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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 Compared With Cefepime In Children From 3 Months To Less Than 18 Years Of Age With Complicated Urinary Tract Infections (cUTIs)

Title page

Sponsor: *Pfizer Inc., 235 East 42nd Street, New York, NY 10017, USA (as of Version/Amendment 3)*
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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**

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	17 July 2017	The previous version of the protocol (Edition 2, dated 07 March 2017) has been revised to reflect change in Sponsorship to Pfizer Inc, and to include some of the latest Pfizer protocol template language. In addition, minor text changes were made to improve protocol clarity.
Amendment [2]	07 March 2017	To include Immunosuppressed patients in the study per PDCO request
Amendment [1]	22 September 2015	To amend the following sections of the protocol: Synopsis, Study sites(s) and number of patients planned; Synopsis, Pharmacokinetic data; Section 1.4, Study design; Section 3.1, Inclusion criteria; Section 3.5, Methods for assigning treatment groups; Table 1, Study plan detailing study procedures; Section 5.3.2, Physical

[redacted]

		examination; Section 5.5.1, Collection of samples; Section 5.9; Volume of blood; Table 4, Volume of blood per patient – Cohorts 3 and 4; Section 8.2, Sample size estimate; and Section 8.5.2.1, Pharmacokinetic outcome variables
Original protocol	14 January 2015	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

The clinical study protocol is publicly registered and the results are disclosed and/or published according to the Sponsor publication policy and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Single Blind, Randomised, Multi-Centre, Active Controlled, Trial To Evaluate Safety, Tolerability, Pharmacokinetics And Efficacy Of Ceftazidime And Avibactam Compared With Cefepime In Children From 3 Months To Less Than 18 Years Of Age With Complicated Urinary Tract Infections (cUTIs)

International Co-ordinating Investigator

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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 if given 3 times daily, or 6 doses if given twice daily) of study treatment (ie, evaluable patients; at least 60 patients in the ceftazidime and avibactam [CAZ-AVI] group and at least 20 patients in the cefepime group).

Considering patients over all cohorts combined, at least 10% of evaluable patients with urological abnormalities in the urinary tract should be included. Each of the patient cohorts is required to have a minimum number of evaluable patients as follows:

- Cohort 1: At least 6:2 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 6:2 evaluable patients aged from 6 years to <12 years;
- Cohort 3: At least 9:3 evaluable patients aged from 2 years to <6 years;
- Cohort 4: At least 18:6 evaluable patients aged from 3 months to <2 years comprising Cohorts 4a and 4b as follows:
    - Cohort 4a: At least 9:3 evaluable patients aged from 1 year to <2 years.
    - Cohort 4b: At least 6:2 evaluable patients aged from 3 months to <1 year, with a minimum of 3 patients with at least 1 PK sample aged from 3 months to <6 months treated with CAZ-AVI

Approximately 65 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 2018	

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 urinary tract infections (cUTIs) will be randomised to 1 of 2 treatment groups (3:1 ratio): CAZ-AVI or cefepime. Randomisation will be stratified as appropriate. 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 if given 3 times daily, or 6 doses if given twice daily) 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 36 days after the last dose of any treatment.

Objectives

Primary (Safety) Objective:	**Outcome Measure:**
Evaluate the safety and tolerability of CAZ-AVI given at the selected dose regimen versus cefepime in paediatric patients aged ≥3 months to <18 years with cUTI	• Adverse events (AEs) and serious adverse events (SAEs) from the signing of the Informed Consent/Assent Form to the LFU (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 versus cefepime in paediatric patients aged ≥3 months to <18 years with cUTI	• 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 • Combined response
Evaluate the PK of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cUTI	• 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 cUTI.

Duration of treatment

Patients will receive IV treatment for a minimum of 72 hours (3 full days, ie, 9 doses if given 3 times daily, or 6 doses if given twice daily) 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 can continue to take IV CAZ-AVI up to Day 14. 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 including (IV drug or oral switch therapy) 7 to 14 days of active treatment.

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:

[redacted]

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)	
11	12 years to <18 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
11	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
21	6 years to <12 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
21	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
31	2 years to <6 years	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4a2	1 year to <2 years	All	50 mg/kg ceftazidime /12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b2	6 months to <1 year	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b2	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.

[redacted]

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.

An optional switch to oral therapy is permitted on or after 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 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), or
- Oral cefixime (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 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 sulfamethoxazole/trimethoprim (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
- 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.

[redacted]

The patient may continue on IV study drug for the entire duration of the study therapy (7 to 14 days), at the discretion of the Investigator.

Comparator

Patients randomised to receive cefepime should receive the dose, schedule and infusion duration as recommended in the local prescribing information or as prescribed by the investigator. The maximum dose of cefepime in any single infusion should not exceed 2000 mg. Patients randomised to cefepime treatment may undergo the optional oral switch as described above.

Statistical methods

Block randomisation using an interactive voice/web response system, stratified by age cohort, will be used to assign patients (3:1) to the CAZ-AVI or cefepime study treatment 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 compared with comparator (cefepime). 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 versus cefepime, 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 intra-abdominal infections (D4280C00015) 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 cUTI), the clinically evaluable (CE) analysis set (patients

who meet minimal disease criteria for cUTI 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 cUTI and all evaluability criteria similar to the CE analysis set, and have at least 1 typical UTI bacterial pathogen at Baseline that is susceptible to both study agents, ie, CAZ-AVI and cefepime).

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, at EOIV, EOT, and at the TOC visit) and clinical response outcome of relapse (at the LFU visit). Favourable microbiological response will be assessed in the micro-ITT and ME analysis sets, and the number of patients with emergent infections (up to LFU) will be assessed in the ME analysis set. Combined clinical and microbiological response will be summarised in the ITT and micro-ITT analysis sets at EOIV and TOC visits. 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 cUTI. 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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APPENDICES

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
CFU	Colony-forming units
cIAI	Complicated intra-abdominal infections
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
DILI	Drug-induced liver injury
DSMB	Data and Safety Monitoring Board
EDP	Exposure During Pregnancy
ECG	Electrocardiogram
EOIV	End of Intravenous Treatment
EOT	End of Treatment
ESR	Erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
β-hCG	ß-human chorionic gonadotropin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalised ratio
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

Abbreviation or special term	Explanation
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
OAT	Organic anion transporter
PD	Pharmacodynamic
PK	Pharmacokinetic
PRA	PRA Health Sciences
QTcB	QT interval corrected using Bazett's formula
QTcF	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
US	United States
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).[4] 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 versus cefepime in patients aged from 3 months to less than 18 years with cUTI. 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.

A 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 un-blinded observers to interject when needed whilst the blind 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 paediatric patients with cUTI requiring treatment with intravenous (IV) antibiotics. The CAZ-AVI doses in this trial have been selected to achieve similar exposures reached in the Phase 3 adult studies (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).

The active comparator chosen for this study is IV cefepime. Cefepime has been widely used for the safe treatment of pyelonephritis and cUTIs in children. Details of the dosing regimen can be found in Section 7.2.

Complicated UTIs are defined as a clinical syndrome characterised by pyuria and a documented microbial pathogen on culture of urine or blood accompanied by local and systemic signs and symptoms, including fever (ie, oral or tympanic temperature greater than 38 degrees Celsius), chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness, that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterisation. Patients with pyelonephritis, regardless of underlying abnormalities of the urinary tract, are considered a subset of patients with cUTIs.

Complicated UTIs are frequently managed initially with IV antibacterial therapy, with subsequent conversion to oral antibacterial therapy after an improvement in clinical symptoms. In clinical practice, the oral agent chosen is dependent upon the results of culture, susceptibility testing and regional common practice. The oral step-down antimicrobial of choice is described in Section 7.

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

1.3. Benefit/Risk And Ethical Assessment

This study is the first study with therapeutic intent for CAZ-AVI in children with cUTIs; 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 cUTIs 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 the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for cUTIs 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 for cUTIs. This risk is mitigated in that the patients are closely monitored and will be managed with appropriate therapies as determined by the Investigator who is providing treatment. Furthermore, studies have indicated that there are no drug interactions between ceftazidime and avibactam when co-administered, and also that there are no safety implications.

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. Treatment duration was 5 to 15 days (RECAIM 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 should encompass the known and potential risks for the development product CAZ-AVI and its component products ceftazidime and avibactam, as well as the risks associated with other treatments that might be administered as described in this protocol. Other possible treatments include the marketed product cefepime. As the risk profile for the marketed product is widely available in the respective prescribing information, such risks will not be discussed in 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 study experience with CAZ-AVI, avibactam alone, and 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 pre-clinical 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, of those reported, there was 1 report in the CAZ-AVI clinical trials for which 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 study therapy 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. Side effects for the avibactam part of CAZ-AVI include injection site redness and injection site bruising. The risks of the marketed antibiotics are considered acceptable. While it is anticipated that CAZ-AVI will have similar efficacy for the treatment of cUTIs, it is possible that efficacy will not be demonstrated. For each patient in the trial, appropriate treatment of the cUTI is 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 cUTIs will be randomised to 1 of 2 treatment groups (3:1 ratio): CAZ-AVI or cefepime. 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 if given 3 times daily, or 6 doses if given twice daily) of study treatment (ie, evaluable patients; at least 60 patients in the CAZ-AVI group and at least 20 patients in the cefepime group).

Patients will be allocated to 1 of 4 cohorts based on age. Each cohort is required to have a minimum number of evaluable patients, and randomisation will be stratified as follows:

- Cohort 1: At least 6:2 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 6:2 evaluable patients aged from 6 years to <12 years;
- Cohort 3: At least 9:3 evaluable patients aged from 2 years to <6 years;

- Cohort 4: At least 18:6 evaluable patients aged from 3 months to <2 years comprising Cohorts 4a and 4b as follows:
    - Cohort 4a: At least 9:3 evaluable patients aged from 1 year to <2 years;
    - Cohort 4b: At least 6:2 evaluable patients aged from 3 months to <1 year, with a minimum of 3 patients with at least 1 PK sample aged from 3 months to <6 months treated with CAZ-AVI.

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.

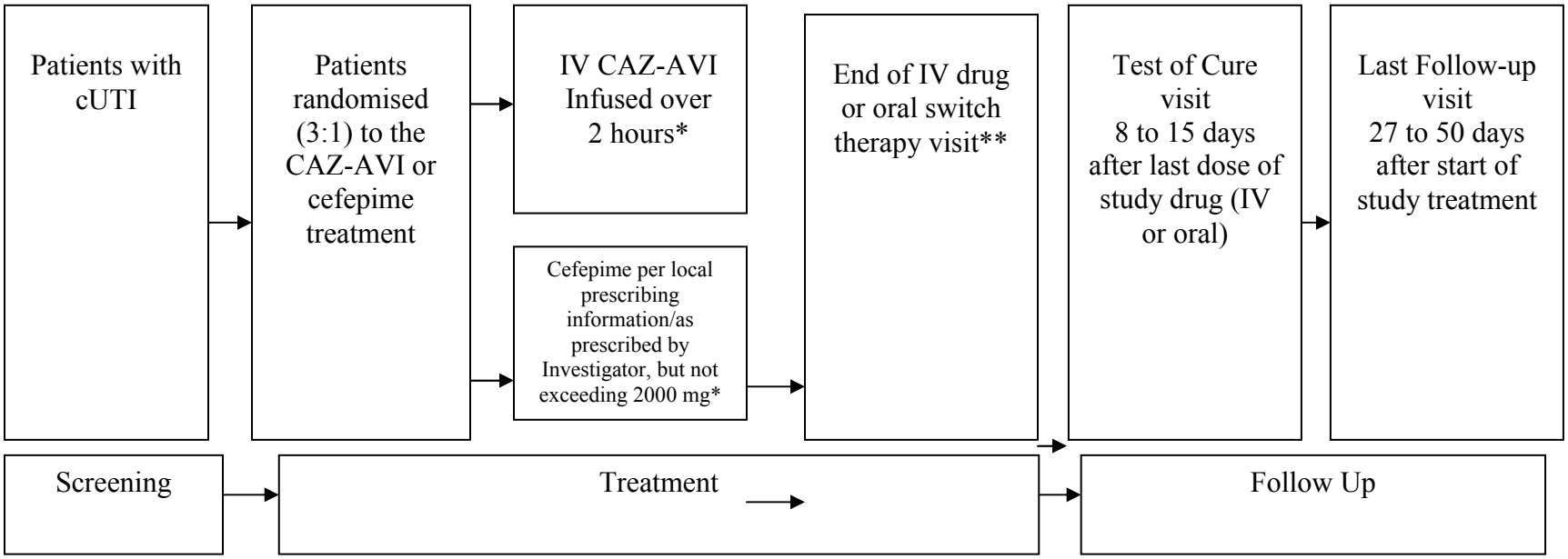
Patients randomised to receive cefepime should receive the dose, schedule and infusion duration as recommended in the local prescribing information or as prescribed by the investigator. The maximum dose of cefepime in any single infusion should not exceed 2000 mg.

Patients will receive IV treatment for a minimum of 72 hours (3 full days, ie, 9 doses if given 3 times daily, or 6 doses if given twice daily) 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 14. Patients requiring systemic prophylactic antibiotic medication for any reason at Screening are allowed to enter the study provided that they discontinue this medication prior to first dose of randomised study treatment (see Section 7.8 for further details).

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 (including 7 to 14 days of active treatment), at which time there will be a LFU assessment visit. The LFU is to be performed 20 to 36 days after the last dose of any treatment.

[redacted]

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 if given 3 times daily, or 6 doses if given twice daily] 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 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), or oral cefixime (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 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 sulfamethoxazole/trimethoprim (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 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 14 days), at the discretion of the Investigator.
** 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 Safety Objective:	Outcome Measure:
Evaluate the safety and tolerability of CAZ-AVI given at the selected dose regimen versus cefepime in paediatric patients aged ≥3 months to <18 years with cUTI	• 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 versus cefepime in paediatric patients aged ≥3 months to <18 years with cUTI	• 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 • Combined response

Evaluate the PK of CAZ-AVI in paediatric patients aged ≥3 months to <18 years with cUTI	• 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

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study. 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

- (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

- 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

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

- 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. Patient has a clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the Investigator to be serious and requires the patient to be hospitalised for treatment with IV therapy.

5. Patient has pyuria:

   - Cohorts 1 to 3 as determined by a midstream clean catch or clean urethral catheterisation urine specimen with ≥10 white blood cells (WBCs) per high-power field on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine;

- Cohorts 4a and 4b as determined by a midstream clean catch or clean urethral catheterisation urine specimen, or urine specimen obtained using urine collection pads (or supra-pubic collection if standard procedure in the assigned sites) ≥5 WBCs per high-power field on standard examination of urine sediment or ≥5 WBCs/mm^3 in unspun urine.

6. Patient has a positive urine culture: 1 midstream clean catch or clean urethral catheterisation urine specimen taken within 48 hours of randomisation containing $\geq 10^5$ colony-forming units (CFU)/mL of a recognised uropathogen known to be susceptible to the IV study therapy (CAZ-AVI and cefepime).

Note: If patients meet all of entry criteria except for positive urine culture as outlined above, the patients may be enrolled before urine culture results are available if the results are likely (based on urinalysis and clinical findings) to be positive and study drugs are considered appropriate empiric therapy. If a patient urine culture is negative after 24 or 48 hours of treatment but the patient is improving, the Investigator can keep the patient on treatment. If the urine culture is negative and the patient is not improving, study treatment will be stopped, and the patient will be followed for the rest of the study including undergoing all safety assessments until LFU.

7. Demonstrates either acute pyelonephritis or complicated lower UTI as defined by the following criteria:

    a. Qualifying criteria: patients must have at least 1 of the following signs/symptoms (signs/symptoms must have onset or have worsened within 7 days of enrolment) in addition to pyuria:

        - Dysuria (including perceived dysuria as referred by parent/caregiver);
        - Urgency;
        - Frequency;
        - Abdominal pain;
        - Fever defined as oral temperature >38.5°C (or equivalent by other methods) with or without patient symptoms of rigor, chills, warmth;
        - Nausea;
        - Vomiting;
        - Irritability;
        - Loss of appetite;

- Flank pain.

b. Or patients considered to have complicated UTI as indicated by 2 of the previous qualifying signs/symptoms in (a) plus at least 1 complicating factor from the following:

- Recurrent UTI (2 or more within 12 months period);
- Obstructive uropathy that is scheduled to be surgically relieved during IV study therapy and before the EOT;
- Functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder;
- Vesicoureteral reflux;
- Use of intermittent bladder catheterisation or presence of an indwelling bladder catheter for >48 hours prior to the diagnosis of Cuti;
- Urogenital procedure (eg, cystoscopy or urogenital surgery) within the 7 days prior to study entry;

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 Sponsor 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, penicillins or other β-lactam antibiotics.
5. Concurrent infection, including, but not limited to, central nervous system infection requiring systemic antibiotics in addition to the IV study drug therapy at the time of randomization.
6. Receipt of more than 24 hours of any systemic antibiotics after culture and before study drug therapy.

7. Receipt of systemic antibiotics within 24 hours before obtaining the study-qualifying pre-treatment baseline urine sample and before study drug therapy.

8. The child is suspected or documented to have an infection caused by organisms resistant to the prophylactic antibiotics.

9. A permanent indwelling bladder catheter or instrumentation including nephrostomy or current urinary catheter that will not be removed or anticipation of urinary catheter placement that will not be removed during the course of IV study drug therapy administration.

10. Patient has suspected or known complete obstruction of any portion of the urinary tract, perinephric abscess, or ileal loops.

11. Patient has had trauma to the pelvis or urinary tract.

12. Patient has undergone renal transplantation.

13. Patient has a condition or history of any illness that, in the opinion of the Investigator, would make the patient unsuitable for the study (eg, may confound the results of the study or pose additional risk in administering the study therapy to the patient).

14. Patient is considered unlikely to survive the 6 to 8 week study period or have a rapidly progressive illness, including septic shock that is associated with a high risk of mortality.

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

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

    a. Haematocrit <25% or haemoglobin <8 g/dL (<80 g/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.

17. 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)[3]:

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

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

19. 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 PPD

3. Determine patient eligibility (see Section 3.1 and Section 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 potential 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 or cefepime respectively in each of the cohorts for the age groups (see Section 8.2 for a description of the sample size).

A representative of Sponsor, under the supervision of Sponsor 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 Health Sciences (PRA) if the observer blind is broken for any reason and the Blinded Observer was unable to contact PRA before unblinding. PRA Health Sciences is a contract research organization that manages various aspects of this study on behalf of the Sponsor. PRA will inform Sponsor 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 the 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) at the time of discontinuation from the IP and at the LFU visit.

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 3.10.3 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

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

3.10.1. Screen Failures

Screen failures are patients who have provided informed consent/assent and subsequently 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). For details on the

procedures to follow regarding negative urine culture results after the test at Baseline, see Section 3.1.

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 the parent/legally-acceptable representative withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

3.10.3. Lost to Follow-up

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's source documentation. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved adverse events (AEs).

3.11. Discontinuation of the Study

The study may be stopped if, in the judgment of Sponsor, 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.

[redacted]

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 provides an overview of the protocol visits and procedures. Refer to the Study assessments section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Study plan detailing the procedures

Table 1. Study Plan Detailing The Procedures

	Assessment or Procedure	Baseline[1]	Treatment				Follow-up	
			Day 1[2]	Days 2 and 3	Days 4 to ≤14[3]	EOIV[4]	EOT[5] (Oral only)	TOC[6]	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
	Urine or serum pregnancy test[22]	X						X	
	Urine sample routine analysis[23]	X			If clinically indicated				
Micro	Urine culture[24]	X				X	X	X	X

[redacted]

	Assessment or Procedure	Baseline[1]	Treatment					Follow-up	
			Day 1[2]	Days 2 and 3	Days 4 to ≤14[3]	EOIV[4]	EOT[5] (Oral only)	TOC[6]	LFU[7]
	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				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 ≤14, 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 ≤14) 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 36 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, computed tomography (CT) scans, voiding cystourethrogram, ultrasound and/or MRI scans with or without contrast.

15. Blinded Observer: Assess clinical outcome per protocol, after 72 hours' 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 6.5.1. 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, before any antibiotics administered.
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 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, CrCl calculation, ESR (if clinically indicated or if required per standard of care), 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 6.5.1. 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 before administration of any antibiotics;

- Urine culture (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 or cefepime; 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, 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, 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 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 ≤14

On Days 4 to ≤14, 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 if given 3 times daily, or 6 doses if given twice daily) 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 14. 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, 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 ≤14) 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. 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, 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;

- Urine culture;

- 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, 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.

- Urine culture

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, 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;
- Urine culture.

4.3.2. Late Follow-up

Assessments at LFU should be performed 20 to 36 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, 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;
- Urine culture.

5. STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

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 blood and urine culture samples or isolates.

5.2.1. Urine Samples For Microbiological Analysis And Culture

Urine samples should be obtained for culture and routine quantitative analysis (including microscopic examination) at Baseline (before any antibiotics are administered) and at EOIV, EOT, TOC, and LFU. Cultures should be repeated per standard of care upon knowledge of a positive result until sterilisation is confirmed.

5.2.2. Blood Samples For Microbiological Analysis And Culture

If clinically indicated, blood samples (1 mL) may be obtained for culture and routine analysis (including microscopic examination) at Baseline (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)[1] and the World Health Organisation guidelines "Blood Sample Volumes in Child Health Research: Review of Safe Limits" (Howie 2011).[2] 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 Parameters

Comprehensive Metabolic Panel	Haematology	Urinalysis
Magnesium	Haematocrita	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 rateb	

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.

[redacted]

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 6.1.1.

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).[3] 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:

$$\text{CrCl (mL/min/1.73m}^2\text{)} = 0.413 \times \text{height (length) (cm)/serum creatinine (mg/dL)}$$

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 $kg/(\text{height in cm}/100)^2$. 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 screening only (Day 1/Day1) 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 as part of the standard of care for the patient, the first set of vital sign measurements for the day and the highest temperature of the day should be recorded in the CRF.

[redacted]

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.

5.3.4.4. Adverse Events

Adverse events will be collected at Baseline, throughout the Treatment Period, and at EOT, TOC and LFU. AEs and SAEs are defined in Sections Section 6.1.4 and Section 6.1.4.1 and, respectively. AEs will be collected and reported as described in Section 6.1.4.2.

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, voiding cystourethrogram, 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 Sponsor, 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

Blood Volume (mL)	Day	Baseline	Day 3	EOIV	TOC	Totals (minimum blood volume)
	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

Blood Volume (mL)	Day	Baseline	Day 3	EOIV	TOC	Totals (minimum blood volume)
	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. ADVERSE EVENT 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. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

6.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

6.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the parent(s)/legal guardian/legally acceptable representative. In addition, each parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

6.1.3. Withdrawal From the Study Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

6.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including the LFU visit.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

[redacted]

6.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

6.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

6.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable

possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

6.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

6.2. Definitions

6.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

6.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

6.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
    a. Requires inpatient hospitalization or prolongation of existing hospitalization. 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).
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

6.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

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)

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

[redacted]

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

6.3. Severity Assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

6.3.1. 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 3.9 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).

6.4. Special Situations

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

6.4.1. Medication Errors, and Lack of Efficacy

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors and lack of efficacy	If associated with an AE	Only if associated with an SAE

6.4.1.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength, or at the wrong infusion rate.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

In the event of a medication dosing error, the Sponsor should be notified immediately.

When the medication error is accompanied by an AE, as determined by the investigator, the associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

6.4.1.2. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

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 Pfizer IV study therapy occurs in the course of the study, then Investigators or other study centre personnel will inform appropriate Pfizer 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 Pfizer representative works with the Investigator to ensure that all relevant information is provided to the Pfizer patient safety data entry site.

- For overdoses associated with an SAE, standard reporting time lines apply, see Section. For other overdoses, reporting should be done **within 30 days**.

6.5.1. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Occupational exposure also includes an exposure during pregnancy if:

- A female becomes, or is found to be, pregnant while having been exposed (because of environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

The investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the Exposure During Pregnancy (EDP) supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

6.6. Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Pfizer 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 Pfizer 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 Pfizer Drug Safety Department **within 1 or 3 calendar days for SAEs (see Section 6.6) 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 Pfizer 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 Pfizer and the regulatory authorities.

A pregnancy report form (electronic copy of the PREGREP form) will be used to report the pregnancy to the Pfizer 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 Pfizer 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 Pfizer clinical studies is closely monitored on an on-going basis by the Sponsor 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 multicentre 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 Sponsor regarding the study, including, but not limited to: continue the study without modification, modify the protocol or informed consent/assent document(s), or temporarily stop enrolment in all or some of the study centres. The recommendations made by the DSMB to alter the conduct of the study will be forwarded to the Sponsor for final decision. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. The Sponsor 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

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

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
Cefepime	Cefepime hydrochloride powder for solution for infusion 1000 mg and 2000 mg to 50 mg/kg IV every 12 hours

CAZ-AVI and cefepime will be supplied centrally by Sponsor. 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.

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.

[redacted]

[redacted]

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)	
11	12 years to <18 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
11	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
21	6 years to <12 years	≥40 kg	2000 mg ceftazidime/500 mg avibactam	1000 mg ceftazidime/250 mg avibactam
21	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
31	2 years to <6 years	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4a2	1 year to <2 years	All	50 mg/kg ceftazidime /12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b2	6 months to <1 year	All	50 mg/kg ceftazidime/12.5 mg/kg avibactam	25 mg/kg ceftazidime/6.25 mg/kg avibactam
4b2	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.

[redacted]

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.

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.

Patients randomised to receive cefepime should receive the dose, schedule and infusion duration as recommended in the local prescribing information or as prescribed by the investigator. The maximum dose of cefepime in any single infusion should not exceed 2000 mg.

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

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. 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.

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.

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. 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), the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor, and all destruction must be adequately documented... 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 Sponsor identifying that this is the case. IP associated with a recall, Sponsor or its representative will determine what is to be destroyed, but PRA will manage the execution of destruction using standards acceptable to Sponsor 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 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), or
- Oral cefixime (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 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 sulfamethoxazole/trimethoprim (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

- 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 patients for the 2 weeks prior to study entry (considered prior treatment) and from enrolment 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.

Patients requiring systemic prophylactic antibiotic medication for any reason at Screening are allowed to enter the study provided that they discontinue this medication prior to first dose of randomised study treatment. Prophylactic use is prohibited between the time point of first dose of study treatment and the EOT assessment. Any violations of this will result in the patient being assigned an "indeterminate" clinical response at all future clinical outcome assessments.

Prophylactic use is permitted after EOT until study end and will not result in a change to the patient's clinical outcome, provided that the patient had not previously violated the aforementioned prophylactic use criterion between first dose of study treatment and the EOT assessment.

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. Patients who meet protocol-specific criteria may be switched to oral ciprofloxacin (only in countries where its use for children is

permitted, according to local guidelines) or cefixime after a minimum of 72 hours IV infusion of study therapy.

No other oral, intramuscular, or IV concomitant antibacterial treatments are permitted while receiving study therapy at any time up to the LFU visit. A patient requiring such antibacterial treatments other than the allowed study therapy for the treatment of the cUTI will be considered a treatment failure.

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 medications 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 Sponsor 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 was to continue in the study. Patients who have completed study therapy and are in the Follow-up Period should remain in the study, as they are not actively on study therapy but are being followed for outcomes.

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

Table 6. Contraindications And Drug-Drug interactions

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.

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.
Cefixime	Administration in pregnant or lactating women is not recommended unless clearly indicated. Concurrent administration with carbamazepine may result in increased plasma levels of carbamazepine; monitoring of drug levels is recommended. Concurrent administration with warfarin and anticoagulants may increase prothrombin time, with or without clinical bleeding. It is recommended that international normalised ratio (INR) be monitored frequently during and shortly after co-administration of cefixime with an oral anticoagulant agent. Administration of cefixime may result in a false positive reaction for ketones in the urine with tests using nitroprusside but not with those using nitroferricyanide. Administration of cefixime may result in a false positive reaction for glucose in the urine using Clinitest®, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or TesTape) be used. A false positive direct Coombs test has been reported during treatment with other cephalosporins; therefore, it should be recognised that a positive Coombs test may be due to the drug.

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.
Sulfamethoxazole – trimethoprim	Concurrent administration with ACE inhibitors may result in hyperkalaemia, possibly with cardiac arrhythmias or cardiac arrest. Monitoring of serum potassium concentrations is recommended. Concurrent administration with amantadine may cause toxic delirium. Monitoring patients for CNS adverse reactions is recommended. If an interaction is suspected, it may be necessary to discontinue 1 or both drugs. Concurrent administration with dofetilide is contraindicated. Concurrent administration with cyclosporine may cause decreased therapeutic effect of cyclosporine and increased risk of nephrotoxicity. Monitoring of cyclosporine blood or plasma concentrations, and serum creatinine concentrations is recommended. Concomitant administration with digoxin may increase plasma concentrations, especially in elderly patients. Monitoring of digoxin concentrations and dose adjustment as appropriate is recommended. Concurrent administration with diuretics (eg, thiazides) may result in increased incidence of thrombocytopenia with purpura. Monitoring of platelet count is recommended. If an interaction is suspected,

it may be necessary to discontinue 1 or both agents.
Concurrent administration with alcohol may produce an alcohol intolerance reaction. Patients receiving trimethoprim/sulfamethoxazole may be advised to avoid drinking alcohol and taking alcohol-containing medications.
Concurrent administration with Indomethacin may result in elevated sulfamethoxazole blood levels, increasing the pharmacologic effects and risk of adverse reactions.
Concurrent administration with meglitinide may elevate meglitinide plasma concentrations, increasing the risk of hypoglycaemia. Close monitoring of blood glucose after starting or stopping trimethoprim dose adjustment as appropriate is recommended.
Methenamine is contraindicated for use with sulfonamides.
Concurrent administration with methotrexate may increase toxicity of methotrexate. Trimethoprim may increase the risk of methotrexate-induced bone marrow suppression and megaloblastic anaemia. Monitoring hematologic status is recommended and lowering dose of methotrexate or higher leucovorin rescue dose may be needed.
Concurrent administration with phenytoin may increase the pharmacologic effects and risk of toxicity. Monitoring of phenytoin concentrations and toxicity and dose adjustment as appropriate is recommended.
Concurrent administration with procainamide may increase the pharmacologic effects and risk of toxicity. Monitoring of procainamide and its metabolite, N-acetylprocainamide and cardiac function and dose adjustment as appropriate is recommended.
Concurrent administration with pyrimethamine may increase the risk of megaloblastic anaemia. Assessment for haematologic and neurologic manifestations of megaloblastic anaemia, if an interaction is suspected, corrective treatment (eg, folic acid if indicated) and if necessary discontinuation of 1 or both drugs is recommended.
Concurrent administration with sulfones (eg, dapsone) may increase the pharmacologic effects and toxicity of both agents. Monitoring plasma concentrations of both agents and patients for sulfone toxicity (eg, methemoglobinaemia) is recommended. Adjust doses or discontinue therapy as necessary.
Concurrent administration with sulfonylureas may increase hypoglycaemic response. Monitoring of blood glucose and dose adjustment as appropriate as needed is recommended.
Concomitant administration of thiazolidinediones (eg, pioglitazone) may increase the risk of hypoglycaemia and other adverse reactions. Monitoring of blood glucose and for other adverse reactions, dose adjustment as appropriate is recommended.

Concurrent administration with tretinoin may augment phototoxicity, hence co-administration should be avoided.
Concomitant tricyclic antidepressants (eg, amitriptyline) may decrease the efficacy of tricyclic antidepressants. Monitoring the response of the patient and dose adjustment as appropriate is recommended.
Concurrent administration with live vaccines is not recommended.
Concurrent administration with warfarin may increase anticoagulant effect of warfarin. Monitoring of coagulation parameters and dose adjustment as appropriate is recommended.
Trimethoprim can interfere with serum methotrexate assay. Trimethoprim/sulfamethoxazole may interfere with Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations.

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 Sponsor 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 if given 3 times daily, or 6 doses if given twice daily) of study treatment (deemed to be evaluable patients). Patients will be randomised 3:1 to the CAZ-AVI or cefepime study treatment groups. At least 60 and 20 evaluable patients, respectively, are required in the CAZ-AVI and cefepime groups.

The proposed sample size is based on the probability of observing a 'rare' safety event. Safety data from this study and from Study D4280C00015 for cIAI will be combined for analysis. As a total of at least 120 patients will be treated with CAZ-AVI in both studies combined, when assuming an underlying incidence rate of 3% for a specific 'rare' event, this will ensure that the probability of observing such an event in at least 1 patient treated with CAZ-AVI exceeds 95%.

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

- Cohort 1: At least 6:2 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 6:2 evaluable patients aged from 6 years to <12 years;
- Cohort 3: At least 9:3 evaluable patients aged from 2 years to <6 years;

- Cohort 4: At least 18:6 evaluable patients aged from 3 months to <2 years comprising Cohorts 4a and 4b as follows:
    - Cohort 4a: At least 9:3 evaluable patients aged from 1 year to <2 years;
    - Cohort 4b: At least 6:2 evaluable patients aged from 3 months to <1 year, with a minimum of 3 patients with at least 1 PK sample aged from 3 months to <6 months treated with CAZ-AVI.

The inclusion of more patients in the younger age cohorts (Cohorts 3, 4a, and 4b) compared to Cohorts 1 and 2 was based on epidemiological data.

Considering patients over all cohorts combined, at least 10% of evaluable patients with urological abnormalities in the urinary tract should be included.

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 or cefepime). 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 if given 3 times daily, or at least 6 doses if given twice daily. 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 Section 8.3.4.1 to Section 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 at least 1 Gram-negative typical pathogen at baseline known to cause cUTI and no Gram-positive pathogen at baseline.

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 cUTI; 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 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 Gram-positive pathogen identified at baseline,
- Had no important protocol deviations that would affect assessment of efficacy

8.3.4.4. Microbiologically Evaluable Analysis Set

The ME analysis set will be 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 cUTI;

- 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;
- Had no Gram-positive pathogen identified at baseline;
- Had no important protocol deviations that would affect assessment of efficacy;
- Have at least 1 typical UTI bacterial pathogen which has been isolated from an adequate microbiological specimen at Baseline that is susceptible to both study agents (CAZ-AVI and cefepime).

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;
- Combined response.

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 or cefepime), 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 D4280C00015 for cIAI 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 QTcF 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 patient with cUTI. 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 cUTI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients who are improving but not enough to switch to oral therapy and are still on IV study drug at End of 72 hours and meet the following criterion: • Absence of new signs and symptoms, and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign
Clinical Failure	Patients who meet any of the following criteria: Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cUTI that requires alternative non-study antimicrobial therapy • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cUTI • Death in which cUTI is contributory • 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[a]	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory • Extenuating circumstances precluding classification as a cure or failure or improvement (eg, patient lost to follow-up)

CRP = C-reactive protein
[a] Any prophylactic systemic prophylactic antibiotic medication use after first dose until the End of 72 hours assessment will result in a clinical outcome of Indeterminate. See Section 7.8 for further details.

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

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

[redacted]

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 cUTI 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 cUTI that requires alternative non-study antimicrobial therapy • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cUTI • Death in which cUTI is contributory
Indeterminate[b]	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI 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.
[b] Any prophylactic systemic prophylactic antibiotic medication use after first dose until the EOIV assessment will result in a clinical outcome of Indeterminate. See Section 7.8 for further details.

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

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

[redacted]

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 cUTI 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 cUTI that requires alternative non-study antimicrobial therapy • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cUTI • Death in which cUTI is contributory
Indeterminate[b]	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI 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.
[b] Any prophylactic systemic prophylactic antibiotic medication use after first dose until the EOT assessment will result in a clinical outcome of Indeterminate. See Section 7.8 for further details.

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 cUTI 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 cUTI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy • Death in which cUTI is contributory
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up)

Any prophylactic systemic prophylactic antibiotic medication use after the EOT assessment will not impact clinical outcome at TOC. See Section 7.8 for further details.

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

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

8.5.2.2.1. 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 cUTI 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 cUTI 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 cUTI that requires further antimicrobial therapy and/or surgery • Death after TOC in which cUTI is contributory
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI 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. Any prophylactic systemic prophylactic antibiotic medication use after the EOT assessment will not impact clinical outcome at LFU. See Section 7.8 for further details.

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) 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. 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). If the outcome for any pathogen is 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
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
Indeterminate	Source specimen was not available to culture

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

For patients who have a microbiological outcome of 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

Emergent infections	Definition
Superinfection	A urine culture identified pathogen other than a baseline pathogen during the course of active treatment with IV study therapy along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy.
New infection	A urine culture identified pathogen other than a baseline pathogen at any time after IV study treatment has finished along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy.

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.

8.5.2.5. Combined Response

Combined clinical and microbiological response will be summarised in the ITT and the micro-ITT analysis sets at EOIV and TOC visits. The number and percentage of patients for combined response outcome at each visit will be summarised by response categories, cohort, and treatment group.

At the EOIV and TOC assessments, the clinical and per-patient microbiological responses will be used to create a combined response. If either clinical or microbiological response is unfavourable, then the combined response will be unfavourable. Otherwise, in the absence of unfavourable responses, if either clinical or microbiological response is indeterminate or missing, then the response will be indeterminate. Finally, if both clinical and microbiological

responses are favourable, then the outcome will be favourable. This is all summarised in cross-tabulation form in Table 14.

Table 14 Per-Patient Combined Response

		Clinical Outcome	
Microbiological Outcome	**Favourable**	**Indeterminate**	**Unfavourable**
Favourable	Favourable	Indeterminate	Unfavourable
Indeterminate	Indeterminate	Indeterminate	Unfavourable
Unfavourable	Unfavourable	Unfavourable	Unfavourable

8.6. Interim Analysis

No formal interim analysis will be conducted for this study.

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 Sponsor 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 Sponsor 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. In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at the Sponsor that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

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 Sponsor or Sponsor'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.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent[/assent] documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.2.3.1. Data Handling And Record Keeping

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.3. Study Timetable And End Of Study

The end of the study in all participating countries is defined as ‘the last visit of the last patient undergoing the study’ or date of study closure in the case of early study termination, whichever date is later.

The study is expected to start in Q3 2015 and to end by Q3 2018.

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. Sponsor 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. Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of CAZ-AVI at any time.

If a study is prematurely terminated, the Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within seven days. As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

9.5. Data Management

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 Sponsor 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 conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guidelines for Good Clinical Practices, and the Declaration of Helsinki.

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.

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer or its representative.

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 and Sponsor 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. The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

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

The Sponsor or 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 IECs/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 informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. 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 given to the patient's parent(s) or other legally acceptable representative(s);

- Ensure that any reimbursement for study visits 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 Sponsor.

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.

Sponsor or its representative 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, the Sponsor or its representative 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

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, authorised representatives of Pfizer, or companies working on behalf of Pfizer, a regulatory authority, or an IEC/IRB 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(s) will notify Pfizer or its agent immediately if contacted by a regulatory agency about an inspection at the centre. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.7. Reporting Of Safety Issues And Serious Breaches Of The Protocol Or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.8. Publication Of Study Results

10.8.1. Communication of Results by the Sponsor

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

10.8.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

[redacted]

11. LIST OF REFERENCES

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

3. Schwartz et al 2009,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.

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Appendix 1. 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.

Appendix 2. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS

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 Sponsor 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 (ie, 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 Sponsor 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 Sponsor representative who will then inform the central Study Team

The Medical Monitor 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. The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor. In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

- Complete the three Liver CRF Modules as information becomes available

- All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

- A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology

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 Medical Monitor 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 Sponsor Medical Monitor 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 Pfizer 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:

- Update the report of the prior reported SAE (report term now 'Hy's Law') according to Pfizer 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.

16. 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

Appendix 3. 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 2 and Figure 3 depict the somatic changes which are also described in Table 15.

Figure 2. Sexual Maturity Ratings (2 To 5) Of Pubic Hair Changes In Adolescent Girls. (Courtesy Of PPD , MD, PPD England)

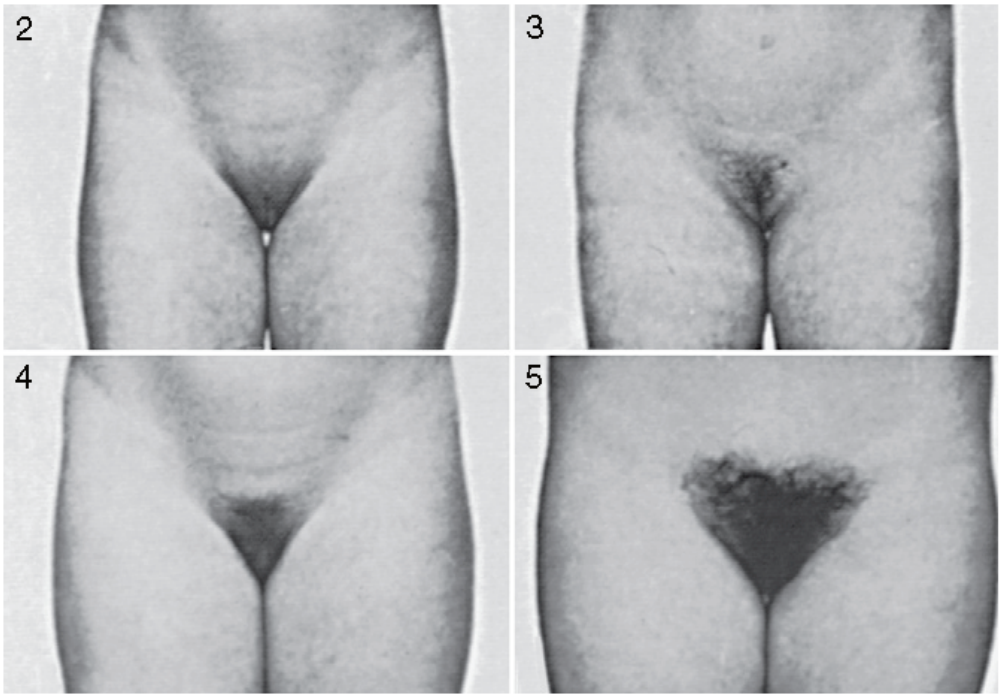

Figure 3. Sexual Maturity Ratings (1 To 5) Of Breast Changes In Adolescent Girls. (Courtesy Of PPD , MD, PPD England)

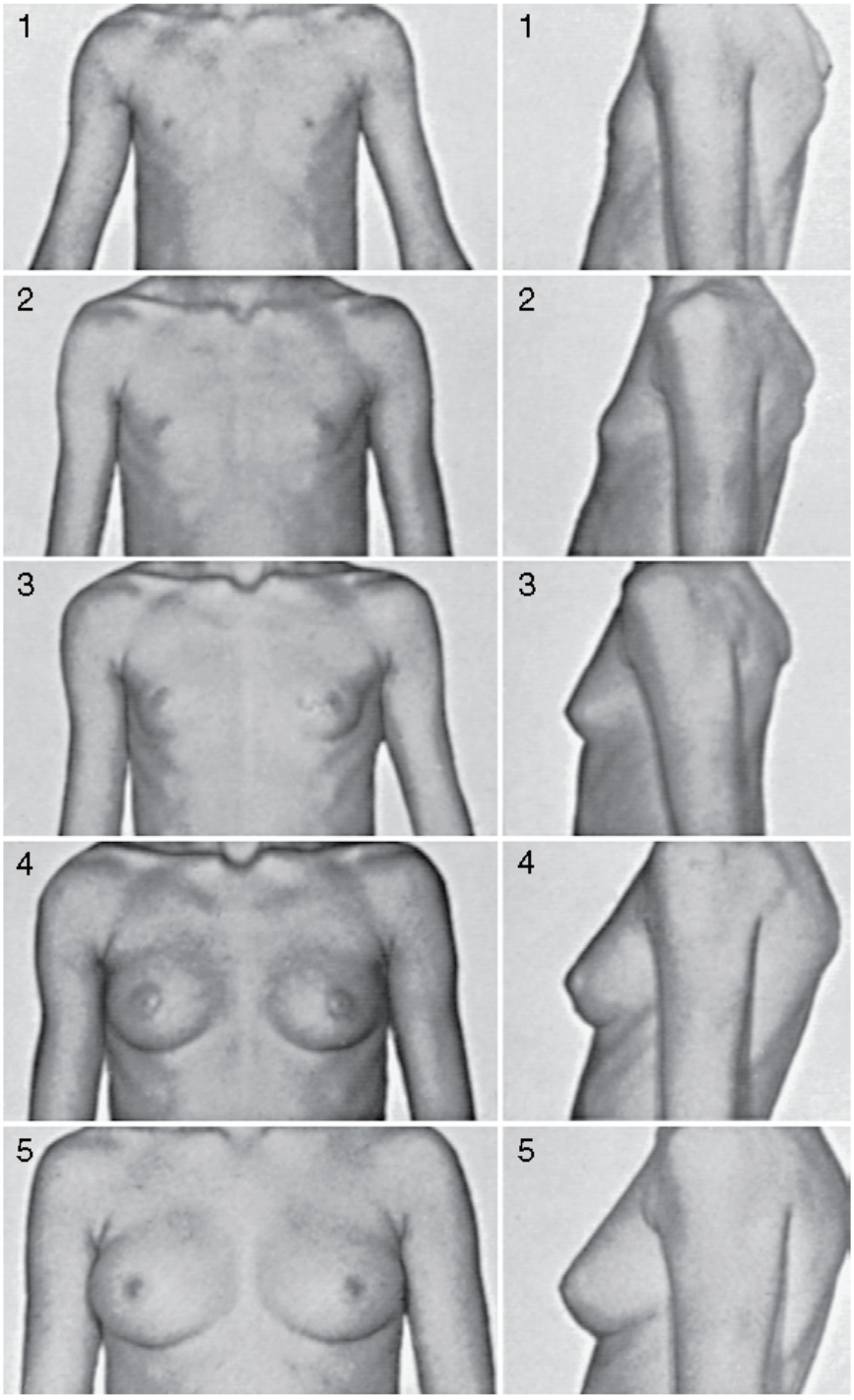

Table 15. Classification Of Sexual Maturity States In Girls

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.