Revised Clinical Study Protocol

Drug Substance	Ceftazidime-Avibactam (CAZ-AVI)
Study Code	D4280C00014
Edition Number	1
Date	[redacted]

A Phase I Study to Assess the Pharmacokinetics, Safety and Tolerability of a Single Dose of Ceftazidime-Avibactam (CAZ-AVI) in Children From 3 Months of Age to <18 Years Who Are Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Infection

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AstraZeneca Research and Development site representative

[redacted] Date

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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	[redacted]		

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

PROTOCOL SYNOPSIS

International Coordinating Investigator

[redacted]

Study centers and number of patients planned

This will be a multicenter study (approximately 15 centers) enrolling at least 32 patients (4 cohorts, each consisting of at least 8 evaluable patients) aged ≥3 months to <18 years. The study may include additional cohorts or increase the number of patients in cohorts depending upon real-time results and discussions during the Safety Review Committee (SRC) meetings after cohort completion.

Study period		Phase of development
Estimated date of first patient enrolled	Quarter 3 [redacted]	Phase I
Estimated date of last patient completed	Quarter 3 [redacted]	Phase I

Objectives

The primary objective of this study is:

- To characterize the pharmacokinetics (PK) of single-dose CAZ-AVI in a pediatric population.

The secondary objective of this study is:

- To assess the safety and tolerability of a single intravenous (IV) dose of CAZ-AVI given to hospitalized pediatric patients.

Study design

This is a phase I, open-label, single-dose study. The study aims to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single IV dose given to hospitalized pediatric patients receiving systemic antibiotic therapy for suspected or confirmed infection.

This study will include 4 cohorts, each consisting of at least 8 evaluable pediatric patients, aged ≥3 months to <18 years, who are hospitalized with infections. An evaluable patient is one who has provided PK blood samples at ≥50% of the sampling time points. Patients will be followed for 48 hours after the end of infusion. The total number of patients will be at least 32 but the study may include additional cohorts or increase the number of patients in each cohort depending upon real-time results and discussions during the SRC meetings. The patients in this study will be stratified by age and each cohort will enroll patients 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). Babies born prior to 37 weeks gestation are not to be included in Cohort 4.

Based on age requirements for the appropriate cohort and after confirming eligibility and obtaining written informed consent from a legal guardian and assent from patients (as appropriate), patients will be selected. Each patient will receive a single IV dose of CAZ-AVI administered as a continuous infusion over a 2-hour period. Blood samples will be collected to evaluate the PK of ceftazidime and avibactam from all patients in all cohorts.

Cohorts 1 and 2 will run in parallel and all available patient data from these 2 cohorts will be reviewed by the SRC prior to proceeding to Cohort 3. All available PK, safety, and tolerability data from each subsequent cohort will be reviewed by the SRC; however, a minimum of 8 evaluable patients for each cohort is required to support the SRC in making decisions regarding the safety, tolerability, and dosing recommendations for the next planned cohort. The SRC will consist of the study team physician/clinical pharmacology physician, international coordinating investigator or delegate, global safety physician or delegate, medical science director or delegate and the pharmacokineticist and pharmacometrician or delegates.

The dose regimens of Cohorts 1 and 2 have been determined by Monte Carlo simulations of the ceftazidime and avibactam exposure to approximately match that observed in adults. A population PK model developed in adults incorporating age and body weight as covariates impacting the PK of ceftazidime and avibactam was used in the simulation. For Cohorts 3 and 4, the PK data of ceftazidime and avibactam from the previous cohorts will be used to update the PK model and determine the dose to be administered to younger patients. The SRC will consider all available safety, tolerability, and predicted exposure for Cohorts 3 and 4 dose decisions. In addition, data from 2 nonclinical dose-ranging studies conducted in juvenile animals will be available for consideration prior to the start of Cohort 4. Cohort 4 will not be initiated until the nonclinical data are available.

Target patient population

At least 32 male or female patients (8 patients per cohort) aged ≥3 months to <18 years are expected to be enrolled in this study. These will be hospitalized patients receiving systemic antibiotic therapy for treatment of a suspected or confirmed infection who are expected to require hospitalization for at least 24 hours after the end of CAZ-AVI infusion and, preferably, until after the end of follow-up evaluations are completed, on Days 2 or 3. In the event of an early discharge from the hospital before Day 3, the patient will be expected to return to the hospital or clinic for follow-up evaluations on Day 3.

Investigational product, dosage and mode of administration

Patients in Cohort 1 will receive a single IV infusion of CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) administered over a 2-hour period on Day 1. Patients in Cohort 2 who weigh <40 kg will receive 50 mg/kg CAZ and 12.5 mg/kg AVI, and patients who weigh ≥40 kg will receive 2000 mg CAZ and 500 mg AVI as a single IV infusion administered over a 2-hour period on Day 1. These doses are applicable for patients with normal renal function and mild renal insufficiency; for patients with moderate renal insufficiency, the dose for both ceftazidime and avibactam should be halved (Section 3.2). The patients will be followed for 48 hours after the end of infusion for clinical and laboratory safety. Doses administered to Cohort 3 will be determined following population PK modeling and simulation using data from Cohorts 1 and 2 and doses administered to Cohort 4 will be determined following population PK modeling and simulation using data from Cohorts 1 through 3. Dosing in Cohorts 3 and 4 will also be as a single IV infusion administered over a 2-hour period.

Comparator, dosage and mode of administration

None

Duration of treatment

Patients will receive a single IV infusion of study dose of CAZ-AVI, administered over a 2-hour period, and will be followed for 48 hours after the end of infusion.

Outcome variables:

- Primary outcome variables

  The primary outcome variable is the determination of plasma PK parameters of ceftazidime and avibactam in pediatric patients.

- Secondary outcome variables

  The secondary outcome variables include safety and tolerability assessed by:

  – adverse events (AEs)

  – vital signs

- physical examination
- laboratory parameters
- electrocardiogram (ECG).

Statistical methods

PK analysis set: the PK analysis set will consist of all patients who received IV study dose of CAZ-AVI and have at least one postdose blood sample.

The PK analysis set will be used in the noncompartmental analysis (NCA), population PK/pharmacodynamic (PD) analysis, and in the summary presentation of the concentration and PK parameters.

A listing of ceftazidime and avibactam collection times and plasma concentration data by patient and cohort for each analyte will be provided. For Cohorts 1 through 4, the plasma concentration will be summarized; for Cohort 1 it will be summarized by nominal sampling time and for Cohorts 2, 3, and 4 it will be summarized by sampling time window. Pharmacokinetic variables (ceftazidime and avibactam plasma concentrations and PK parameters, when applicable) will be summarized by analyte and measurement time using appropriate descriptive statistics (eg, n, mean, standard deviation [SD], minimum, median, maximum, geometric mean [gmean], lower and upper SD bounds [gmean ± SD], and coefficient of variation [CV]).

Individual plasma concentration profiles, using the PK analysis set for Cohorts 1 to 4, will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all patients on a single plot for each cohort and analyte. Geometric mean concentration-time profiles (with lower/upper SD bounds as defined above) will be presented on both linear and semilogarithmic scales using nominal time for both ceftazidime and avibactam for Cohort 1. Additional graphical presentations of PK data may be included at the discretion of the PK scientist.

In addition, NCA PK parameters will be calculated for Cohort 1. The following PK parameters will be determined for ceftazidime and avibactam for Cohort 1, if the data allow, and will be listed and summarized: maximum plasma concentration (C_{max}; µg/mL) following a single-dose administration; time to C_{max} (t_{max}; in hours) following a single-dose administration; area under the plasma concentration-time curve from zero to 8 hours after the end of infusion ($AUC_{[0-8]}$), the time of the last quantifiable concentration ($AUC_{[0-t]}$), extrapolated to infinity ($AUC_{[0-\infty]}$); time of last quantifiable plasma concentration (t_{last}; in hours) taken directly from the individual concentration-time curve; terminal plasma half-life ($t_{½}$; in hours) estimated as $(\ln 2)/\lambda_z$; systemic plasma clearance (CL; L/hour) estimated as dose divided by $AUC_{(0-\infty)}$; volume of distribution at the terminal phase (V_z; L) estimated by dividing the systemic clearance by λ_z; volume of distribution at steady state (V_{ss}, L) estimated by multiplying the mean residence time (MRT) by the CL; and terminal elimination phase rate

constant (λ_z). These NCA PK parameters will also be summarized by descriptive statistics as described above.

Further, the avibactam and ceftazidime concentration, pediatric patient demographics, and disease status data from Cohorts 1 through 4 will be combined with the data from appropriate previous clinical studies in adults for a population PK modeling analysis. The actual dosing and plasma sampling times will be used for the analysis. Individual compartmental PK parameters for pediatric patients with available avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters such as C_{max}, minimum concentration (C_{min}), area under the plasma concentration-time curves at steady-state (AUC_{ss}), and $t_{½}$, will be derived from the determined avibactam and ceftazidime concentration time courses. The developed population PK model will be used to conduct the simulation of probability of PK/PD target attainment to help to justify the dose selection for the phase III studies in pediatric patients with complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI). A stand-alone population PK modeling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report outside of the clinical study report (CSR).

Safety analysis set: the safety analysis set will consist of all patients who received any amount of IV study dose of CAZ-AVI.

Unless otherwise specified, the safety analysis set will be used for summaries and listings. No inferential statistical tests will be performed for any safety analyses. Safety assessments will be based on AE reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, and ECGs. All recorded AEs will be listed and tabulated by system organ class, preferred term and for each cohort. Tabulations and listings of data for vital signs, physical examinations, clinical laboratory tests, and ECGs will be presented. The data will be summarized for the observed value by cohort and scheduled assessment and for corresponding change from baseline values. In addition, any significant results for these data will be listed by cohort.

For clinical laboratory values and vital signs, listings of values for each will be presented with abnormal or out-of-range values flagged. Adverse events occurring from the start of study dose of CAZ-AVI infusion up to 48 hours after the end of infusion will be summarized by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) vocabulary (Version 14.0 or higher) by cohort.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this clinical study protocol (CSP).

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-8)}$	Area under the plasma concentration-time curve from zero to 8 hours after end of infusion
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from zero extrapolated to infinity
AUC_{SS}	Area under the plasma concentration-time curves at steady state
$\%AUC_{ex}$	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
β-hCG	β-human chorionic gonadotrophin
BMI	Body mass index
CAZ-AVI	Ceftazidime-avibactam
cIAI	Complicated intra-abdominal infection
CL	Plasma clearance
CLcr	Creatinine clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CRF	Case report form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical study protocol
CSR	Clinical study report
C_T	Critical threshold concentration

Abbreviation or special term	Explanation
cUTI	Complicated urinary tract infection
CV	Coefficient of variation
DDI	Drug-drug interaction
EC	Ethics committee
EDC	Electronic data capture
ECG	Electrocardiogram
fT	Free time
GCP	Good Clinical Practice
gmean	Geometric mean
ICF	Informed consent form
ICH	International Conference on Harmonization
International coordinating investigator	The international coordinating investigator is the investigator coordinating the investigators and/or activities internationally.
IP	Investigational product
IRB	Institutional review board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KPC	*Klebsiella pneumoniae* carbapenemase
λ_Z	Terminal elimination phase rate constant
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
LOQ	Limit of quantification
MIC	Minimum inhibitory concentration
MRT	Mean residence time
NCA	Noncompartmental analysis
NQ	Nonquantifiable
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
[redacted]	[redacted]
prn	As needed (pro re nata)

Abbreviation or special term	Explanation
PTA	Probability of target attainment
[redacted]	[redacted]
QTcF	QT interval for heart rate corrected using Fridericia's formula
R_{sq}	Coefficient of determination
SD	Standard deviation
SAE	Serious adverse event (see definition in Section 6.3.2).
SRC	Safety Review Committee
$t_{½}$	Terminal plasma half-life
tbd	To be decided
t_{last}	Time of last quantifiable plasma concentration
t_{max}	Time to C_{max}
TOC	Test-of-cure
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution at the terminal phase

1. INTRODUCTION

1.1 Background

1.1.1 Ceftazidime-avibactam

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 infection (cUTI). Avibactam, when associated 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 did other currently marketed β-lactamase inhibitors such as clavulanic acid, tazobactam, and sulbactam. In addition, avibactam is a potent inhibitor of Class C enzymes whereas clavulanic acid, tazobactam, and sulbactam lack any activity against

this class of enzymes. Unlike currently available β-lactamase inhibitors, avibactam does not induce β–lactamase production.

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

Currently the options for the treatment of Gram-negative infections, especially multidrug-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.

1.1.2 Human experience - Phase I

At the time of this protocol, 7 clinical pharmacology studies have been completed:

- A phase I double-blind, placebo-controlled, escalating single-dose study with and without ceftazidime in healthy adult male patients (Study NXL104/1001)
- A phase I double-blind, placebo-controlled, multiple-dose study over 5 or 10 days with and without ceftazidime, intravenous (IV) and oral formulations, in healthy adult male patients (Study NXL104/1002)
- A phase I open-label, single-dose study to assess the effect of renal impairment on pharmacokinetic (PK) parameters in patients with varying degrees of renal insufficiency and in patients with end-stage renal failure on hemodialysis (Study NXL104/1003)
- A phase I open-label, single-dose study to assess effect of age and gender in healthy young and elderly male and female patients (Study NXL104/1004)
- A phase I double-blind, randomized, placebo-controlled, 4-way crossover thorough QT interval (QT) study to assess PK and safety in healthy volunteers (Study D4280C00007)
- A phase I single and multiple dose study in healthy male Japanese patients (Study D4280C00010)
- A phase I open-label, single dose study to investigate the excretion and metabolism of [^{14}C] avibactam in healthy patients (Study D4280C00008).

The phase I studies completed to date have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly male and female patients. The [^{14}C] avibactam study D4280C00008 showed that an average of 97% (range 95% to 98%) of administered radioactivity was recovered from the urine, over 95% within 12 hours of dosing. Avibactam is predominantly renally cleared with little contribution from metabolism. An average of 85% (range 67% to 101%) of administered avibactam was recovered from the urine during the study, with >50% being recovered within 2 hours of the start of the infusion. Renal clearance was 158 mL/min suggesting active tubular secretion. The PK and tolerability of avibactam have also been determined in patients with different degrees of renal impairment (Study NXL104/1003). The relationship between avibactam renal clearance and calculated creatinine clearance (CL_{cr}) was found to be linear, consistent with the predominantly renal excretion of avibactam. Based on the data from Study NXL104/1003, dosage adjustments are required in patients with moderate or severe renal impairment.

Based on the data from Study NXL104/1004, dose adjustments based on age (young adult or elderly) or gender are not required. Overall, preliminary data indicate that there were no major safety and tolerability concerns identified in this study. Additional details can be found in Section 5.1 of the CAZ-AVI Investigator's Brochure.

In Study D4280C00007, a supratherapeutic dose of avibactam was investigated for QT effects in combination with ceftazidime and ceftaroline fosamil, with moxifloxacin as a positive control. A single IV dose of avibactam 2000 mg and ceftazidime 3000 mg or avibactam 2000 mg and ceftaroline fosamil 1500 mg did not prolong QTcF beyond 10 milliseconds. There were no QTcF intervals >450 ms nor were there any QTcF interval changes from baseline >30 ms after a single IV dose of avibactam 2000 mg/ceftazidime 3000 mg or avibactam 2000 mg/ceftaroline fosamil 1500 mg.

In Study D4280C00010, avibactam alone and in combination with ceftazidime were well tolerated at the doses tested when administered as single and multiple doses to healthy male Japanese patients. There were no clinically significant electrocardiogram (ECG) measurements, physical examination findings, or intestinal flora measurements following either treatment. Liver function parameter values were noteworthy for one patient, a healthy 41-year-old Japanese male (randomized to avibactam alone), who experienced transaminase elevations that were classified as other significant adverse events (AEs). After receiving multiple doses of avibactam, his highest transaminase results were: alanine aminotransferase (ALT) 522 U/L (reference range: 17 to 63 U/L) and aspartate aminotransferase (AST) 246 U/L (reference range: 15 to 41 U/L). His transaminase levels decreased but had not normalized at the time of the last follow-up visit. The patient had no symptoms at the time of the transaminase elevations. According to the investigator, the increases in the transaminase values were considered mild in severity and related to the investigational product. Given these findings, drug-induced liver injury is now considered an important potential risk for which appropriate clinical study program [redacted] and risk mitigation measures have been outlined. Details pertaining to these measures are specified in each individual clinical study protocol (CSP) (eg, targeted follow-up study case report forms [CRFs] for

potential Hy's Law reports). While increases in transaminase levels are not currently considered expected adverse drug reactions with avibactam alone, increases in transaminase levels are noted as expected adverse drug reactions for ceftazidime alone and ceftazidime combined with avibactam. Currently, this finding does not alter the benefit-risk profile for CAZ-AVI. The PK of avibactam alone or in combination with ceftazidime was similar in Japanese patients to that observed in studies of Western patients.

Study D4280C00011, which explores whether there is a drug-drug interaction (DDI) between ceftazidime and avibactam, is currently underway. The live phase of the study and analysis is complete, with the study report in progress. The preliminary analysis demonstrates that there is no DDI between avibactam and ceftazidime.

1.1.3 Human experience - Phase II

At the time of this protocol, 2 phase II studies have been completed.

Study NXL104/2002 was a prospective, multicenter, double-blind, randomized, 2-arm, parallel-group (1:1) study in 203 patients between the ages of 18 and 88 years with a cIAI (Lucasti et al 2011). This study was designed to assess safety, tolerability, and efficacy of CAZ-AVI (2000 mg ceftazidime plus 500 mg avibactam IV every 8 hours over 30 minutes) plus metronidazole (500 mg IV every 8 hours over 60 minutes) versus meropenem (1000 mg IV every 8 hours over 30 minutes) in the treatment of cIAI. The primary objective of the study was to estimate the efficacy of CAZ-AVI plus metronidazole with respect to the clinical response in baseline microbiologically evaluable (ME) patients (ie, patients with at least one pathogen isolated that was susceptible to both study therapies) with cIAI at the test-of-cure (TOC) visit, 2 weeks after treatment compared with meropenem. Similar clinical response rates were seen in both treatment groups for the primary endpoint; 91.2% in the CAZ-AVI plus metronidazole group and 93.4% in the meropenem group. The most common AEs reported (>7.5% incidence overall) were nausea, vomiting, pyrexia, increased ALT, increased AST, and increased alkaline phosphatase (ALP). Discontinuations due to AEs were infrequent (3.4% overall) in both groups. Five deaths were reported in the study (three in the CAZ-AVI plus metronidazole group and two in the meropenem group); none were considered related to study therapy. Clinically significant laboratory abnormalities occurred uncommonly, including abnormalities in liver enzymes.

Study NXL104/2001 (Vasquez et al 2011) was a multicenter, investigator-blinded, randomized, 2-arm, parallel-group (1:1) study to estimate the efficacy, safety, and tolerability of CAZ-AVI (500 mg ceftazidime/125 mg avibactam IV every 8 hours over 30 minutes) versus imipenem (imipenem cilastatin 500 mg IV every 6 hours over 30 minutes) in 137 patients between the ages of 18 and 90 years with a cUTI. Twenty-seven patients (39.1%) in the CAZ-AVI group and 35 patients (51.5%) in the imipenem group were ME (ie, had at least one pathogen isolated that was susceptible to both study therapies). The primary objective of the study was to estimate the efficacy of CAZ-AVI with respect to microbiological response in ME patients with cUTIs at the TOC visit (5 to 9 days after treatment) compared with imipenem. Similar microbiological response rates were seen in both treatment groups; at the TOC visit, 19 of 27 patients (70.4%) in the CAZ-AVI group and

25 of 35 patients (71.4%) in the imipenem group had a favorable microbiological response (eradication). The most common AEs reported (overall incidence >7.5%) were headache, diarrhea, anxiety, and infusion site reaction. Discontinuations due to AEs were uncommon (2 patients in the CAZ-AVI group, none in the imipenem group). One death was reported in the study (in the imipenem group). Clinically significant laboratory abnormalities occurred uncommonly, including abnormalities in liver enzymes.

Additional details can be found in Section 5.2.2 of the CAZ-AVI Investigator's Brochure.

1.2 Rationale for conducting this study

CAZ-AVI is being co-developed by AstraZeneca and [redacted] for parenteral treatment of patients with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime alone.

Ceftazidime (a third generation cephalosporin) is a long-established therapy shown to be safe and effective in adult and pediatric patients (neonates to adolescents <18 years of age) for a range of indications, including cIAI and cUTI (FORTUM® SmPC 2010).

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 cIAIs and cUTI. Avibactam is being developed as an IV antibiotic formulation in combination with ceftazidime for the treatment of patients with serious Gram-negative bacterial infections. The strategy of using β-lactam, β-lactamase inhibitor combinations has been successful against Class A β-lactamases in a variety of bacterial infections including those commonly associated with cIAIs and cUTI. Therefore CAZ-AVI has the potential to provide a much needed therapeutic option for adult and pediatric patients with cIAI and cUTI.

This study will be conducted in hospitalized pediatric patients aged ≥3 months to <18 years that are receiving systemic antibiotic therapy for infections of any type. The patients will be stratified by age into 4 cohorts, each consisting of at least 8 evaluable patients (See Table 1). Data for Cohorts 1 and 2, which will be run in parallel, (safety assessments [AEs, laboratory assessments, physical examination, ECG, and vital signs], and PK) will be reviewed prior to commencing Cohort 3. All data from Cohorts 1, 2, and 3 as described above will be reviewed prior to commencing Cohort 4.

The inclusion and exclusion criteria have been chosen in order to select appropriate pediatric patients who are being treated for suspected or confirmed infection.

The long-established efficacy and safety of ceftazidime in pediatric patients, the mode of action of avibactam, and the available phase II clinical data for CAZ-AVI in adults provide a strong rationale to investigate CAZ-AVI in the pediatric setting.

Since the antimicrobial spectrum of CAZ-AVI includes pathogens resistant to other β-lactam antibiotics (notably bacteria producing extended-spectrum β-lactamases and KPCs), CAZ-AVI is expected to provide positive clinical outcomes in those pediatrics patients infected with pathogens resistant to β-lactam antibiotics due to the presence of avibactam sensitive β-lactamases. CAZ-AVI has the potential to address the significant unmet clinical need associated with antibiotic resistance in pediatric patients.

The PK sampling and safety assessments are judged to be sufficient to fulfill the primary and secondary objectives of the study.

1.3 Benefit/risk and ethical assessment

Patients enrolled into this clinical study will have infections that are of sufficient severity to require hospitalization and treatment with systemic antibiotics. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for infections, in the face of the changing pattern of antibiotic resistance. CAZ-AVI will not be used to treat the infection for which the patient has been admitted as this is not a therapeutic study.

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.

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

- 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
- Seizures have been reported with various cephalosporins including ceftazidime
- Treatment with IV chloramphenicol within 24 hours of administration of study dose of CAZ-AVI

The AEs described below for ceftazidime may occur with multiple administrations and are unlikely to occur with the single dose that patients will be receiving in this study:

- Antibiotic-associated diarrhea, *Clostridium difficile* diarrhea, colitis, and pseudomembranous colitis
- Bacterial overgrowth with nonsusceptible organisms
- Distal necrosis as a result of inadvertent intraarterial administration of ceftazidime

- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae such as tremor, myoclonus, seizures, encephalopathy, and coma.

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 are located in the CAZ-AVI Investigator's Brochure.

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

In regard to hypersensitivity reactions, there was one report in the CAZ-AVI clinical trials in which the 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. In the CAZ-AVI development program, rashes have been reported. Elevations of liver enzymes independent of skin rashes or other potential signs of hypersensitivity have also been reported. In addition, drug-induced liver injury is considered an important potential risk.

In summary, the known and potential risks of receiving the developmental antibiotic combination CAZ-AVI are expected to be similar to those seen with ceftazidime and cephalosporins in general. Thus far, no unique risks have been identified for the combination of ceftazidime and avibactam. 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.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is:

- To characterize the pharmacokinetics (PK) of single-dose CAZ-AVI in a pediatric population.

2.2 Secondary objective

The secondary objective of this study is:

- To assess the safety and tolerability of a single IV dose of CAZ-AVI given to hospitalized pediatric patients.

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design

This is a phase I, open-label, single-dose study. The study aims to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single IV dose given to hospitalized pediatric patients receiving systemic antibiotic therapy for suspected or confirmed infection. The results of this study will aid appropriate dose selection for different age groups.

This study will include 4 cohorts, each consisting of at least 8 evaluable pediatric patients, aged ≥3 months to <18 years, hospitalized with infections. An evaluable patient is one who has provided PK blood samples at ≥50% of the sampling time points, as indicated in Table 6, Table 7, and Table 8 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively. Patients will be followed for 48 hours after the end of infusion. The total number of patients will be at least 32 but the study may include additional cohorts or increase the number of patients in each cohort depending upon real-time results and discussions during the Safety Review Committee (SRC) meetings. The patients in this study will be stratified by age and each cohort will enroll patients 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). Babies born prior to 37 weeks gestation are not to be included in Cohort 4.

Based on age requirements for the appropriate cohort and after obtaining written informed consent from a legal guardian and assent from patients (as appropriate), patients will be selected. Each patient will receive a single IV dose of CAZ-AVI administered as a continuous infusion over a 2-hour period. Details of the dosing regimen for each cohort will be determined as indicated in Table 1. Blood samples will be collected to evaluate the PK of ceftazidime and avibactam from all patients in all cohorts as indicated in Table 6, Table 7, and Table 8 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively. To support the use of population PK modeling and simulation to determine the CAZ-AVI dose in pediatric patients, the actual dose amount administered, the accurate date and time of start and end of the IV infusion, and the blood sample times for all patients will be required.

Cohorts 1 and 2 will run in parallel and all available patient data from these 2 cohorts will be reviewed by the SRC prior to proceeding to Cohort 3. All available PK, safety, and tolerability data from each subsequent cohort will be reviewed by the SRC; however, a minimum of 8 evaluable patients for each cohort is required to support the SRC in making decisions regarding the safety, tolerability and dosing recommendations for the next planned cohort. The SRC consists of the study team physician/clinical pharmacology physician, international coordinating investigator or delegate, global safety physician or delegate, medical science director or delegate and the pharmacokineticist and pharmacometrician or delegates.

The dose regimens of Cohorts 1 and 2 have been determined by Monte Carlo simulation of the ceftazidime and avibactam exposure to approximately match that observed in adults. A population PK model developed in adults incorporating age and body weight as covariates impacting the PK of ceftazidime and avibactam was used in the simulation. For Cohorts 3 and 4, the PK data of CAZ-AVI from the previous cohorts will be used to update the PK model and determine the dose to be administered to younger patients. The SRC will consider all available safety, tolerability, and predicted exposure for Cohorts 3 and 4 dose decisions. In addition, data from 2 nonclinical dose-ranging studies conducted in juvenile animals will be available for consideration prior to the start of Cohort 4. Cohort 4 will not be initiated until the nonclinical data are available.

Assessments required throughout the study are summarized in the study plan (Table 2).

Table 1 Study Population

Cohort	Age	CAZ-AVI Dose	Number of Patients	Comments
1[a]	≥12 to <18 years	2000 mg CAZ and 500 mg AVI 2-hour IV infusion	At least 8	
2[a]	≥6 to <12 years	Weight <40 kg: 50 mg/kg CAZ and 12.5 mg/kg AVI Weight ≥40 kg: 2000 mg CAZ and 500 mg AVI 2-hour IV infusion	At least 8	
3[a]	≥2 to <6 years	mg/kg tbd	At least 8	Dosing for patients in this age group will be determined using population PK modeling of the PK data from Cohorts 1 and 2 and safety and tolerability data to select a safe and effective dose based upon anticipated exposure levels.
4	≥3 months to <2 years	mg/kg tbd	At least 8 split into 2 groups: ≥3 months to <1 year (at least 4) AND 1 year to <2 years (at least 4)	Dosing for patients in this age group will be determined using population PK modeling of the PK data from Cohorts 1 through 3 and safety and tolerability data to select a safe and effective dose based upon anticipated exposure levels. 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.

[a] 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.

Abbreviations: AVI, avibactam; BMI, body mass index; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; IV, intravenous; PK, pharmacokinetic; tbd, to be decided.

Table 2 Study Plan

	Screening Visit[a]	Baseline/Treatment Visit[a]	Follow-up	
	Study Days			
Assessment	**Day -1[a]**	**Day 1[a]**	**Day 2**	**Day 3**
Informed consent	X			
Demography	X			
Medical/surgical history	X			
Physical examination (including height and weight)	X[b,c]			X[d]
Vital signs evaluation[e]	X	X	X	X
Inclusion/exclusion criteria	X			
Safety laboratory assessments[f] (chemistry, hematology, and urinalysis)	X[g]			X
CL_{cr} estimation[h]	X			X
Pregnancy test[i] (female patients, if applicable)	X			
CAZ-AVI infusion		X		
PK blood sampling[j]		X		
ECG (paper)	X[k]	X[l]		
Concomitant medication	X[m]	X	X	X
Adverse events	X	X	X	X

[a] Screening assessments (Day -1) and baseline assessments (Day 1) can be completed on the same calendar day, prior to study drug administration.

[b] Tanner staging of development to be assessed at screening for all female patients and a serum pregnancy test to be performed on all female patients who have achieved menarche or have reached Tanner stage 3 development (refer to Appendix E for further details on Tanner staging).

[c] BMI will only be calculated at screening. The 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.

[d] Physical examination, including weight measurement only, will take place at the follow-up assessment (Day 3).

[e] Vital signs (blood pressure, pulse rate, respiratory rate and temperature) will be taken at the following time points: before infusion and at 2 (± 15 minutes), 4 (± 15 minutes), 6 (± 30 minutes), 12 (± 30 minutes), 24 (± 1 hour), and 48 (± 4 hours) hours after the end of the CAZ-AVI infusion. On Day 2 and Day 3, vital sign measurements should be obtained before any other assessments or procedures have been performed. Additional vitals may be taken prn.

[f] Including but not limited to ALT, AST, and bilirubin; see Table 5 for laboratory assessments.

[g] If patient is improving and laboratory assessments were performed within 48 hours of screening, they may be used to determine eligibility.

[h] Creatinine values will be used to calculate CLcr using the Schwartz formula (refer to Section 4.2, exclusion criterion 3 for further details).

[i] Serum pregnancy test to be performed on all female patients who have achieved menarche or have reached Tanner stage 3 development (refer to Appendix E for further details on Tanner staging). CAZ-AVI infusion should not occur until after serum pregnancy test results have been received.

[j] PK samples will be drawn at time points indicated in Table 6, Table 7, and Table 8 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively.

[k] An ECG will be performed prior to obtaining any blood samples for laboratory testing.

[l] An ECG will be performed within 15 minutes following the end of the CAZ-AVI infusion.

[m] Review prior and concomitant medications.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAZ-AVI, ceftazidime-avibactam; CLcr, creatinine clearance; ECG, electrocardiogram; PK, pharmacokinetic; prn, as needed (pro re nata).

3.2 Rationale for study design and doses

The dose regimen of CAZ-AVI for Cohort 1 will be the same as previously studied in the adult population, 2000/500mg. The dose regimen for Cohort 2 will be 50/12.5 mg/kg for CAZ-AVI if the body weight of a pediatric patient is less than 40 kg, otherwise, 2000/500 mg CAZ-AVI.

The selection of the dose regimens for Cohorts 1 and 2 was based on Monte Carlo simulation of the ceftazidime and avibactam exposure (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) and probability of target attainment (PTA) in 1000 pediatric patients at each cohort. For Cohort 1, body weights ranging from 30 to 94 kg were included in the simulation, and in Cohort 2, the body weight range was 16 to 65 kg. The aim for dose selection in terms of exposure (C_{max} and AUC) in pediatric patients was to select a dose that achieved approximately no more than 20% higher exposure than an adult. In terms of efficacy, the aim was to select a dose with a predicted PTA comparable to adults, which is to achieve approximately 90% target attainments.

The PK/pharmacodynamic (PD) index of β-lactams, including ceftazidime, has been well established as the time that the free drug concentration exceeds the minimum inhibitory concentration (MIC), conventionally expressed as the percentage time free drug above the MIC (%fT>MIC). The magnitude of this index for ceftazidime was set at 50% fT>MIC, based on previous PTA analyses for this cephalosporin (Frei et al 2008; EUCAST 2012). Nonclinical data from in vitro susceptibility testing and PD hollow-fiber experiments support the concept that a critical threshold (C_T) free concentration of avibactam is required to maintain continued suppression of β-lactamase activity for the same duration of the dosing interval that ceftazidime must be maintained above its MIC (ie, ≥50% fT>C_T).

Two joint PK/PD targets as follows are evaluated:

- Medium: 50% fT>MIC of 4.0 mg/L for ceftazidime and 50% fT>C_T of 1.0 mg/L for avibactam
- High: 50% fT>MIC of 8.0 mg/L for ceftazidime and 50% fT>C_T 1.0 mg/L for avibactam.

The PK/PD target appropriate to 8 mg/L was set on the basis of PK-PD in adults, encompassing the MIC frequency distributions of CAZ-AVI versus both Enterobacteriaceae and *Pseudomonas aeruginosa*. In the case of the PTA analyses in simulated pediatric patients, the overall safety-based exposure limits of C_{max} and AUC resulted in lower pharmacodynamic PTA values; therefore, MICs of both 8 mg/L and 4 mg/L were investigated.

Based on the population PK model developed from adult patients with cIAI and incorporating changes in CAZ-AVI PK according to allometric scaling for body weight, the simulation demonstrated that the proposed dose regimen for adolescents in Cohort 1 (ie, 2000 mg CAZ and 500 mg AVI) will have comparable exposure and PTA to adults for both medium and high PK/PD targets. The simulation also demonstrated that the proposed dose regimen for

Cohort 2 (50 mg/kg CAZ and 12.5 mg/kg AVI for children with weight <40 kg, and 2000 mg CAZ and 500 mg AVI for children with weight ≥40 kg) will have comparable exposure and adequate PTA for the medium PK/PD target. The PTA for the high PK/PD target for Cohort 2 pediatric patients is lower (73%) than for adults (87%) due to the very stringent and conservative setting of the PK/PD target of 50% fT>MIC of 8.0 mg/L for ceftazidime and 50% fT>C_T 1.0 mg/L for avibactam. However, the recommended dose regimen is considered to be appropriate for the pediatric patient group since the exposure predicted from the dose regimen is approximately 20% higher than that for adults. In addition, the proposed dose regimen is in alignment with the recommended highest ceftazidime dose regimen for pediatric patients of 1 month to 12 years of age according to the FORTUM® package insert (FORTUM® SmPC 2010). Furthermore, this dose regimen has been used in clinical practice for many years and is generally deemed to be effective in treatment of pediatric patients with various infections.

The CAZ-AVI dose selection for Cohort 3 and 4 will be made sequentially. The dose regimen for Cohort 3 will be determined after the completion of the PK studies in Cohort 1 and 2. Population PK modeling will be conducted for Cohort 1 and 2 with appropriate data pooled from the clinical studies in adults. Simulations will be conducted to determine the dose regimen for Cohort 3; the dose will approximately match CAZ-AVI exposure observed in adults for C_{max}, AUC, and PTAs.

A similar approach will be applied to the dose determination of CAZ-AVI for Cohort 4 after the completion of the PK study in Cohort 3. The population PK model developed for Cohort 1 and 2 will be updated with an adding of the PK data from Cohort 3, and the simulation described above will be conducted to determine the dose regimen for Cohort 4.

For patients with renal impairment the same simulation approach was used as described above, using the dose modifications recommended in the adult program. Based on assessment of both target attainment analysis and exposure, no dose modification is required for patients with mild renal impairment (CL_{cr} >50-≤80 mL/min); however, for patients with moderate renal impairment (CL_{cr} >30-≤50 mL/min) the dose for both ceftazidime and avibactam should be halved.

Proposed maximum dose and exposure limits

The aim for dose selection for each cohort is to achieve exposure comparable to the median model-derived values for adult patients dosed with 2000 mg CAZ and 500 mg avibactam given as a 2-hour infusion. Critically, the selected dose should maintain a %fT >MIC in pediatric patients that is similar to that in adult patients, while not appreciably exceeding (no more than 20% greater than) the AUC and C_{max} values in adults.

If either of these is not achieved, then an additional cohort may be repeated or added with a different dose.

4. PATIENT SELECTION CRITERIA

Investigators should keep a record, using the patient screening log, of patients who entered Screening.

To be eligible to receive the study dose of CAZ-AVI, each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study dose of CAZ-AVI.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Written informed consent will be obtained from parent(s) or other legally acceptable representative(s), and informed assent from patient (if age appropriate) will be obtained. Written assent or documented verbal assent will be obtained according to local requirements.

2. Male or female children ages ≥3 months to <18 years.

3. Hospitalized, receiving systemic antibiotic therapy for the treatment of a suspected or confirmed infection, and expected to require hospitalization for at least 24 hours and, preferably, 48 hours until after the follow-up evaluations are completed on Day 3 (48 hours after the end of infusion). Hospitalization is mandatory for the 24 hours after infusion. In the event of an early discharge from the hospital before Day 3, the patient's family agrees that the patient will return to the hospital or clinic for the assessments on Day 3 (Table 2).

4. Likely to survive the current illness or hospitalization.

5. Sufficient IV access (peripheral or central) to receive study drug and dedicated access for PK sampling (see Section 6.4.1).

6. 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 authorized to participate in this clinical study if the following criteria are met:

   – At screening:

(i) (a). Patient reports sexual abstinence for the prior 3 months or reports use of at least one 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 receipt of study drug; and

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

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

(iv) Patient has a negative serum β-human chorionic gonadotropin (β-hCG) test just prior to study entry. Since serum tests may miss an early pregnancy, relevant menstrual history and sexual history, including methods of contraception, should be considered.

Note 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.

4.2 Exclusion criteria

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

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

2. Past or current history of epilepsy or seizure disorder (excluding childhood febrile seizures).

3. Severe renal impairment:

Creatinine clearance (CL_{cr}) ≤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):

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

4. Female who is currently pregnant or breast-feeding or has a positive serum β hCG pregnancy test. Since a serum test may miss a pregnancy in the first days after conception, relevant sexual history, including methods of contraception, should be considered. Any patient whose sexual and contraceptive history suggests the possibility of early pregnancy must be excluded.

5. Previous participation in this study or in any study involving administration of an investigational agent within 30 days prior to enrollment into this study where the patient was randomized and received an active study dose of CAZ-AVI (not placebo).

6. Acute hepatitis in the prior 6 months, a prior history of cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure; and/or

   Any of the following blood test results, for any individual, when assessed for eligibility:

(a) Bilirubin >3 × upper limit of normal (ULN), unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease;

(b) ALT or AST >3 × ULN values used by the laboratory performing the test. Patients with values >3 × ULN and <5 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented;

(c) ALP >3 × ULN. Patients with values >3 × ULN and <5 × ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

7. Any condition (eg, septic shock, burns, cystic fibrosis, acute hemodynamic instability, including those conditions not responding to pressor support) that would make the patient, in the opinion of the investigator, unsuitable for the study (eg, would place a patient at risk; compromise the quality of the data; or interfere with the absorption, distribution, metabolism, or excretion of CAZ-AVI).

8. Receipt of a blood or blood component or scheduled for transfusion within the PK sampling period (eg, red blood cells, fresh frozen plasma, platelets) transfusion during the 24-hour period before enrollment.

9. Unwilling or unable to adhere to study procedures or restrictions.

10. Body mass index (BMI) outside the range (below the 5th percentile or above the 95th percentile) for height, age, and weight except for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

11. Treatment with ceftazidime within 12 hours of study drug administration or treatment with ceftazidime within 24 hours of study treatment in patients with renal impairment (CL_{cr} ≤50 mL/min).

12. Intravenous treatment with chloramphenicol within 24 hours of administration of study dose of CAZ-AVI.

13. Babies born prior to 37 weeks gestation (Cohort 4 only).

See Section 5.3 for procedures for withdrawal of incorrectly enrolled patients.

5. STUDY CONDUCT

5.1 Restrictions during the study

Oral, transdermal, and vaginal hormonal contraceptives potentially subject to DDI, 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 a female study participant was previously using hormonal contraceptives such as pills, patches, and intravaginal devices, she should follow her healthcare provider's specific recommendations for effective use of these methods after completing study dose of CAZ-AVI. Such recommendations may address the need for a second method of contraception until the hormonal method becomes fully effective.

5.2 Patient enrollment and initiation of investigational product

Prior to enrollment, the investigator will:

1. Determine initial eligibility prior to performing any study-specific procedures.

2. Obtain signed informed consent from the potential patient's guardian/legal representative and assent from the patient, as appropriate, before any study-specific procedures are performed.

3. Review patient eligibility.

4. Assign potential patient a unique enrollment number, beginning with "E0001001 (EXXXXYYY)", where XXXX reflects the center number and YYY will be allocated sequentially to enrolled patients at each center.

5. Confirm patient eligibility (see Sections 4.1 and 4.2).

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

5.3 Procedures for handling patients incorrectly enrolled or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There will be no exceptions to this rule.

Where patients who do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria after initiation, the investigator should inform the [redacted] physician immediately.

5.4 Blinding and procedures for unblinding the study (Not Applicable)

This is an open-label study. Blinding procedures will not be applicable

5.5 Treatments

5.5.1 Identity of investigational product

The ceftazidime and avibactam will be supplied by AstraZeneca. Normal saline solution (0.9%) for CAZ-AVI will be supplied by the study centers. Detailed instructions for the preparation of CAZ-AVI aqueous solution for infusion will be supplied in the Handling Instructions.

Investigational product	Dosage form and strength
Ceftazidime	2 g per vial, powder for injection
Avibactam	600 mg per vial lyophilisate for concentrate for solution for infusion

5.5.2 CAZ-AVI doses and treatment regimens

Patients in Cohort 1 and any Cohort 2 patients weighing ≥40 kg will receive a single IV dose of CAZ-AVI (2000 mg CAZ and 500 mg AVI) administered as a single infusion over a 2-hour period on Day 1. Patients in Cohort 2 weighing <40 kg will receive a single IV dose of CAZ-AVI (50 mg/kg CAZ and 12.5 mg/kg AVI) administered as a single infusion over a 2-hour period on Day 1. These doses are applicable for patients with normal renal function and mild renal insufficiency; for patients with moderate renal insufficiency the dose for both ceftazidime and avibactam should be halved (see Section 3.2 and Handling Instructions). Dosage for patients in Cohorts 3 and 4 will be decided after PK, safety, and tolerability data from Cohorts 1 and 2 are reviewed by the SRC. The doses to be infused in these patients are described in detail in Table 1. The patients will be followed for 48 hours after the end of infusion.

5.5.3 Additional study drug

No additional study doses of CAZ-AVI will be provided during this study.

5.5.4 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines.

5.5.5 Storage

All IV study doses of CAZ-AVI should be kept in a secure place under appropriate storage conditions. The storage conditions will be stated on the study dose of CAZ-AVI labeling and in the Handling Instructions.

5.6 Concomitant and poststudy treatment(s)

Prescribed antibiotics used to treat the patient's infection should be continued or modified according to the investigator's decision.

All prescription and over-the-counter medications being taken by the patient for 5 days prior to study entry (considered prior treatment) and from enrollment through Day 2 and Day 3 (follow-up period) (considered concomitant treatments) must be documented on the appropriate pages of the eCRF.

Other medication that 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 eCRF. Patients who have completed study dose of CAZ-AVI infusion and are in the follow-up period should remain in the study as they are not actively on study dose of CAZ-AVI but being followed for outcomes.

Treatment with ceftazidime within 12 hours of study drug administration, or treatment with ceftazidime within 24 hours of study treatment in patients with renal impairment (CL_{cr} ≤50 mL/min) and treatment with chloramphenicol within 24 hours of administration of study dose of CAZ-AVI is not permitted.

5.7 Study dose compliance

The administration of the study dose of CAZ-AVI should be recorded in the appropriate sections of the eCRF.

The qualified study center personnel at the investigative study center will administer study dose of CAZ-AVI and study compliance will be assured. The dose, date, and exact start and stop time of administration of the study therapy will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

The IV study dose of CAZ-AVI provided for this study will be used only as directed in the study protocol.

Intravenous study dose of CAZ-AVI will be dispensed to the investigator or medically qualified personnel by the study center pharmacist. Intravenous study dose of CAZ-AVI will only be prepared by the study center pharmacists who have been appropriately trained to prepare IV study dose of CAZ-AVI. Written authorization of study personnel to administer CAZ-AVI must be documented for hospital staff in 1 of 2 ways:

- All study staff trained and authorized by the investigator to administer study dose of CAZ-AVI are listed on the Delegation of Authority Log, OR
- The nurse manager(s)/supervisor(s), research manager/coordinator (s) and/or study pharmacists authorized by the investigator are listed on the Delegation of Authority

Log as the person(s) responsible for ensuring that the nursing/pharmacy staff are appropriately trained on study dose of CAZ-AVI preparation/administration prior to preparing/administering it, and for maintaining current and complete training documentation at all times.

Written documentation of training of study dose of CAZ-AVI administration and pharmacy study center personnel will be kept current throughout the study, and ongoing training will be provided by study center personnel as assigned by the investigator on the Delegation of Authority Log. CAZ-AVI administration orders will be given by personnel authorized to do so on the Delegation of Authority Log. Staff will administer the IV study dose of CAZ-AVI according to the orders and will be qualified to administer IV therapy as documented according to the institution's standard operating procedures. It is the investigator's responsibility to ensure that all documentation remains current and complete throughout the study. The investigator will document how he or she will ensure that the staff are adequately trained before they perform the infusion, and he or she will ensure that there is a system in place that will guarantee supervision of the study dose of CAZ-AVI administration process and patient safety (eg, study dose of CAZ-AVI will only be administered to patients under supervision of an investigator). Source documentation should clearly indicate who administered the infusion.

Records of study dose of CAZ-AVI usage should include the identification of the person to whom the study dose of CAZ-AVI was administered, the quantity and date of administration, and a record of unused study dose of CAZ-AVI. The investigator and pharmacist are responsible for maintaining accurate study dose of CAZ-AVI accountability records throughout the study on the relevant forms provided by AstraZeneca/[redacted] Each administration of study dose of CAZ-AVI will be documented in the eCRF.

It is the investigator's responsibility to establish a system for handling study treatments, including investigational medicinal products to ensure that:

- Delivery of such product is correctly received by a responsible person (eg, pharmacist).
- Deliveries are recorded.
- Intravenous study dose of CAZ-AVI is handled and stored safely and properly.
- Intravenous study dose of CAZ-AVI provided for this study is used only as directed in the study protocol.
- Study center personnel account for all therapy received at the study center, dispensed for the patient, and returned to the pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved.

The [redacted] representative performs complete study dose of CAZ-AVI accountability during each monitoring visit, including verifying documentation of receipt, dispensing, return, and

destruction of study dose of CAZ-AVI and consistency of this documentation with physical inventory and interactive voice response system (IVRS)/interactive web response system (IWRS).

At the end of the study, study center personnel account for all unused study doses of CAZ-AVI and for appropriate destruction or return of all unused study doses of CAZ-AVI to a designated facility. It must be possible to reconcile delivery records with records of study dose of CAZ-AVI use and destroyed/returned stock. The investigator or pharmacist should sign certificates of delivery and return.

5.8 Discontinuation of investigational product

In this single-dose study, the study drug infusion should not be discontinued before the 2-hour administration is complete unless the following events occur:

- Patient decision. The patient or the patient's parent(s) or other legally acceptable representative(s) is at any time free to discontinue treatment infusion, without prejudice to further treatment
- Clinically significant AE, as judged by the investigator
- Investigator evaluation and decision.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue CAZ-AVI will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (Sections 6.3.3 and 6.3.4); and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (CAZ-AVI and assessments), without prejudice to further treatment (withdrawal of consent). The patients or parent(s), or other legally acceptable representative(s), will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator at the time of withdrawal. Adverse events and serious adverse events (SAEs) will be followed up (Sections 6.3.3 and 6.3.4).

5.9.1 Rescreening

Patients for whom informed consent is obtained who do not meet the study entry criteria are defined as screen failures and should not be rescreened.

5.9.2 Replacement of patients

A patient who withdraws or is withdrawn from the study before receipt of the full dose of CAZ-AVI, who received a blood or blood component (eg, red blood cells, fresh frozen plasma, or platelets) transfusion within 24 hours prior to the first PK sample or within the PK sampling period (from the first to the last PK sample taken), or who has provided PK samples at <50% of the sampling time points, as indicated in Table 6, Table 7, and Table 8 for Cohort 1, Cohort2, and Cohorts 3 and 4, respectively, will be replaced by an alternate patient. Additional patients will be enrolled in the same manner as all other patients. Patient numbers are not to be reused. Patients who received any amount of CAZ-AVI will be followed for 48 hours after the end of infusion.

A patient who withdraws or is withdrawn from the study after receipt of the full dose of CAZ-AVI and who has provided PK samples at ≥50% of the sampling time points, as indicated in Table 6, Table 7, and Table 8 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively is not to be replaced. Patients who received any amount of CAZ-AVI will be followed for 48 hours after the end of infusion.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

For this study, patient data will be collected by electronic data capture (EDC).

The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided. He or she will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study center.

6.1.1 Electronic data capture

Data will be collected electronically for each study patient by an EDC data management and workflow system. Source data supporting all EDC entries will be recorded in the study patient's medical records as per the site's standard practice. Investigators and study center personnel will be responsible for the data capture and will respond to queries within the EDC data management system.

Correction of any data errors and other such changes will be made by changing or updating the data in the system which also requires the entry of the user's name and a password for each change that will be captured in the electronic audit trail.

Clinical data (including AEs and concomitant medications) will be entered into a data management system that is compliant with Title 21 of the United States Code of Federal Regulations Part 11 and provided by [redacted]. The data system includes password protection and internal quality checks, such as automatic verification range checks, to identify data that

appear to be out of the specified ranges. Programmed edit specifications identify discrepancies in the data that may be addressed by the study center personnel.

6.2 Data collection at enrollment and follow-up

Every effort should be made to collect all the required data, including blood samples and to complete all assessments required for each visit as detailed in the study plan (Table 2) and discussed by visit in Sections 6.2.1 to 6.2.4.

Clinical information obtained as part of standard clinical care before the informed consent is signed may be used as part of the screening and evaluation process.

6.2.1 Screening Visit (Day -1)

At the Screening Visit (Day -1), informed consent from parent(s) or other legally acceptable representative(s), and informed assent from patient (as appropriate) will be obtained. Written assent or documented verbal assent will be obtained according to local requirements prior to starting any study-specific procedures.

Screening assessments will consist of:

1. Obtaining informed consent by the parent(s) or other legally acceptable representative and informed assent from patient (as appropriate).

2. Reviewing inclusion and exclusion criteria.

3. Collecting demographics.

4. Collecting medical and surgical history.

5. Reviewing prior and concomitant medications.

6. Performing complete physical examination, including height and weight. Body mass index (kg/m^2) will be calculated as the ratio of weight in kg/(height in $cm/100)^2$. The 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. Tanner staging of development (refer to Appendix E for further details on Tanner staging) will also be assessed at screening for female patients who have not reached menarche but may reasonably have the potential to become pregnant.

7. Measuring vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature (oral, rectal, or tympanic, as appropriate). Vital signs will be measured at the following time points: before infusion and 2 (± 15 minutes), 4 (± 15 minutes), 6 (± 30 minutes), 12 (± 30 minutes), 24 (± 1 hour) and 48 (± 4 hours) hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken as needed (pro re nata [prn]).

8. Performing a single 12-lead (or as appropriate per investigator decision) ECG prior to obtaining blood samples for laboratory testing. The patient should be resting in a recumbent position for at least 10 minutes prior to the evaluation. The ECG will be recorded on paper.

9. Monitoring for AEs and SAEs.

10. Obtaining a blood sample for clinical chemistry and hematology assessments (see Table 2 for details of laboratory assessments). Prior laboratory assessments should be performed within 48 hours of screening if they are to be used to determine eligibility.

11. Obtaining a urine sample for routine analysis.

12. Creatinine clearance will be determined using the Schwartz formula (refer to Section 4.2, exclusion criterion 3 for further details).

13. Obtaining a blood sample for serum β-hCG for females who have achieved menarche or have reached Tanner stage 3 development (refer to Appendix E for further details on Tanner staging). If the test is positive, the patient must be excluded.

6.2.2 Baseline/Treatment Visit (Day 1)

Day -1 and Day 1 activities may be combined if Screening and Baseline entry requirements can be completed jointly on the same calendar day. The following assessments will be performed on the day of treatment (Day 1):

1. Reviewing prior and concomitant medications.

2. Measuring vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be measured at the following time points: before infusion and 2 (± 15 minutes), 4 (± 15 minutes), 6 (± 30 minutes), 12 (± 30 minutes), 24 (± 1 hour), and 48 (± 4 hours) hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken prn.

3. Monitoring for AEs and SAEs.

4. Infusion of study dose of CAZ-AVI. If all screening and entry requirements are completed on Day -1, the single study dose of CAZ-AVI will be administered on Day 1. Start and stop times of the infusion will be recorded.

5. Performing a single 12-lead (or as appropriate per investigator decision) ECG recording within 15 minutes following the end of the CAZ-AVI infusion. The patient should be resting in a recumbent position for at least 10 minutes prior to the evaluation. The ECG will be recorded on paper.

6. Obtaining PK blood samples according to the detailed schedule in Table 6, Table 7, and Table 8 if study dose of CAZ-AVI is administered on Day 1. To support the use of population PK modeling and simulation to determine the CAZ-AVI dose in pediatric patients and dose determination for Cohorts 3 and 4 the CAZ-AVI the actual dose amount administered, the accurate date and time of start and end of the IV infusion, and the actual blood sample times will be required.

6.2.3 Follow-up assessment (Day 2)

The following assessments will be performed on Day 2 as part of the follow-up visit:

1. Measuring vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be measured at the following time points: preinfusion and 2 (± 15 minutes), 4 (± 15 minutes), 6 (± 30 minutes), 12 (± 30 minutes), 24 (± 1 hour), and 48 (± 4 hours) hours after the end of the CAZ-AVI infusion. Additional vital signs may also be taken prn.

2. Reviewing concomitant medications.

3. Monitoring for AEs and SAEs.

6.2.4 Follow-up assessment (Day 3)

The following assessments will be performed on Day 3 as part of the 48-hour (± 4 hours) follow-up visit:

1. Measuring vital signs including supine blood pressure, pulse rate, respiratory rate, and temperature.

2. Reviewing concomitant medications.

3. Performing complete physical examination, including weight.

4. Monitoring for AEs.

5. Obtaining a blood sample for clinical chemistry and hematology assessments (see Table 2 for details of laboratory assessments).

6. Obtaining a urine sample for routine analysis.

7. Creatinine clearance will be determined using the Schwartz formula (refer to Section 4.2, exclusion criterion 3 for further details).

6.3 Safety

It is of the utmost importance that all study center personnel involved in the study are familiar with the content of this section. The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time after written consent from parent(s) or other legally acceptable representative(s), and verbal informed assent from patient (as appropriate), even if no study treatment has been administered.

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

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study period (ie, Treatment or Follow-up), that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization excluding hospitalization due to worsening or failure of treatment for primary infection under study.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above, including suspected transmission via the IV study therapy for an infectious agent.

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

Cases of liver dysfunction that meet Hy's Law criteria are defined and reported as SAEs, using the "important medical event" serious criterion if no other criteria are applicable (see Appendix D).

6.3.3 Recording of adverse events

Time period for collection of adverse events

Non-serious AEs and SAEs will be collected for each patient from the time of informed consent from parent(s) or other legally acceptable representative(s), and informed assent from patient (as appropriate) (Day -1/Day1) through the follow-up period (Days 2 and 3).

Follow-up of unresolved adverse events

Any AEs that are unresolved 48 hours after the end of infusion of a single study dose of CAZ-AVI (ie, by Day 3) will be followed by the investigator until the event is resolved or stabilized. AstraZeneca [redacted] retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- Date and time when the AE started and stopped
- Maximum intensity of AE
- Whether the AE is serious or not
- Investigator causality rating against the study dose of CAZ-AVI (yes or no)
- Action taken with regard to study dose of CAZ-AVI
- Outcome of the AE.

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

- Onset date (date AE met serious criteria)
- Date the investigator became aware of the SAE
- AE is serious due to:

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

  – Date of death

  – Autopsy performed

  – Primary/secondary cause of death

(b) Life threatening

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

- Date of hospitalization
- Date of discharge

(d) Congenital abnormality or birth defect

(e) Important medical event

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

- Causality assessment in relation to study procedures
- Causality assessment in relation to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Adverse events based on signs and symptoms

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

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline (Day -1 or Day1) in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AEs.

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

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

6.3.3.1 Assessment of severity

The investigator will assess the severity of each AE by recording a severity rating on the appropriate AE screen(s) of the patient's eCRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 6.3.4). Severity will be assessed according to the scale in Table 3.

Table 3 Guidelines for Severity Assessments

Mild	Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention
Moderate	Discomfort that interferes with usual activities and may require minimal intervention
Severe	Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention

6.3.3.2 Relationship to study drug

The investigator will assess causal relationship between the study dose of CAZ-AVI and each AE, and answer 'yes' or 'no' to the question 'Is there is a reasonable possibility that the event may have been caused by the IV study dose of CAZ-AVI?' If answered yes, there is a possible or probable relationship, or if answered no, the relationship is unlikely as described in Table 4. The causality must be recorded on the appropriate AE reporting screen(s) of the patient's eCRF.

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

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

Table 4 Guidelines for the Assessment of the Relationship of an Adverse Event to Study Drug

Yes	There is a possible or probable relationship (ie, there is reasonable or strong temporal relationship, and the events are unlikely to be attributable to other drugs, underlying diseases, or other factors)
No	The relationship is unlikely or nonexistent (ie, there is no strong temporal relationship and/or the use of other drugs, underlying diseases, or other factors provide plausible explanations for the event), or the patient did not take the study drug

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study dose of CAZ-AVI, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other study center personnel will inform appropriate AstraZeneca [redacted] representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca/[redacted] representatives will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 3 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately by the investigator. Investigators or other study center personnel inform AstraZeneca [redacted] representatives of any follow-up information on a previously reported SAE immediately, or no later than 24 hours of when he or she becomes aware of it (see Section 13.1 for contact details for reporting medical emergencies and SAEs).

If the EDC system is not available, then the investigator or other study center personnel reports the SAE to the appropriate AstraZeneca/[redacted] representative by telephone.

The AstraZeneca [redacted] representative will advise the investigator or study center personnel how to proceed.

6.3.5 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in Table 2. An indwelling catheter will be used for repeated sampling, to minimize the discomfort.

Blood and urine samples will be processed at the local laboratories at each site. Each site will be required to provide their normal ranges for the pediatric population, and the dates these were established. Reference ranges from the local institution or ± 5% of those found in the Nelson (Kliegman et al 2011) will be used to evaluate the laboratory data.

Table 5 presents the safety laboratory variables that will be measured in this study.

Table 5 Safety Laboratory Tests

Comprehensive Metabolic Panel	Hematology	Urinalysis
Magnesium	Hematocrit[a]	Appearance (color, clarity)
Bicarbonate	Hemoglobin	Bilirubin
Sodium	Erythrocyte count	Glucose
Potassium	Mean cell volume	Ketones
Phosphorus	Mean cell hemoglobin	Leukocyte esterase
Chloride	Leukocyte count (WBC)	Nitrite
Calcium	Neutrophils	pH
Alkaline phosphatase	Lymphocytes	Protein
GGT	Monocytes	Specific gravity
ALT	Eosinophils	Urobilinogen
AST	Basophils	Microscopic examination
Creatine kinase	Platelets	• Red blood cells
LDH	**Coagulation[b]**	• White blood cells
Total bilirubin	INR	• Casts
Indirect bilirubin	PTT	• Crystals
Glucose, nonfasting		• Bacteria, yeast cells, or parasites
Creatinine		

[a] If a patient's hemoglobin or hematocrit decreases significantly (in the investigator's judgment) after administration of the CAZ-AVI infusion, a workup for hemolytic anemia should be performed per standard of care.

[b] Coagulation studies in Cohort 4 will only be performed if judged necessary by the investigator and/or the institute management protocol.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time; WBC, white blood cells.

The criteria for potentially clinically significant clinical laboratory tests are presented in Appendix F.

A potential Hy's Law case is defined as any situation where a study patient has an increase in both AST **or** ALT ≥3 × ULN, **and** total bilirubin ≥ 2 × ULN, irrespective of ALP, at any point during the study. The elevations do not have to occur at the same time or within a specified timeframe.

Hy's Law should be considered satisfied if ALT is increased 3 × ULN and total bilirubin is increased 2 × ULN in the absence of a significant increase in ALP and in the absence of an alternative diagnosis that explains the increase in total bilirubin.

The process described in Appendix D, 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law', will be applied to any patient who meets the criteria for a potential Hy's Law case or the discontinuation criteria. A thorough investigation into other potential causes must be conducted and follow-up monitoring as detailed in Appendix D. This monitoring includes the liver CRFs and must be filled out by the investigator.

For blood volume, see Section 7.1.

6.3.6 Physical examination

The timing of individual examinations is indicated in Table 2.

A complete physical examination will be performed and will include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, respiratory, cardiovascular, abdomen, musculoskeletal (including spine and extremities) and neurological systems, including height and weight. Body mass index (kg/m^2) will be calculated as the ratio of weight in kg/(height in $cm/100)^2$. The BMI will only be calculated at screening (Day -1/Day1). The BMI will not be calculated for children <2 years of age (Cohort 4) as BMI is not considered a screening tool for healthy weight in children under 2. 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.

6.3.7 Electrocardiogram

A single 12-lead (or as appropriate per investigator decision) ECG recording will be performed at the times indicated in Table 2. At screening, the ECG will be performed prior to obtaining blood samples for laboratory testing. The Day 1 ECG will be performed within 15 minutes following the end of the CAZ-AVI 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.

6.3.8 Vital signs

Vital signs will be measured as required as well as at the time intervals indicated in Table 2.

6.3.8.1 Pulse rate and blood pressure

Supine blood pressure, respiratory rate and pulse rate will be measured using a semiautomatic blood pressure recording device with an appropriate cuff size. 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 2.

6.3.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in Table 2 and the actual time of body temperature collection will be recorded. For each individual patient, the method of temperature measurement (oral, rectal, or tympanic, as appropriate) ideally should be consistent for the duration of the study.

6.3.8.3 Respiratory rate

Respiratory rate will be measured in breaths per minute at the times indicated in Table 2.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Sparse PK sampling, especially for pediatric patients younger than 12 years of age, has been employed to minimize blood sampling requirements. The use of analgesic creams to minimize discomfort will be considered. An indwelling catheter will be used for the repeated PK sampling, to minimize the discomfort; this catheter/port will not be used for administration of any medication. Prior to obtaining each sample the saline used to flush the catheter will be discarded.

6.4.1.1 PK Blood sample collection

Samples may be obtained by venipuncture, through a saline/heparin lock, peripherally inserted central catheter, or through a central line. A site other than the infusion site is preferred; however, samples may be drawn from the same site as the infusion site, by use of a multi-lumen catheter, with the exception of the blood drawn immediately after infusion.

In cases where a multi-lumen catheter is used for drug delivery and blood draws, the PK blood sample must be taken from a lumen that was NOT used for drug delivery. Detailed instructions for PK sample collection will be provided in the Laboratory Manual.

Venous blood samples for the determination of CAZ-AVI PK for each cohort are presented in Table 6, Table 7, and Table 8 for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively. These time points may be amended in response to analysis of the PK data from previous cohorts, if appropriate (ie, with increased understanding of the PK of CAZ-AVI in pediatric patients). However, blood volumes will not be exceeded. The actual date and time of collection of each sample will be recorded in the CRF.

Detailed instructions for the collection, labeling, storage, and shipment of samples will be provided in the Laboratory Manual.

For blood volume see Section 7.1.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses may be reported separately from the CSR.

Table 6 Cohort 1 - Schedule for PK Assessments

Nominal sampling time	Blood volume
End of CAZ-AVI infusion ± 5 minutes after the end of infusion	1 mL
30 minutes after the end of the CAZ-AVI infusion ± 5 minutes	1 mL
1.5 hours after the end of the CAZ-AVI infusion ± 15 minutes	1 mL
3 hours after the end of the CAZ-AVI infusion ± 30minutes	1 mL
6 hours after the end of the CAZ-AVI infusion ± 30 minutes	1 mL
10 hours after the end of the CAZ-AVI infusion ± 30 minutes	1 mL
22 hours after the end of the CAZ-AVI infusion ± 30 minutes	1 mL

Table 7 Cohort 2 - Schedule for PK Assessments

Sampling time window	Blood volume
End of CAZ-AVI infusion ± 5 minutes after the end of infusion	1 mL
15 to 45 minutes after the end of the CAZ-AVI infusion	1 mL
1 to 2 hours after the end of the CAZ-AVI infusion	1 mL
2 to 3 hours after the end of the CAZ-AVI infusion	1 mL
4 to 6 hours after the end of the CAZ-AVI infusion	1 mL
11 to 13 hours after the end of the CAZ-AVI infusion	1 mL

Table 8 Cohorts 3 and 4 - Schedule for PK Assessments

Sampling time window	Blood volume
End of CAZ-AVI infusion ± 5 minutes after the end of infusion	0.5 mL
15 to 45 minutes after the end of the CAZ-AVI infusion	0.5 mL
2 to 3 hours after the end of the CAZ-AVI infusion	0.5 mL
4 to 6 hours after the end of the CAZ-AVI infusion	0.5 mL

6.4.2 Determination of drug concentration

Samples for determination of ceftazidime and avibactam in plasma will be analyzed by [redacted] on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate validated bioanalytical method. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

Results will only be reported for samples shipped within a timeframe for which the stability of ceftazidime and avibactam in the samples has been validated and shown to be acceptable.

6.5 Pharmacogenetics (Not Applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is presented in Table 9.

Table 9 Volume of Blood to be Drawn From Each Patient

Assessment		Sample volume (mL) All Cohorts	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2	2	4
	Hematology	2	2	4
Pharmacokinetics Cohort 1 (≥12 to <18 years)		1	7	7
Pharmacokinetics Cohort 2 (≥6 to <12 years)		1	6	6
Pharmacokinetics Cohort 3 (≥2 to <6 years)		0.5	4	2
Pharmacokinetics Cohort 4 (≥3 months to <2 years)		0.5	4	2
Total Cohort 1				15
Total Cohort 2				14
Total Cohort 3				10
Total Cohort 4				10

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Pharmacokinetic samples

Pharmacokinetic samples will be anonymized by pooling or will be disposed of after the CSR has been finalized. Pooled, anonymized samples may be used for analytical method development and/or validation and will be retained for no more than 5 years after the CSR has been finalized.

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.

Key samples for investigation of metabolite identification and/or analysis may be retained at AstraZeneca, at the central laboratory, or possibly a contract research organization on behalf of AstraZeneca for a maximum of 5 years following the finalization of the CSR. The results from the investigation will not be reported in the CSR but separately in a metabolism report.

7.3 Labeling and shipment of biohazard samples

The investigator ensures that samples are labeled and shipped in accordance with the laboratory manual and the Infectious Substances, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria [see Appendix C, International Airline Transportation Association 6.2 Guidance Document]).

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of biological samples collected from the patients and stored at the center until shipment or disposal (where appropriate). The investigator at each center will also keep documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

[redacted] keeps oversight of the samples during the study through monitoring and AstraZeneca keeps oversight of the entire life cycle through internal procedures and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for PK analysis samples

If a patient withdraws consent to the use of PK samples, the samples will be disposed of or destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the PK samples is an integral part of the study, then the patient is withdrawn from further study participation.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of PK samples is notified immediately to AstraZeneca
- Ensures that PK samples from that patient, if stored at the study center, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study center

- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central and bioanalytical laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study center.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1) Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document that incorporates) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An institutional review board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study center staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to AstraZeneca/[redacted] before enrollment of any patient into the study. The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca/[redacted] should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be reapproved by the IRB annually.

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

AstraZeneca [redacted] will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRBs, and investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

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

8.4 Informed consent

The investigator(s) at each center will:

- Ensure that each patient, parent or legally acceptable representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient, parent or legally acceptable representative is notified that they are free to discontinue from the study at any time
- Ensure that each patient, parent or legally acceptable representative is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient, parent or legally acceptable representative provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file
- Ensure a copy of the signed ICF(s) is/are given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised CSP). Decisions on doses to be used in Cohorts 3 and 4, and modifications to cohort size or PK sampling times will be appropriately documented and communicated to the IRBs and all study centers.

The amendment is to be approved by the relevant ethics committee (EC) and, if applicable, the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca [redacted] will distribute any subsequent amendments and new versions of the protocol to each investigator(s). For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca [redacted] and the center's IRB are to approve the revised ICF before the revised form is used.

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

8.6 Audits and inspections

Authorized representatives of AstraZeneca/[redacted] any regulatory authority, or an EC may perform audits or inspections at the center, 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, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca [redacted] immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT

9.1 Prestudy activities

Before the first patient is entered into the study, it is necessary for a representative of [redacted] to visit the investigational study center to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca [redacted]. This will be documented in a CSA between AstraZeneca [redacted] and the investigator.

9.2 Training of study center personnel

Before the first patient is entered into the study, a [redacted] representative will conduct an on-site initiation visit to review and discuss the requirements of this CSP and related documents with

the investigational staff and also train them in any study-specific procedures and system(s) utilized and review training of staff for the EDC system utilized in this study.

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

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

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study center, including telephone contact and on-site visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the study canter personnel are adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that the IV study dose of CAZ-AVI accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts and electronic and paper medical records)
- Ensure withdrawal of informed consent to the use of the patient's PK samples is reported and PK samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient, parent or legally acceptable representative
- Ensure Cohort 3 and 4 dose decisions and any other cohort modifications or safety findings are communicated to the IRB.

The [redacted] representative will be available between visits if the investigator(s) or other study center personnel at the center need information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The investigator at each center 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 CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca [redacted] and the investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as the last visit of the last patient participating in the study.

The study is expected to enroll the first patient in the third quarter of [redacted] and the estimated date of last patient completed is the third quarter of [redacted].

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

Completion of the study

Upon terminating the study, the investigator/sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the study center in accordance with the institution's rules. The head of the study center, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca. Notification of study termination should be timed in a manner that will allow sites to access patients' records for study purposes after last patient last visit in order to address any potential data queries.

10. DATA MANAGEMENT

Data management will be performed by [redacted].

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

Adverse events and medical and surgical history will be classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA), (Version 14 or

higher). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by [redacted].

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 data validation manual. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and verified, the investigator will electronically sign the data, a clean file will be declared by data management, and the data will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variables

All nonserious AEs and SAEs will be collected for each patient from the time when informed consent is obtained up to 48 hours after the end of infusion. Any AEs that are unresolved at the patient's last AE assessment will be followed by the investigator until the event is resolved or stabilized. Adverse events that occur before dosing will be reported separately.

11.1.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuations due to AEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs, and other safety assessments will be performed for identification of other significant AEs.

Examples of these are marked hematological and other laboratory abnormalities and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2 Calculation or derivation of patient-reported outcome variables (Not Applicable)

11.3 Calculation or derivation of pharmacokinetic variables

The PK analysis set will be used in the noncompartmental analysis (NCA), population PK/PD analysis, and in the summary presentation of the concentration and PK parameters.

A listing of ceftazidime and avibactam collection times and plasma concentration data by patient and cohort for each analyte will be provided. For Cohort 1, the collection times will be the nominal sampling times specified in the protocol and the deviation of the actual sampling times from the nominal sampling times will be also provided. For Cohorts 2 through 4, the collection times will be the sampling windows specified in the protocol.

For Cohorts 1 through 4, the plasma concentration will be summarized; for Cohort 1 it will be summarized by nominal sampling time and for Cohorts 2, 3, and 4 it will be summarized by sampling time window. In addition, for Cohort 1, NCA of PK parameters will be summarized. Pharmacokinetic variables (ceftazidime and avibactam plasma concentrations and PK parameters, when applicable) will be summarized by analyte and measurement time using appropriate descriptive statistics (eg, n, mean, standard deviation [SD], minimum, median, maximum, geometric mean [gmean], lower and upper SD bounds [gmean ± SD], and coefficient of variation [CV]).

The gmean is calculated as exp(u) where u is the arithmetic mean calculated from data on a log(base e) scale. The CV is calculated as $100\sqrt{(\exp(s^2)-1)}$ where s is the SD of the data on a log(base e) scale. The lower and upper SD bounds [gmean ± SD] are defined as exp(u ± s). Mean, SD, gmean and CV will not be calculated for t_{max}.

For descriptive statistics, nonquantifiable (NQ) values of plasma concentrations will be handled as follows:

- If, at a given time point, 50% or fewer of the plasma concentrations are NQ, the mean, SD, gmean, gmean ± SD, and CV will be calculated by substituting the limit of quantification (LOQ) for values which are NQ. If the calculation of the gmean minus SD results in a value less than the LOQ, NQ will be displayed

- If more than 50%, but not all, of the concentrations are NQ, the mean, SD, gmean, gmean ± SD, and CV will be reported as not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ

- If all concentrations are NQ, the gmean and mean will be reported as NQ and the gmean ± SD, SD and CV as NC

- The number of quantifiable values (n above LOQ) will be reported for each time point. Individual plasma concentration profiles will be presented graphically on both linear and semilogarithmic scales, showing all patients on a single plot for each cohort/analyte.

Individual plasma concentration profiles, using the PK analysis set for Cohorts 1 to 4, will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all patients on a single plot for each cohort and analyte. Geometric mean concentration-time profiles (with lower/upper SD bounds as defined above) will be presented

on both linear and semilogarithmic scales using nominal time for both ceftazidime and avibactam for Cohort 1. Additional graphical presentations of PK data may be presented at the discretion of the PK scientist.

The NCA PK analyses will be performed at [redacted]. The population PK/PD modeling and simulation analyses will be performed at AstraZeneca R&D, and reported in a stand-alone report outside of the CSR.

The actual sampling times will be used in the PK calculations. For the calculation of the PK parameters by NCA, all NQ values that occur before the first measureable concentration will be replaced with zero (0). If an NQ occurs between two measureable concentrations, it will be set to missing. The NQ values that occur at the end of the profile will be set to zero (0). The PK parameters will be determined using standard noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp, Mountain View, California).

The NCA PK parameters will be calculated for Cohort 1. The following PK parameters will be determined for ceftazidime and avibactam for Cohort 1, if the data allow, and will be listed and summarized:

- C_{max} (μg/mL) following a single dose administration
- Time to C_{max} (t_{max}; in hours) following a single dose administration
- AUC calculated using the linear-up/log-down trapezoidal method from zero to:
  - 8 hours after the end of infusion ($AUC_{[0-8]}$)
  - the time of the last quantifiable concentration ($AUC_{[0-t]}$)
  - extrapolated to infinity ($AUC_{[0-\infty]}$)
- Time of last quantifiable plasma concentration (t_{last}; in hours) taken directly from the individual concentration-time curve
- Terminal plasma half-life ($t_{½}$; in hours) estimated as $(\ln 2)/\lambda_z$
- Systemic plasma clearance (CL; L/hour) estimated as dose divided by $AUC_{(0-\infty)}$
- Volume of distribution at the terminal phase (V_z; L) estimated by dividing the systemic clearance by λ_z
- Volume of distribution at steady state (V_{ss}, L) estimated by multiplying the mean residence time (MRT) by the CL
- Terminal elimination phase rate constant (λ_z).

These NCA PK parameters will also be summarized by descriptive statistics as described above.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression to determine $t_{½}$ ($t_{½\lambda Z,}$ interval; in hours)
- Number of data points ($t_{½}$; N) included in the log-linear regression analysis to determine $t_{½}$
- Coefficient of determination (Rsq) for calculation of λ_z. If Rsq is <0.8, λ_z and related parameters ($t_{½}$, $AUC_{(0-\infty)}$, CL, V_z, V_{ss} and MRT) will not be reported
- Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation ($\%AUC_{ex}$); if $\%AUC_{ex}$ is >20%, then $AUC_{(0-\infty)}$, and the related parameters ($t_{½}$, CL, V_Z, V_{SS}, and MRT) will not be reported.

The PK variables for Cohort 1 (avibactam and ceftazidime plasma concentrations and PK parameters, when applicable) will be summarized by analyte and nominal time using appropriate descriptive statistics (eg, n, mean, SD, minimum, median, maximum, geometric mean, and CV). The PK concentrations for Cohorts 2, 3, and 4 will be summarized by sampling time window.

Further, the avibactam and ceftazidime concentration, pediatric patient demographics, disease status data, etc., from Cohorts 1 through 4 will be combined with the data from appropriate previous clinical studies in adults for a population PK modeling analysis. The actual dosing and plasma sampling times will be used for the analysis. Individual compartmental PK parameters for pediatric patients with available avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual noncompartmental PK parameters such as C_{max}, minimum plasma concentration (C_{min}), area under the plasma concentration-time curves at steady-state (AUC_{ss}), and elimination half-life ($t_{1/2}$), will be derived from the predicted avibactam and ceftazidime concentration time courses. The developed population PK model will be used to conduct the simulation of probability of PK/PD target attainment to help to justify the dose selection for the phase III studies in pediatric patients with cIAI or cUTI. A stand-alone population PK modeling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report outside of CSR.

11.3.1 Population analysis of pharmacokinetic/pharmacodynamic variables

The population PK analysis will be reported separately.

11.4 Calculation or derivation of pharmacogenetic variables (Not Applicable)

11.5 Calculation or derivation of health economic variables (Not Applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Pharmacokinetic analysis set

The PK Analysis set will consist of all patients who received IV study dose of CAZ-AVI and have at least one postdose blood sample.

12.1.2 Safety analysis set

All patients who received any amount of IV study dose of CAZ-AVI will be included in the safety population.

12.2 Methods of statistical analyses

12.2.1 Safety analysis

Unless otherwise specified, the safety analysis set will be used for summaries and listings. No inferential statistical tests will be performed for any safety analyses.

Safety assessments will be based on AE reports and the results of vital sign measurements, physical examinations, ECGs, and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

All recorded AEs will be listed and tabulated by system organ class, preferred term and for each cohort. Tabulations and listings of data for vital signs, physical examinations, clinical laboratory tests, and ECGs will be presented. The data will be summarized for the observed value by cohort and scheduled assessment and for corresponding change from baseline values. In addition, any significant results for these data will be listed by cohort.

For clinical laboratory values and vital signs, listings of values for each patient will be presented with abnormal or out-of-range values flagged.

For the reporting of descriptive statistics of safety variables (ie, AEs, clinical laboratory values, vital sign values, and ECG values), the mean and median values will be presented to 1 more decimal precision as the source data, SD will be presented to 2 more decimal precision, and minimum and maximum values will be presented to the same precision as the source data, and percentages will be presented with 1 decimal precision.

Adverse events occurring from the start of study dose of CAZ-AVI infusion up to 48 hours after the end of infusion will be summarized by preferred term and system organ class using MedDRA vocabulary (Version 14.0 or higher) by cohort.

12.2.2 Interim report

An interim report may be prepared to summarize existing cohort data at the time of the phase III submission, if required.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

12.4 Safety review committee

An SRC will assess PK, safety and tolerability from each cohort. All available patient data from Cohorts 1 and 2, which will be run in parallel, will be reviewed by the SRC prior to proceeding to Cohort 3. All available patient data from each subsequent cohort will be reviewed by the SRC; however, a minimum of 8 evaluable patients for each cohort is required to support the SRC in making decisions regarding safety, tolerability and dosing recommendations for the next planned cohort.

For Cohorts 3 and 4, PK data of ceftazidime and avibactam from the previous cohorts will be used to update the PK model and determine the dose for younger patients. The SRC will consider all available safety, tolerability and modeled dose determinations for Cohort 3 and 4 dose decisions. Data from 2 nonclinical dose-ranging studies conducted in juvenile animals will be available prior to the start of Cohort 4. Cohort 4 will not be initiated until the nonclinical data are available.

The SRC will consist of the study team physician/clinical pharmacology physician, international coordinating investigator or delegate, global safety physician or delegate, medical science director or delegate and the pharmacokineticist and pharmacometrician or delegates that have reviewed and analyzed the PK results. With the exception of the international coordinating investigator or delegate, all members of the SRC will be members of the sponsor organization. Other team members may be asked to join as needed.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and SAE contacts

The investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4. In the case of urgent safety concerns, the investigator should contact the [redacted] physician via the numbers listed below.

In the event of an SAE-related question, the investigator should contact the [redacted] Hotline number.

Region	Role in the study	Address & telephone number
North America	Medical Monitor	[redacted]
	[redacted] Hotline 24-hour Service	[redacted]

13.2 Overdose

Overdose is defined as a dose administered to a patient in excess of that specified in the AstraZeneca Core Data Sheet or Investigator's Brochure for that product, unless specified otherwise in the CSP. Overdose does not automatically make an AE serious but if the consequences of the overdose are serious for example death or hospitalization, 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 eCRF and in the Overdose eCRF module
- An overdose without associated symptoms is only reported in the Overdose eCRF module.

If an overdose on an AstraZeneca study dose of CAZ-AVI occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting time lines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

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

13.3.1 Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study dose of CAZ-AVI 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 investigators or other site personnel inform appropriate AstraZeneca/[redacted] representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca [redacted] representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca patient safety data entry site within 1 or 3 days for SAEs (see Section 6.3.4) and within 30 days for all other pregnancies.

The same time lines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT (also a paper CRF) is used to report the outcome of the pregnancy. These modules are not entered into the clinical database.

13.3.2 Paternal exposure

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 study dose of CAZ-AVI administration until 7 days after the infusion of study dose of CAZ-AVI must be reported to AstraZeneca within 5 days and documented as specified in Section 13.3.1.

14. LIST OF REFERENCES

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