such.

Recording an overdose will be done according to the following:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.
- If an overdose on an AstraZeneca IV study therapy occurs in the course of the study, then Investigators or other study centre personnel will inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than the end of the next business day from when he or she becomes aware of it.
- The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca patient safety data entry site.
- For overdoses associated with an SAE, standard reporting time lines apply, see Section 6.4. For other overdoses, reporting should be done **within 30 days**.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the PRA Drug Safety Department.

6.6.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the PRA Drug Safety Department immediately but **no later than 24 hours** of when he or she becomes aware of it.

PRA works with the Investigator to ensure that all relevant information is provided to the PRA Drug Safety Department **within 1 or 3 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies**.

The same timelines apply when outcome information is available.

All outcomes of pregnancy should be reported to the PRA Drug Safety Department. Any patient who becomes pregnant during the course of the study will be followed so that pregnancy outcome can be determined and reported to AstraZeneca and the regulatory authorities.

A pregnancy report form (electronic copy of the PREGREP form) will be used to report the pregnancy to the PRA Drug Safety Department. The outcome of the pregnancy will be reported on the pregnancy report form (paper copy of the PREGOUT form) and provided by site staff to the PRA Drug Safety Department, but the outcome of the pregnancy will not be documented in the clinical database.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study. Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up and documented. The outcome of any conception occurring from the date of the first IP administration until 7 days after the last IP administration should be followed up and documented.

6.7 Management of investigational product-related toxicities

Clostridium difficile-associated diarrhoea has been reported with ceftazidime as with nearly all antibacterial agents, and may range in severity from mild diarrhoea to fatal colitis. This is as a result of alteration of the normal flora of the colon by ceftazidime leading to overgrowth of *C. difficile*. If *C. difficile*-associated diarrhoea is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included tremors, myoclonus, seizures, encephalopathy, and coma. Patients who receive an acute overdosage should be carefully observed and given supportive treatment. In the presence of renal insufficiency, haemodialysis or peritoneal dialysis may aid in the removal of ceftazidime from the body. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

6.8 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

6.8.1 Data and Safety Monitoring Board

As this study is descriptive in nature, no interim or final inferential analyses will be performed for either efficacy or safety. A Data and Safety Monitoring Board (DSMB) is deemed necessary since the trial has a long period of enrolment, is multi-centre and multi-national, and represents one of the first safety and efficacy trials of CAZ-AVI in children.

The DSMB is charged with reviewing and evaluating the study safety (AEs, SAEs, and potentially clinically significant 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 AstraZeneca 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. AstraZeneca will be responsible for discussing and, if considered appropriate, implementing the DSMB recommendations. Further details can be found in the DSMB charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength
CAZ-AVI	Ceftazidime avibactam powder for concentrate for solution for infusion 2000 mg/500 mg
Meropenem	Meropenem powder for solution for infusion 1000 mg

CAZ-AVI and meropenem will be supplied centrally by AstraZeneca. Kits containing the labelled vials will be provided to the study centre as an open label supply for reconstitution and dilution in accordance with the handling instructions.

Commercially available IV metronidazole for infusion will be provided centrally by AstraZeneca.

For metronidazole, consult the product package insert, label, and local dosing guidelines for further information regarding dosage, administration, storage, maximum doses, contraindications, warnings, precautions, and AEs reported.

7.2 Dose and treatment regimens

The study is single blind, ie, a Blinded Observer will not know the patient's treatment assignment and will conduct clinical assessments (including efficacy and safety). There is no use of placebo to act as a treatment blind.

The doses of CAZ-AVI are based on age and weight with adjustment according to renal function as detailed in Table 5.

Table 5 CAZ-AVI doses by age, weight, and creatinine clearance

Cohort	Age range	Body weight	CAZ-AVI dose CrCl ≥50 mL/min	CAZ-AVI dose CrCl ≥30 to <50 mL/min
			CAZ-AVI must be administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes)	
1[1]	12 years to <18 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
1[1]	12 years to <18 years	<40 kg	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
2[1]	6 years to <12 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
2[1]	6 years to <12 years	<40 kg	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
3[1]	2 years to <6 years	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4a[2]	1 year to <2 years	All	50 mg/kg ceftazidime /12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b[2]	6 months to <1 year	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b[2]	3 months to <6 months	All	40 mg/kg ceftazidime/10 mg/kg avibactam	20 mg/kg ceftazidime/5 mg/kg avibactam

[1] Patients considered for entry into the study will be within the normal range of BMI for their age, (2 to <18). A healthy weight BMI for this age group falls between the 5th percentile and ≤95th percentile according to height, weight, and age.

[2] BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

Full details of infusion preparation are given in the Pharmacy Manual.

Patients whose CrCl changes during treatment should receive the appropriate dose reduction or increase according to Table 5.

The Investigator should follow the package insert for meropenem for dose modifications associated with renal impairment.

Patients whose CrCL drops below 30 mL/min should be withdrawn from study therapy. Patients withdrawing from study therapy can be administered alternative therapies at the Investigator's choice, which should be recorded in the CRF. If possible, patients should still be followed for safety (see Section 3.9.1). 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. If in the opinion of the Investigator there is a clinically significant reduction in a patient's estimated CrCl during the treatment period, then the Investigator should contact the Medical Monitor to discuss the above mentioned options (immediate dose change, a short period of continued observation, or discontinuation of therapy). Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of CrCl monitoring, depending on the patient's clinical status, extent of renal function change and Investigator's clinical evaluation.

The suggested dosing regimen of metronidazole is 10 mg/kg IV over 20 to 30 minutes every 8 hours (±30 minutes), but it can also be prescribed/adjusted by the Investigator according to local labels. The metronidazole infusion will be started no later than 30 minutes after completion of the CAZ-AVI infusion.

The dose/regimen of meropenem will be 20 mg/kg every 8 hours (±1 hour) infused over approximately 15 to 30 minutes or up to 1 hour (or infusion duration as per local guidelines). For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours. The time interval between the beginning of reconstitution and the end of the infusion should not exceed 1 hour due to the stability of meropenem when reconstituted with sodium chloride.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into the local language.

Personnel at the study centre will prepare and label the individual IV infusions as assigned by the IXRS, and according to the handling instructions.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The storage conditions will be stated on the study drug labelling and in the handling instructions.

7.5 Compliance

The site will monitor patient compliance, which will be documented in the patient's source documents, and relevant data will be reported in the CRF. To ensure that the patient is compliant with administration of study drug, oral switch therapy, and study procedures, the date and dose of the medication should be recorded in the appropriate sections of the CRF.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel, if applicable, or the PRA monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction, and return should be signed. For general drug destruction (eg, left over drug at site), accepted practices for destruction within specific sites, countries, or regions should be used, through PRA's standard operating procedures (SOPs). Therefore, where at all possible the IP should be destroyed locally at site and a third party supplier for return and destruction should only be used where specific country regulations or local procedures state this is not possible. Documentation should be provided by PRA or AstraZeneca's Research and Development Procurement Manager identifying that this is the case. For IP associated with a recall, AstraZeneca will determine what is to be destroyed, but PRA will manage the execution of destruction using standards acceptable to AstraZeneca or its representative.

7.7 Oral switch therapy

The choice of oral switch therapy, among the options listed below, should be in line with the approved and marketed drugs in the respective country, and should observe the local specific regulations and local therapeutic guidelines (if existent), regarding posology. The decision to switch to oral therapy is entirely at the Investigator's discretion, if the patient has good or sufficient clinical response, and the patient is tolerating oral fluids or food.

For the optional oral switch therapy, the following should be given:

- Oral amoxicillin/clavulanic acid (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or

- Oral ciprofloxacin (only in countries where its use for children is permitted; according to local guidelines, administered at a dose and formulation per standard of care) plus metronidazole (administered at a dose and formulation per standard of care), or

- Pathogen-based therapy (in discussion with the Medical Monitor). The choice of oral antibacterial agent for pathogen-based therapy will be driven by the results of a susceptibility test, which will be provided to the Investigator by either the local or central laboratory. Initiation of pathogen-based therapy is at the Investigator's discretion. Before administering pathogen-based therapy, the Investigator will discuss the results of the susceptibility test and the selected antibacterial drug (which should be approved for use in children) with the Medical Monitor.

The optional oral switch therapies will be sourced locally by the study centres or sourced as agreed between the study centres and PRA.

Consult the Summary of Product Characteristics or product package insert, label, and local dosing guidelines for further information regarding dosage, administration, storage, maximum doses, contraindications, warnings, precautions, and AEs reported.

7.8 Concomitant and other treatments

All prescription and over-the-counter medications being taken by the patient for the 2 weeks prior to study entry (considered prior treatment) and from randomisation through the LFU visit (considered concomitant treatment) must be documented on the appropriate pages of the CRF. Systemic antibiotics should be documented for the entire duration of the study (from 2 weeks prior to study entry through the LFU visit). For patients who are being breast fed, all medications taken by the lactating mother in the previous 2 weeks before the first dose of study therapy until LFU will also be recorded.

If *Enterococcus* species or methicillin-resistant *staphylococcus aureus* (MRSA) is one of the pathogens suspected or isolated and, in the opinion of the Investigator, specific therapy is indicated, then open-label vancomycin, linezolid, or daptomycin may be added to either of the study regimens according to the usual practice of the Investigator. If vancomycin, linezolid, or daptomycin are started empirically to cover MRSA or *Enterococcus* species, and if final culture results did not isolate MRSA or *Enterococcus* species, then the Investigator should discontinue the additional Gram-positive coverage that was empirically added.

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

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF. If analgesic medications are needed for pain, the use of analgesic medication without antipyretic properties is preferred. Should a patient require immunosuppressive agents or chemotherapy after being randomised to IV study therapy, the Investigator should contact the PRA Medical Monitor (as an AstraZeneca delegate) before initiating therapy. Continued patient study participation will be determined based upon assessment of the safety risk to the patient if he or she were to continue in the study. Patients who have completed IV study

therapy and are in the follow-up (FU) period should remain in the study as they are not actively on IV study therapy but being followed for outcomes.

Simultaneous administration of meropenem and/or metronidazole with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant agents, including warfarin, in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of the antibiotic to the increase in international normalised ratio (INR) is difficult to assess. In addition to the standard study safety laboratory assessments, frequent monitoring of the INR should be performed during and shortly after co-administration of study therapy with an oral anticoagulant agent, as per local practice.

In vitro, avibactam is a substrate of organic anion transporter (OAT) 1 and OAT3, which might contribute to the active uptake from the blood compartment and, thereby its excretion. Probenecid (a potent OAT inhibitor) inhibits this uptake by 55% to 70% in vitro and, therefore, has the potential to alter the elimination of avibactam when co-dosed. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-dosing of avibactam with probenecid is not recommended. Probenecid interferes with the active tubular secretion of meropenem, resulting in increased plasma concentrations of meropenem. Therefore, co-administration of probenecid with meropenem is not recommended. There is significant drug-drug interaction between meropenem and valproic acid or sodium valproate; therefore co-administration of meropenem and valproic acid or sodium valproate should be avoided.

A number of unfavourable reactions with other drugs are known for ceftazidime. Contraindications and known drug interactions for ceftazidime are summarised in Table 6.

Table 6 Contraindications and drug-drug interactions

Ceftazidime	Concurrent administration with chloramphenicol should be avoided. Chloramphenicol has been shown to be antagonistic to β-lactam antibiotics, including ceftazidime. Concurrent administration with aminoglycoside antibiotics or potent diuretics such as furosemide may result in nephrotoxicity. Because of potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics, renal function should be carefully monitored, especially if higher dosages of aminoglycosides are to be administered or if therapy is prolonged. Concurrent administration with combined oral oestrogen/progesterone contraceptives may result in lower oestrogen reabsorption and reduced efficacy of these contraceptives secondary to the effects of ceftazidime on gut flora.

Ciprofloxacin	Administration in pregnant or lactating women is contraindicated. Concurrent administration with tizanidine is contraindicated. Concurrent administration with methotrexate is not recommended; methotrexate may inhibit renal tubular transport of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. Concurrent administration with theophylline decreases theophylline clearance, resulting in elevated serum theophylline levels and increased risk of a patient developing central nervous system or other adverse reactions. Concurrent administration with caffeine or pentoxifylline (oxpentifylline) may raise serum concentrations of these xanthine derivatives. Concurrent administration with antacids containing magnesium hydroxide or aluminium hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. Concurrent administration with probenecid interferes with renal secretion of ciprofloxacin and increases ciprofloxacin serum concentrations. Concurrent administration with phenytoin may result in increased or reduced serum levels of phenytoin; monitoring of drug levels is recommended. Concurrent administration with warfarin may augment its anticoagulant effects. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of a fluoroquinolone to an increased INR is difficult to assess. It is recommended that INR be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent. Concurrent administration with ropinirole increases the maximum plasma concentration of ropinirole by as much as 60%. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin. Concurrent administration with clozapine increases serum concentrations of clozapine and N-desmethylclozapine, a metabolite, by as much as 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are recommended.

Amoxicillin-clavulanic acid	Concurrent administration with probenecid decreases the renal tubular secretion of amoxicillin but does not delay renal excretion of clavulanic acid. Concurrent use with amoxicillin-clavulanic acid may result in increased and prolonged blood concentrations of amoxicillin. Co-administration of probenecid is not recommended. Concurrent administration of amoxicillin with oral anticoagulants may result in abnormal prolongation of prothrombin time (increased INR). Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently with amoxicillin-clavulanic acid. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. Concurrent administration of allopurinol and amoxicillin increases the incidence of rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. Concurrent administration of oral contraceptives and amoxicillin-clavulanic acid may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives. High urine concentrations of amoxicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's solution, or Fehling's solution. Since this effect may also occur with amoxicillin-clavulanic acid, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used. Following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

Meropenem	No specific medicinal product interaction studies other than probenecid have been conducted. Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem. The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism. Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60 to 100 % decrease in valproic acid levels in about 2 days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided. <u>Oral anticoagulants</u> Simultaneous administration of antibiotics with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anticoagulant agent.

7.8.1 Drug-drug interactions

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

7.8.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database-lock. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to the randomisation of the first patient to the study. Any subsequent amendments to the SAP will be documented, with final amendments completed prior to unblinding of the data for the analysis.

8.2 Sample size estimate

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. Safety data from this study and from Study D4280C00016 for cUTI 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%.

Patients will be allocated to 1 of 4 cohorts based on age. Randomisation will be stratified 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 cohorts combined, the maximum number of evaluable patients allowed to have been recruited having been diagnosed with complicated appendicitis is 90%.

8.3 Definitions of analysis sets

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

8.3.1 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.

8.3.2 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 the evaluability review committee to confirm whether the scheduling and number of doses received is acceptable for inclusion in the safety evaluable analysis set.

8.3.3 Pharmacokinetic 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.

8.3.4 Efficacy analysis sets

The efficacy analysis of data in this study will be based on 4 analysis sets of patients (intent-to-treat [ITT], microbiological ITT [micro-ITT], clinically evaluable [CE]. and microbiologically evaluable [ME] analysis sets) as defined in Sections 8.3.4.1 to 8.3.4.4. Each of these 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 the CE and ME analysis sets. Patients in the ITT, micro-ITT, CE, and ME analysis sets will be summarised according to the randomised treatment assignment.

8.3.4.1 Intent-to-treat analysis set

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

8.3.4.2 Microbiological intent-to-treat analysis set

The micro-ITT analysis set will include all randomised patients who have a baseline pathogen known to cause cIAI.

8.3.4.3 Clinically evaluable analysis set

The CE analysis set is defined separately at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC and LFU visits. The CE analysis set is a subset of all patients randomised and 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 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 in order to be considered an evaluable clinical cure
- Have been evaluated at the End of 72 hours 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
- Had no important protocol deviations that would affect assessment of efficacy

8.3.4.4 Microbiologically evaluable analysis set

The ME analysis set is defined separately 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:

- Are a subset of all 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 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 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 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)

8.4 Outcome measures for analyses

8.4.1 Primary outcome variables

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

- AEs and SAEs
- Cephalosporin class effects and additional AEs
- Vital signs (pulse, blood pressure, respiratory rate, temperature)
- Physical examination
- Laboratory parameters
- ECG
- CrCl

8.4.2 Secondary outcome variables

- Plasma concentrations of CAZ and AVI will be listed and summarised by nominal sampling time window using appropriate descriptive statistics
- 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

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variables

The primary variables are for safety and tolerability. No inferential statistical tests will be performed for any safety variables. All data will be presented by treatment group and by cohort (and also by summed cohorts). Descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. Demographic data, other baseline characteristic data, and concomitant medications will also be summarised.

Safety assessments will be based on AE reports and the results of vital sign measurements, physical examinations, ECGs and clinical laboratory tests. For each safety variable, the last assessment made prior to the first dose of study drug will be defined as the baseline. All safety data collected from this study up to the LFU visit will be presented within the Safety analysis set (as defined in Section 8.3.1) by the received study treatment group (ie, for CAZ-AVI plus metronidazole or meropenem), irrespective of whether the patient switched to oral therapy. Key safety data reported up to the LFU visit will also be summarised for the Safety evaluable analysis set (ie, those who received at least 72 hours of study treatment as defined in Section 8.3.2) by received treatment group.

Safety data from this study and from Study D4280C00016 for cUTI will be combined for analysis. This analysis of combined safety data will be reported separately of the data from this study, and will include the summaries of top-line data using the same formats as presented for this study.

8.5.1.1 Adverse events

The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. AEs occurring before the start of study treatment will be reported separately from all other AEs. AEs occurring from the start of the first infusion of IV study therapy will be summarised by preferred term and system organ class using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) vocabulary.

All recorded AEs will be listed and tabulated by system organ class, preferred term and for each cohort.

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 relationship to IV study therapy and by AE intensity.

The number of patients reporting AEs among the following topic groups of AEoSI, for which prior review has identified groupings of specific AE preferred terms from the MedDRA vocabulary, will also be tabulated by cohort:

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

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

8.5.1.2 Other safety data

Summaries and listings of data for vital signs, clinical laboratory and urinalysis laboratory tests, ECGs and physical examination findings will be presented. Appropriate data will be summarised for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For clinical laboratory tests, listings of patient data will also flag up any abnormal or out-of-range values. Potentially clinically significant changes in the laboratory test parameters will also be identified, listed, and summarised at scheduled visits. This summary will present data for patients meeting the criteria at any time during the study up to the EOT visit, and separately at any time up to the LFU visit. Clinical laboratory data will be reported in Système International units.

The following number of patients meeting the following criteria at any time during the study up to the LFU visit will be assessed: (maximum ALT ≥3×ULN or maximum AST ≥3×ULN) and (maximum total bilirubin ≥2×ULN). The AST, ALT, total bilirubin elevations can occur at any time in the specific review period and do not need to occur simultaneously.

For ECG variables, the QT correction factor will be based on both the Bazett and Fridericia formulae (QT_cB and QT_cF). Categorical summaries of absolute QT, QT_cB and QT_cF values (≥450 ms, ≥480 ms, ≥500 ms) and change from Day 1 (Baseline) values in QT, QT_cB and QT_cF values (≥30 ms, ≥60 ms), and additionally the number and percentage of patients who have a post-baseline value of ≥500 ms with a change from Day 1 of ≥60 ms will be presented by treatment, visit and cohort. The number of patients meeting these criteria at any time after the start of study treatment until the LFU visit will also be summarised by treatment and cohort.

The number and percentage of patients with CrCl in the following ranges: <30 mL/min, 30 to 50 mL/min, >50 mL/min will be tabulated at each of the TOC and LFU visits for each treatment group.

8.5.2 Analysis of the secondary variable(s)

No inferential statistical tests will be performed for any secondary variables.

8.5.2.1 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 4b, the plasma concentration will be summarised 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).

In addition, the avibactam and ceftazidime concentration, paediatric patient demographics, and disease status data from Cohorts 1 to 4b will be combined with the data from appropriate previous clinical studies in paediatric patients and/or adults for a population PK analysis. The actual dosing and plasma sampling times will be used for the analysis. The developed

population PK model may be used to conduct simulations to determine probability of PK/PD target attainment to help to justify the CAZ-AVI dose regimens for paediatric patients with cIAI. A stand-alone population PK modelling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report outside of the CSR.

Avibactam and ceftazidime PK parameters derived from population PK analysis and potential PK/PD relationships will be reported separately.

8.5.2.2 Clinical outcome definitions

Clinical response outcomes will be summarised by visit, treatment, and cohort in each of the CE and ME analysis sets at End of 72 hours' treatment, EOIV, EOT, TOC, and LFU, as well as the ITT and micro-ITT analysis sets. A clinical failure occurring at the EOIV timepoint or later will always be carried forward to any subsequent assessment time. The Blinded Observer will make the assessment of clinical outcome.

For each baseline pathogen identified with sufficient frequency, the number and percentage of patients in each treatment group and cohort classified as having a favourable clinical outcome for the particular pathogen will also be summarised.

Clinical Outcome at End of 72 hours

The clinical outcome categories at the End of 72 hours are defined in Table 7. Favourable clinical outcomes are clinical improvement and clinical cure.

Table 7 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

Table 7 Clinical outcome assessments at End of 72 hours

Outcome	Definition
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 nonroutine 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, elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign
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)

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

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

Clinical Outcome at EOIV

The clinical outcome categories at EOIV are defined in Table 8. 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 8 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.

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

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

Clinical Outcome at EOT

The clinical outcome categories at EOT are defined in Table 9. A favourable clinical outcome is clinical cure. A clinical failure at EOT will be carried forward to the TOC visit.

Table 9 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.

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

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

Clinical Outcome at TOC

The clinical outcome categories at TOC are defined in Table 10. A favourable clinical outcome is clinical cure. Clinical response by pathogen at TOC will also be determined for each pathogen isolated at Baseline.

Table 10 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)

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

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

Clinical Outcome at LFU

Each patient who was considered clinically cured at TOC will be reassessed at LFU by the Blinded Observer for evidence of clinical relapse of cIAI symptoms. The clinical outcome categories at LFU are defined in Table 11. A favourable clinical outcome at LFU is sustained clinical cure.

Table 11 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.

The proportion of patients with clinical relapse at the LFU visit will be summarised by treatment and cohort in both the CE and ME analysis sets.

Within each analysis set, the proportion of patients with a clinical relapse is defined using the following formula:

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

8.5.2.3 Microbiological response assessments

The proportion of patients with a favourable per-patient microbiological response (ie, eradication or presumed eradication) will be summarised by treatment and cohort in the micro-ITT and ME analysis sets at the EOIV, EOT, TOC and LFU visits.

The per-pathogen microbiological outcome categories are defined in Table 12. Favourable microbiological outcomes are eradication or presumed eradication. Baseline pathogens will

be determined based on central laboratory data (see Section 5.2.1 for details on culture and organism identification). Rules for determination of pathogens will be described in the SAP.

In order for a patient to have a favourable 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 microbiological response.

Table 12 Per-pathogen microbiological outcome categories

Outcome	Definition
Eradication	Source specimen demonstrates absence of the original baseline pathogen
Presumed eradication	Source specimen not available to culture, and the patient 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 (MIC) 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 the EOIV timepoint or later, this outcome will be carried forward to subsequent visits.

8.5.2.4 Emergent infections

Pathogens first appearing after Baseline ("emergent infections") until the LFU in patients with a baseline pathogen are categorised in Table 13 and these will be summarised separately by treatment and cohort.

Table 13 Emergent infections

Infection category	Definition
Superinfection	Isolation of a new pathogen or pathogens (other than the original baseline pathogen[s]) from intra-abdominal cultures which is accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy during the period up to and including EOT.
New infection	Isolation of a new pathogen or pathogens (other than the original baseline pathogen[s]) from intra-abdominal cultures which is accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy in the time period after EOT.

The proportion of patients with an emergent infection (and by infection category) will be summarised by treatment and cohort in both the CE and ME analysis sets.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, a PRA representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the PRA Datalabs data capture system.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent/assent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent/assent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca or AstraZeneca's representatives, and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q3 2015 and to end by Q3 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with CAZ-AVI.

9.4 Data management by PRA

The PRA Datalabs system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the CRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and the provision of answers to data queries according to the CSA. The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

Data management will be performed by PRA, according to the Clinical Informatics Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the PRA coding group. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Clinical Informatics Plan and Edit Specifications Document. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Clinical Informatics Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event Reconciliation

Serious adverse event reconciliation reports are produced and reconciled with the patient safety database and/or the investigational site. SAE reconciliation between safety data and clinical data will be performed by PRA. The frequency depends on the expected volume of SAE reports and will be defined in the AE/SAE Reconciliation Plan.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF/Assent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF, Assent Form, and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable IEC/IRB, and to the study site staff.

The opinion of the IEC/IRB should be given in writing. The Investigator should submit the written approval to PRA before enrolment of any patient into the study.

The IEC/IRB should approve all advertising used to recruit patients for the study.

PRA should approve any modifications to the ICF and Assent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IEC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, and Assent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

PRA will handle the distribution of any of these documents to the national regulatory authorities.

PRA will provide Regulatory Authorities, IECs/IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the IEC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. PRA will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient's parent(s) or other legally acceptable representative(s) and patient when applicable (if age appropriate according to local regulations) is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each patient's parent(s) or other legally acceptable representative(s) and patient when applicable (if age appropriate according to local regulations) is notified that they are free to discontinue from the study at any time

- Ensure that each patient's parent(s) or other legally acceptable representative(s) and patient when applicable (if age appropriate according to local regulations) is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient’s parent(s) or other legally acceptable representative(s) provides signed and dated informed consent and patient (if age appropriate according to local regulations) provides signed and dated assent before conducting any procedure specifically for the study

- Ensure the original, signed ICF(s) and Assent Form (if age appropriate according to local regulations) is/are stored in the Investigator’s Study File

- Ensure a copy of the signed ICF(s) and Assent Form (if age appropriate according to local regulations) is/are given to the patient's parent(s) or other legally acceptable representative(s)

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF(s) and Assent Form (if age appropriate according to local regulations) that is approved by an IEC/IRB

10.5 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant IEC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IEC/IRB see Section 10.3.

If a protocol amendment requires a change to a centre's ICF and/or Assent Form, AstraZeneca and the centre's IEC/IRB are to approve the revised ICF and/or Assent Form (if applicable) before the revised form(s) is/are used.

If local regulations require, any administrative change will be communicated to or approved by each IEC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an IEC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

European Commission 2008
European Commission. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008. Available from: http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf.

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Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89:46-53.

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Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009 Mar;20(3):629-37.

Stachyra et al 2009
Stachyra T, Levasseur P, Péchereau MC, Girard AM, Claudon M, Miossec C, et al. In vitro activity of the β-lactamase inhibitor NXL104 against KPC-2 carbapenemase and Enterobacteriaceae expressing KPC carbapenemases. J Antimicrob Chemother 2009;64(2):326-9.

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Clinical Study Protocol Appendix B

Drug Substance	Ceftazidime-avibactam
Study Code	D4280C00015
Edition Number	1
Date	20 January 2015

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C

Drug Substance	Ceftazidime-avibactam
Study Code	D4280C00015
Edition Number	1
Date	20 January 2015

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D	
Drug Substance	Ceftazidime-avibactam
Study Code	D4280C00015
Edition Number	1
Date	20 January 2015

Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN irrespective of an increase in Alkaline Phosphatase (ALP), at any point during the study following the start of study medication. The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When the identification criteria are met from laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix E

Drug Substance	Ceftazidime-avibactam
Study Code	D4280C00015
Edition Number	1
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Appendix E
Tanner Staging of Development

TANNER STAGING OF DEVELOPMENT IN GIRLS

Once the onset of puberty has begun, the resulting sequence of somatic and physiologic changes gives rise to the sexual maturity rating, or Tanner stages. Figure 1 and Figure 2 depict the somatic changes which are also described in Table 1.

Figure 1 **Sexual maturity ratings (2 to 5) of pubic hair changes in adolescent girls. (Courtesy of PPD , MD, PPD England)**

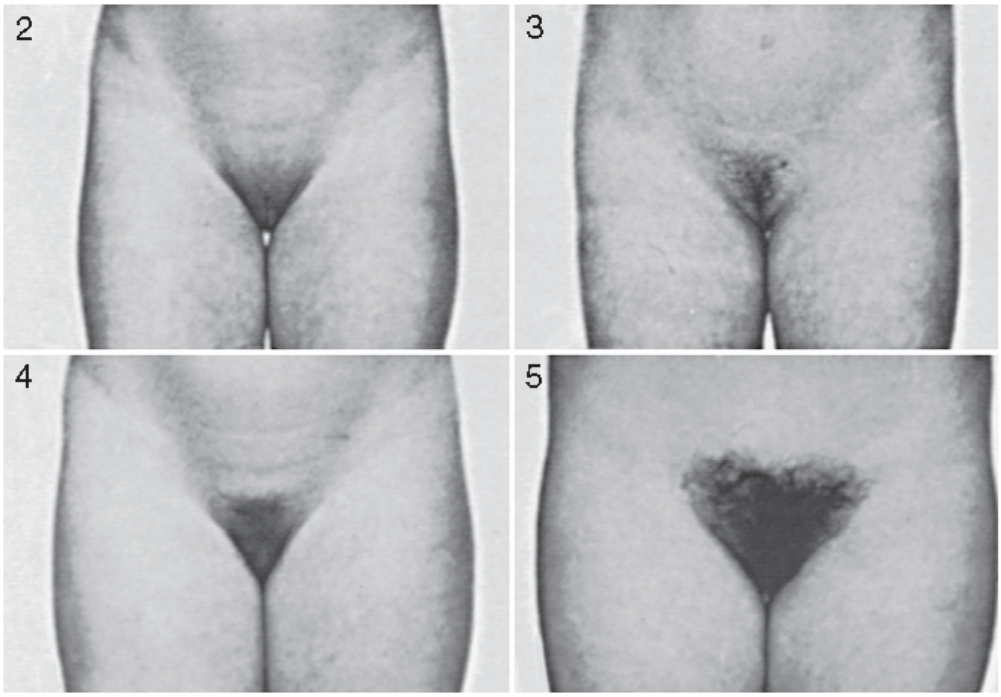

Figure 2 **Sexual maturity ratings (1 to 5) of breast changes in adolescent girls. (Courtesy of PPD , MD, PPD , England)**

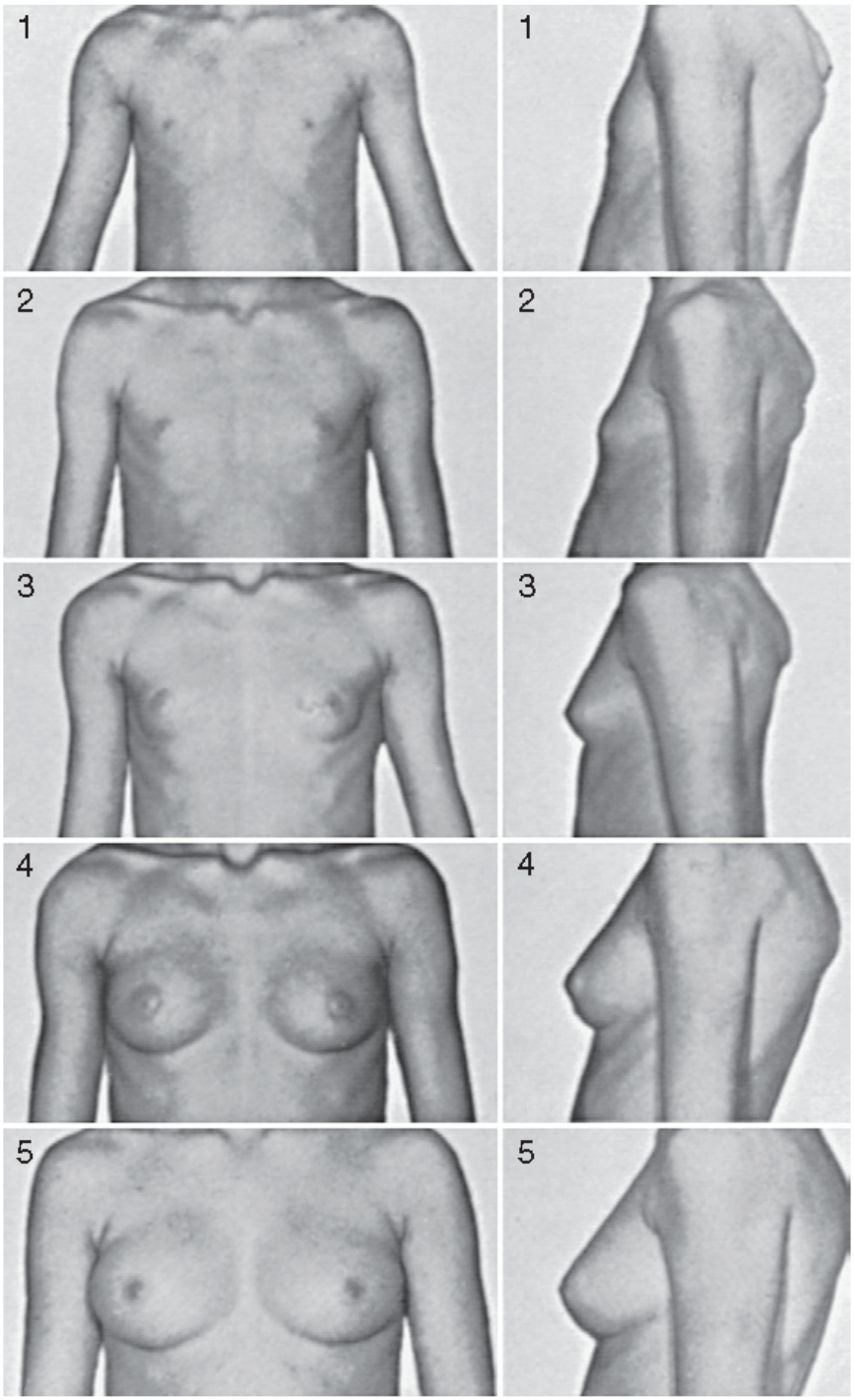

Table 1 Classification of sexual maturity states in girls

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

REFERENCE

Kliegman et al, 2011
Kliegman RM, Bonita S, St. Geme J, Schor N, Behrma.n RE. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA. Elsevier 2011; Part XIII:649-51.