AstraZeneca

Revised Clinical Study Protocol

Drug Substance	CAZ104
Study Code	D4280C00011
Edition Number	2
Date	

A Phase I, 2-Part, Open-Label, Pharmacokinetic and Drug-Drug Interaction Study of CAZ104 (Avibactam and Ceftazidime in Healthy Subjects)

Sponsor:

AstraZeneca Research and Development site representative

_____ _____

Date

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			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

AstraZeneca

PROTOCOL SYNOPSIS

A Phase I, 2-Part, Open-Label, Pharmacokinetic and Drug-Drug Interaction Study of CAZ104 (Avibactam and Ceftazidime in Healthy Subjects)

Chief Investigator

Principal Investigator

Study centre and number of subjects planned

This study will be conducted at 2 study centres,
The study will be conducted in 2 parts. Approximately 16 subjects will be enrolled in Part A to ensure 12 evaluable subjects and approximately 27 subjects will be enrolled in Part B to ensure 24 evaluable subjects.

Study period	Phase of development
Estimated date of first subject enrolled	Clinical Pharmacology (Phase I)
Estimated date of last subject completed	

Objectives

Primary objectives

- Part A: to investigate the single- and multiple-dose pharmacokinetics of avibactam and ceftazidime following a single administration of avibactam plus ceftazidime (CAZ104) on Days 1 and 11 and multiple administrations every 8 hours from Day 2 to Day 10
- Part B: to investigate the effect on the pharmacokinetics of co-administering avibactam plus ceftazidime (CAZ104) compared to administration of the individual components (ceftazidime and avibactam alone)

Secondary objective

- To assess safety and tolerability of avibactam, ceftazidime, and CAZ104 when administered as a 2-hour infusion every 8 hours

Exploratory objective

- To investigate the presence and/or identity of drug metabolites of avibactam

The exploratory results will not be reported in the Clinical Study Report.

Study design

This study will be conducted in 2 parts (Part A and Part B).

Part A is an open-label, single-treatment study in approximately 16 healthy male and female subjects. The investigational product will be administered as a 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime (CAZ104) once on the morning of Day 1 and every 8 hours from Day 2 to Day 10 (inclusive) (3 infusions per day). Subjects will receive a single infusion on Day 11. Serial blood samples for pharmacokinetic assessments will be collected on Day 1, Day 4 (following the morning dose), and Day 11, and urine samples for pharmacokinetic assessments will be collected on Day 1 and Day 11.

Part B is an open-label, randomised, 3-way cross-over study in approximately 27 healthy male and female subjects. Subjects will be randomised to 3 treatment sequences and all subjects will receive all 3 treatments (Treatment A, Treatment B, and Treatment C). Treatment A will be a 2-hour infusion of 500 mg avibactam, Treatment B will be a 2-hour infusion of 2000 mg ceftazidime, and Treatment C will be a 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime (CAZ104). In each cross-over period (Period 1, Period 2, and Period 3) subjects will receive a single infusion on the morning of Day 1 and every 8 hours from Day 2 to Day 3 (inclusive) (3 infusions per day). Subjects will receive a single infusion on Day 4. Serial blood and urine samples for pharmacokinetic assessments will be collected on Day 1 and Day 4 of each treatment period. The treatment periods will be separated by a wash-out period of at least 2 days.

Target subject population

Healthy male and post-menopausal or surgically sterile female subjects aged 18 to 50 years (inclusive) with a body mass index between 19 and 30 kg/m^2.

Investigational product, dosage, and mode of administration

Part A

500 mg avibactam and 2000 mg ceftazidime (CAZ104) intravenously over 2 hours from Day 1 to Day 11, total 29 infusions

Part B

500 mg avibactam intravenously over 2 hours from Day 1 to Day 4, total 8 infusions

2000 mg ceftazidime intravenously over 2 hours from Day 1 to Day 4, total 8 infusions

500 mg avibactam and 2000 mg ceftazidime (CAZ104) intravenously over 2 hours from Day 1 to Day 4, total 8 infusions

Comparator, dosage, and mode of administration

None

Duration of treatment

Part A

This part will comprise 3 visits: Visit 1 (screening), Visit 2 (treatment), and Visit 3 (follow-up). Subjects will be screened for eligibility within 28 days of Visit 2, when subjects will be admitted to the study centre on Day -1. Subjects will be residential in the study centre until Day 12 and will return 7 to 10 days after the last investigational product administration at Visit 2 for follow-up.

Part B

This part will comprise 5 visits: Visit 1 (screening), Visit 2 (Period 1), Visit 3 (Period 2), Visit 4 (Period 3), and Visit 5 (follow-up). Subjects will be screened for eligibility within 28 days of Visit 2, when subjects will be admitted to the study centre on Day -1. Subjects will be residential in the study centre until Day 5. After a wash-out period of at least 2 days, subjects will return to the study centre on Day -1 of Visit 3 for Period 2, again on Day -1 of Visit 4 for Period 3, and 7 to 10 days after the last investigational product administration at Visit 4 for follow-up.

Outcome variables:

- Pharmacokinetic (primary)

  In Parts A and B, on serial pharmacokinetic sampling days, where the data allow, the following pharmacokinetic parameters will be calculated for avibactam and ceftazidime when applicable:

  Plasma: maximum plasma concentration (C_{max}), time of C_{max} (t_{max}), minimum plasma concentration (C_{min}), time of C_{min} (t_{min}), last quantifiable plasma concentration (C_{last}), time of C_{last} (t_{last}), average plasma concentration during a dosing interval (C_{avg}), fluctuation index, area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration [$AUC_{(0-t)}$], from zero to infinity (AUC, Day 1 only), during the dosing interval [$AUC_{(0-\tau)}$], terminal half-life ($t_{1/2}$), systemic plasma clearance (CL), volume of distribution at

steady-state (V_{ss}), and at the terminal phase (V_z), accumulation ratio for C_{max} and $AUC_{(0-\tau)}$, and linearity index

Urine: amount of drug excreted unchanged into urine from zero to time t [$A_{e(0-t)}$], fraction of dose excreted unchanged into urine (f_e; % dose), and renal clearance (CL_R)

Additional pharmacokinetic parameters may be determined if deemed appropriate

- Safety

  Adverse events, clinical laboratory assessments, vital signs, safety electrocardiogram, physical examination, and withdrawals

Statistical methods

Pharmacokinetic variables (avibactam and ceftazidime plasma concentrations and urine amounts and pharmacokinetic parameters) will be summarised using appropriate descriptive statistics.

An exploratory evaluation of achievement of steady-state will be performed graphically.

For Part B only, treatments will be compared between test (Treatment C) and reference (Treatments A - for avibactam only, B – for ceftazidime only). Analyses will be performed by day (1 and 4) with a linear mixed-effects model using the logarithm of AUC (Day 1 only), $AUC_{(0-\tau)}$, (Day 4 only), and C_{max}. Geometric means together with 95% confidence intervals will be estimated and presented. Also, ratios of geometric means together with 90% confidence intervals will be estimated and presented.

Safety variables will be summarised with descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
%AUCex	The percent of area under the concentration-time curve which is extrapolated to infinity
AE	Adverse event (see definition in Section 6.3.1)
$A_{e(0-t)}$	Amount of drug excreted unchanged into urine from zero to time t
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AmpC	Ambler Class C
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration
$AUC_{(0-\tau)}$	Area under the plasma concentration-time curve during the dosing interval
BLQ	Below the limit of quantification
BMI	Body mass index
C_{avg}	Calculated average plasma concentration during a dosing interval
CAZ104	Ceftazidime avibactam
CI	Confidence interval
cIAI	Complicated intra-abdominal infections
CL	Systemic plasma clearance
C_{last}	Last quantifiable plasma concentration
CL_R	Renal clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CPA	Clinical Pharmacology Alliance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTX	Cefotaximase
cUTI	Complicated urinary tract infections
CV%	Geometric coefficient of variation (%)

Abbreviation or special term	Explanation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
dECG	Digital electrocardiogram
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESBL	Extended-spectrum β-lactamases
f_e	Fraction of dose excreted unchanged into urine
FI	Fluctuation index
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
KPC	A type of Class A β-lactamase (*Klebsiella pneumoniae* carbapenemase)
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
NA	Not applicable
ND	Not determined
OAE	Other significant adverse event (see definition in Section 11.1.1)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

Abbreviation or special term	Explanation
$RAUC_{(0-\tau)}$	Accumulation ratio for $AUC_{(0-\tau)}$
RC_{max}	Accumulation ratio for C_{max}
Rsq	Coefficient of determination
SAE	Serious adverse event (see definition in Section 6.3.2)
SBP	Systolic blood pressure
SD	Standard deviation
SHV	A type of Class A β-lactamase
$t_{1/2}$	Terminal half-life
TEM	A type of Class A β-lactamase (Temoniera)
t_{last}	Time of last quantifiable plasma concentration
t_{max}	Time of maximum plasma concentration
t_{min}	Time of minimum plasma concentration
ULN	Upper limit of normal
USA	United States of America
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 β-lactam and β-lactamases resistant Gram-negative bacteria

Beta (β)-lactamases are enzymes that are a major contributing factor to β-lactam resistance among gram-negative bacteria. Although over 890 individual enzymes have been described, only a small number of these are associated with the majority of penicillin, cephalosporin, and carbapenem resistance in gram-negative pathogens (Louie et al 2010). The most important β-lactamases of clinical relevance are enzymes that utilise serine at their active site to facilitate β-lactam hydrolysis (Rossolini and Docquier 2006), these include: 1) the Ambler Class C (AmpC)-type cephalosporinases in the *Enterobacteriaceae* and *Pseudomonas aeruginosa,* enzymes that may be produced either constitutively (chromosomally encoded) or via plasmids; 2) the common TEM and SHV β-lactamases with hydrolytic activity against first and second generation cephalosporins; 3) the extended-spectrum β-lactamases (ESBLs) that hydrolyse later generation cephalosporins and monobactams; and 4) the carbapenemases that confer resistance to most β-lactams, including carbapenems and the monobactams.

Among each of these groups of enzymes, only a few β-lactamases have become prominent; the majority of reports are of a single enzyme from a single, localised, clinical isolate, with characterisation confined to a unique amino acid sequence and minimal, if any, functional information (Louie et al 2010). The AmpC β-lactamases differ slightly in structural properties, but all tend to have similar cephalosporinase activities. TEM-1 and SHV-1 β-lactamases remain important, as they continue to be identified in many clinical isolates. Within the ESBL family, the cefotaximase (CTX)-M enzymes have become well established worldwide, with CTX-M-15 most frequently identified globally, followed by CTX-M-1, CTX-M-3, and CTX-M-14. Occasional ESBLs in the TEM and SHV families are still identified, but are found less often than CTX-M enzymes. The serine carbapenemases, especially *Klebsiella pneumoniae* carbapenemase (KPC)-2 and KPC-3, produced in many species of the *Enterobacteriaceae* and also in non-fermentative bacteria, have become threats to the use of β-lactams in virtually all parts of the world (Schwaber and Carmeli 2008).

β-lactam-resistant infections are appearing in both the hospital and community settings. Since many β-lactamases are now carried on transferable elements, they can be expected to proliferate throughout gram-negative pathogens, with multiple β-lactamases produced in each organism. One therapeutic approach that would allow the continued use of β-lactam antibiotics would be the introduction of a broad-spectrum β-lactamase inhibitor that inactivates multiple groups of enzymes.

1.1.2 Ceftazidime and β-lactamase mediated resistance to ceftazidime

Ceftazidime is an injectable third generation cephalosporin that has been in clinical use worldwide for more than 20 years. Its spectrum of antibacterial activity includes gram-negative organisms (including *Pseudomonas aeruginosa*), and with lower potency, some gram-positive organisms. It is approved for the treatment of lower respiratory tract infections,

skin and skin-structure infections, urinary tract infections, bacterial septicaemia, bone, and joint infections, gynaecological infections, and central nervous system infections (including meningitis) caused by susceptible pathogens.

Over the past 15 years, resistance to ceftazidime has been increasing worldwide. The most common mechanism of that resistance is bacterial production of β-lactamases, in particular the so-called ESBLs, which are molecular Class A enzymes. The range of approved dosage for ceftazidime is from 1 g 8-hourly to 2 g 12-hourly in healthy adults.

1.1.3 Ceftazidime avibactam (CAZ104)

AstraZeneca-Forest-Cerexa are developing ceftazidime in combination with avibactam (ceftazidime avibactam [CAZ104]), a β-lactam – β-lactamase inhibitor, as an intravenously administered compound for parenteral treatment of patients with infections caused by gram-negative pathogens, including pathogens that are resistant to ceftazidime. Clinical development will initially be focused on patients with complicated urinary tract infections (cUTI), including acute pyelonephritis, and patients with complicated intra-abdominal infections (cIAI).

Avibactam, when associated with ceftazidime, has also been shown to be active against strains which express a combination of β- lactamase types, as well as strains which are concomitantly resistant to other antibacterial classes such as fluoroquinolones.

Avibactam is a novel non-β-lactam – β-lactamase inhibitor with a spectrum of activity encompassing both Ambler Class A ESBLs and AmpC enzymes (Livermore 2008). Avibactam binds to these enzymes with a lower inhibition half-maximal inhibitory concentration (IC_{50}) as compared to currently marketed β-lactamase inhibitors clavulanic acid, tazobactam, and sulbactam. In addition, avibactam is a potent inhibitor of AmpC enzymes whereas clavulanic acid, tazobactam, and sulbactam lack any clinically useful activity. Unlike currently available β-lactamase inhibitors, avibactam does not induce β-lactamase production.

At the time of this Clinical Study Protocol (CSP), the options for the treatment of gram-negative infections, especially multi-drug resistant strains including ESBL producers, are extremely limited. Hence development and availability of new agents to treat these infections are seen as important additions to the existing treatment options.

1.2 Summary of relevant pre-clinical/clinical information to date

1.2.1 Pre-clinical information

The pre-clinical safety evaluation programme for avibactam alone includes toxicity studies up to 3 months duration in rats and dogs, safety pharmacology, genetic toxicology, reproductive toxicology (male and female fertility in rats, embryofoetal development in the rat and rabbit), immunotoxicology, local tolerance studies, and an in vitro phototoxicity study. These studies show that avibactam is well tolerated in pre-clinical species and is not associated with target organ toxicity with the exception of local tolerance issues when administered intravenously

via a peripheral vein. These local tolerance issues are not seen when avibactam is administered intravenously via a central vein in surgically prepared animals.

The pre-clinical safety evaluation programme also includes combination toxicity studies of 1 month duration in rats and dogs with avibactam and ceftazidime (ratio at dosing - 1:4 avibactam:ceftazidime). Local tolerance issues were observed at the infusion site in both species (dosing via a peripheral vein). The remaining toxicities observed in animals receiving the combination were considered to be related to the administration of ceftazidime.

For further information refer to the CAZ104 Investigator's Brochure (IB).

1.2.2 Clinical information

At the time of this CSP, 6 clinical pharmacology studies have been completed:

- A Phase I double-blind, placebo-controlled, escalating single dose study with and without ceftazidime in healthy young male subjects (avibactam/1001)

- A Phase I double-blind, placebo-controlled, multiple dose study over 5 or 10 days with and without ceftazidime, intravenous and oral formulations, in healthy young male subjects (avibactam/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 haemodialysis (avibactam/1003)

- A Phase I open-label, single dose study to assess effect of age and gender in healthy young and elderly male and female subjects (avibactam/1004)

- A single-centre, randomised, double-blind, placebo-controlled, four-way crossover Phase I study to investigate the effect on QT/QTc interval of a single dose of intravenous ceftazidime NXL104 (3000/2000 mg) or ceftaroline fosamil NXL104 (1500/2000 mg), compared with placebo, using moxifloxacin (Avelox®) as a positive control, in healthy male volunteers (D4280C00007)

- A Phase I, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability and Pharmacokinetics of NXL104 Alone and in Combination with Ceftazidime Administered as Single and Repeated Intravenous Doses in Healthy Japanese Subjects (D4280C00010)

The completed clinical pharmacology studies at the time of this CSP have demonstrated the PK and tolerability of avibactam alone or in combination with ceftazidime in healthy young and elderly, male and female, and Japanese subjects. The PK and tolerability of avibactam have also been determined in subjects with different degrees of renal impairment. Since CAZ104 is administered by intravenous infusion and both ceftazidime and avibactam are predominately excreted unchanged in urine, the drug-drug interaction potential with

cytochrome P450 (CYP) inducers or inhibitors is unlikely. Furthermore, avibactam exhibited very little metabolism either in vitro or in vivo, and the inhibition or induction potential was determined to be minimal.

In addition, plasma samples and other disease status and demographic factors, were collected from the Phase II studies evaluating CAZ104 plus metronidazole versus meropenem in subjects with cIAI (Study avibactam/2002) and evaluating CAZ104 versus imipenem in the treatment of cUTI (Study avibactam/2001). These studies showed both efficacy and safety of avibactam. A population PK analysis has been conducted using the combined data from Phase I studies in healthy subjects and the Phase II study in subjects with cIAI (Study avibactam/2002), and a population PK/pharmacodynamics (PD) analysis has been conducted using data from the Phase II study in patients with cIAI. These data have supported dose selection for the Phase III clinical programme.

For further information refer to the CAZ104 IB.

1.3 Rationale for conducting this study

This study will be conducted in 2 parts (Part A and Part B).

Part A

The aim of this part of the study is to explore the PK of avibactam and ceftazidime in plasma and urine following a single administration of CAZ104 on Days 1 and 11 and multiple administrations every 8 hours from Day 2 to Day 10 to further understand the PK data obtained in a Phase I study (avibactam/1002), whereby a 26% decrease in avibactam exposure was observed following 10 days administration of the combination. A 10-day multiple dose regimen also represents how CAZ104 may be administered in clinical practice.

Part B

The aim of this part of the study is to examine whether there is a PK interaction between avibactam and ceftazidime following multiple administrations of the combination to steady-state.

Both Part A and Part B will further establish the safety and tolerability of CAZ104.

1.4 Benefit/risk and ethical assessment

The major risk for healthy subjects who participate in the study is from adverse events (AEs) induced by the investigational products. There are no direct benefits for healthy subjects participating in the study.

Expected adverse drug reactions for avibactam include infusion site erythema and infusion site haematoma.

Ceftazidime has been licensed for use since 1983 and has been widely used since then, either alone or in combination with other treatments. The safety profile of ceftazidime is well established due to the large database of clinical study safety information and post-marketing experience with this compound. According to the label, the following adverse effects from clinical studies were considered to be either related to ceftazidime therapy or were of uncertain aetiology:

- Local effect (fewer than 2% of subjects): phlebitis, pain, and inflammation at the site of the infusion
- Hypersensitivity reactions (in 2% of subjects): pruritus, rash, and fever. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including ceftazidime. Angioedema, urticaria, anaphylaxis (bronchospasm and/or hypotension), and allergic reactions, which, in rare instances, are severe (eg, cardiopulmonary arrest)
- Gastrointestinal symptoms (fewer than 2% of subjects): diarrhoea, nausea, vomiting, and abdominal pain. The onset of pseudomembranous colitis symptoms may occur during or after treatment
- Central nervous system reactions (fewer than 1% of subjects): headache, dizziness, and paraesthesia. Seizures have also been reported with several cephalosporins, including ceftazidime
- Less frequent AEs (fewer than 1% of subjects): candidiasis (including oral thrush) and vaginitis
- Haematological: rare cases of haemolytic anaemia
- Laboratory test changes noted during clinical studies were transient and included: eosinophilia, positive Coombs test without haemolysis, thrombocytosis, hyperbilirubinaemia, and slight elevations in one or more of the hepatic enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], gamma-glutamyl transpeptidase [GGT], and alkaline phosphatase)
- Transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine
- Transient leucopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis

Cephalosporin-class adverse reactions: in addition to the adverse reactions listed above that have been observed in subjects treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

- Adverse reactions: colitis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anaemia, haemorrhage, and jaundice

- Altered laboratory tests: prolonged prothrombin time, false-positive test for urinary glucose, and pancytopenia

Theoretical, pre-clinical, and clinical findings from the CAZ104 development programmes as well as known effects of ceftazidime and the cephalosporin class of antibiotics have been considered from a safety perspective and are the basis for the ongoing creation of a Patient Risk Management Plan.

In all of the Phase I studies, there were no serious or severe AEs, or AEs that led to premature withdrawal from the study. The safety profile of CAZ104 appeared to be similar to those following the individual avibactam dose. The safety data from the Phase II study in subjects with cIAI showed that CAZ104 was generally well tolerated.

To ensure subject safety during the study, routine clinical monitoring will include AEs, vital signs, physical examination findings, routine safety laboratory assessments (haematology, coagulation, clinical chemistry, and urinalysis), clinical assessments, and electrocardiogram (ECG).

2. STUDY OBJECTIVES

2.1 Primary objective

- Part A: to investigate the single- and multiple-dose PK of avibactam and ceftazidime following a single administration of avibactam plus ceftazidime (CAZ104) on Days 1 and 11 and multiple administrations every 8 hours from Day 2 to Day 10

- Part B: to investigate the effect on the PK of co-administering avibactam plus ceftazidime (CAZ104) compared to administration of the individual components (ceftazidime and avibactam alone)

2.2 Secondary objectives

- To assess safety and tolerability of avibactam, ceftazidime, and CAZ104 when administered as a 2-hour infusion every 8 hours

2.3 Exploratory objectives

- To investigate the presence and/or identity of drug metabolites of avibactam

The exploratory results will not be reported in the Clinical Study Report (CSR).

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This study will be conducted in 2 parts (Part A and Part B).

Part A

Part A is an open-label study designed to investigate the effect on the PK of avibactam and ceftazidime following multiple investigational product administrations in healthy male and female subjects. Approximately 16 subjects will be enrolled to ensure 12 evaluable subjects.

The investigational product will be administered as a 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime (CAZ104).

Part A will comprise 3 visits:

Visit 1: subjects will be screened for eligibility within 28 days of Visit 2.

Visit 2: subjects will be admitted to the study centre on Day -1. Each subject will receive 500 mg avibactam and 2000 mg ceftazidime (CAZ104) on the morning of Day 1 and every 8 hours from Day 2 to Day 10 (inclusive) (3 infusions per day). Subjects will receive a single infusion on Day 11. All subjects will therefore receive a total of 29 infusions with a volume of 100 mL of CAZ104. Subjects will be discharged on Day 12 after the last PK blood sampling, 24 hours after the last infusion on Day 11.

Visit 3: follow-up assessments will be performed 7 to 10 days after the last investigational product administration at Visit 2.

The flow chart for Part A is presented in Figure 1, the study plan in Table 1, the digital ECG (dECG) time points in Table 2, and the PK blood sampling time points in Table 3.

Figure 1 Part A flow chart

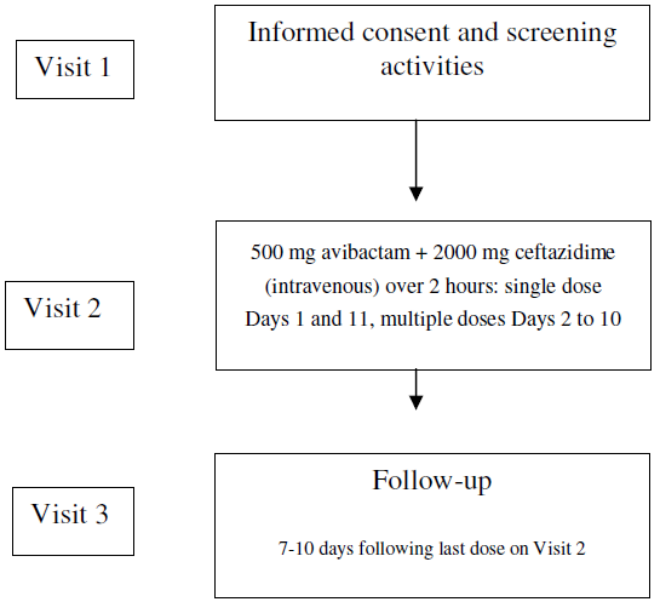

Table 1 Part A study plan

Study Assessments	Visit 1[a] Screening ≤28 days prior to Visit 2	Visit 2 Treatment Days -1 to 12 (residential)	Visit 3 Follow-up 7 to 10 days after Visit 2
Informed consent	X		
Demographics	X		
Medical/surgical history	X		
Physical examination	X	X[b]	X
Inclusion/exclusion criteria	X	X[c]	
Follicle-stimulating hormone (female subjects only)	X		
Pregnancy test (female subjects only)	X	X	X
Weight and height	X		
Vital signs[d]	X	X[b]	X
Safety paper ECG[e]	X	X[b]	X
Safety laboratory sampling (clinical chemistry, haematology, and urinalysis)	X	X[b]	X
Urine drugs of abuse, smoking, and alcohol screen	X	X[k]	
HIV antibody/hepatitis B and C screen	X		
Investigational product administration		X	
Blood sampling for PK analysis		X[f]	
Urine sampling for PK and metabolite identification		X[g]	
Blood sampling for metabolite identification		X[h]	
Digital ECG		X[i]	
Concomitant medication	X	X	X
Adverse event questioning[j]	X	X	X

[a] Screening can occur up to 28 days prior to Visit 2 and may be divided into 2 separate occasions.
[b] Safety laboratory measurements, vital signs, physical examination, and paper ECG will be performed at Day -1, Day 4, Day 7, and before discharge from the study centre.
[c] Only on Day -1 and on Day 1 before administration of the investigational product.
[d] Vital signs will include resting supine blood pressure and pulse rate. Blood pressure will be measured after the paper ECG.
[e] A paper ECG for safety review by the Investigator will be performed.
[f] Time points for the measurement of ceftazidime and avibactam concentrations are presented in Table 3.
[g] Urine will be collected for 24 hours on Days 1 and 11 to estimate renal clearance of ceftazidime and avibactam and for metabolite identification at pre-dose and during the following intervals: 0-2 hours, 2-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours post dose.

[h] On Day 11 at 1, 2, 4, 6, 12, and 24 hours post-dose.
[i] Time points for digital ECGs are presented in Table 2.
[j] All adverse events and serious adverse events will be collected daily from the time of obtaining informed consent through follow-up.
[k] Day -1.
ECG: electrocardiogram; HIV: human immunodeficiency virus; PK: pharmacokinetics.

Table 2 Part A time schedule for digital electrocardiogram assessments

Study day	ECG Number	ECG Number	Time Start hour:min[d]	Dose	Stop time	dECG cont.[a,c,d]	Other
1,11			-01:00				Apply the electrodes[b]
1,11	1	14	-00:30		-00:20	10 minutes	Pre-dose ECG
1,11			-00:20		-00:10		Toilet use recommended
			00:00	Administration of CAZ104			
1,11	2	15	00:55		01:00	5 minutes	
1,11	3	16	01:55		02:00	5 minutes	
1,11	4	17	02:55		03:00	5 minutes	
1,11	5	18	05:55		06:00	5 minutes	
1,11	6	19	11:55		12:00	5 minutes	
2,12	7	20	23:55		24:00	5 minutes	
4	8		-00:30		-00:20	10 minutes	Pre-dose ECG
4	9		01:55		02:00	5 minutes	
5	10		-00:30		-00:20	10 minutes	Pre-dose ECG
5	11		01:55		02:00	5 minutes	
8	12		-00:30		-00:20	10 minutes	Pre-dose ECG
8	13		01:55		02:00	5 minutes	

[a] The subject must be in same supine (max. 30 degrees flexion in the hip) body position at each time point and in all visits and feet not in contact with footboard.
[b] Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied 30 minutes before first recording.
[c] Time points for dECG may be adjusted according to emerging PK data.
[d] All ECG recordings will be preceded by a 10 minute controlled rest period.
The start times of the dECGs are relative to the first dose on each of Days 2, 4, 5, and 8.
dECG: Digitial electrocardiogram; ECG: Electrocardiogram; PK: Pharmacokinetics.

Table 3 Part A pharmacokinetic blood sampling time points

Sample number	Study day	Protocol time (hours post start of first dose on Day 1)	Protocol time (days and hours)[a]
1	1	0 (pre-dose)	Day 1, 0 (pre-dose)
2	1	0.5	Day 1, 0.5
3	1	1	Day 1, 1
4	1	1.5	Day 1, 1.5
5	1	2	Day 1, 2 (end of infusion)
6	1	2.25	Day 1, 2.25
7	1	2.5	Day 1, 2.5
8	1	2.75	Day 1, 2.75
9	1	3	Day 1, 3
10	1	3.5	Day 1, 3.5
11	1	4	Day 1, 4
12	1	6	Day 1, 6
13	1	8	Day 1, 8
14	1	12	Day 1, 12
15	2	24	Day 1, 24 (Day 2, pre-dose)
16	4	72	Day 4, 0 (pre-dose)
17	4	73	Day 4, 1
18	4	74	Day 4, 2 (end of infusion)
19	4	75	Day 4, 3
20	4	76	Day 4, 4
21	4	78	Day 4, 6
22	4	80	Day 4, 8 (prior to next dosing)
23	7	144	Day 7, 0 (pre-dose)
24	7	146	Day 7, 2 (end of infusion)
25	11	240	Day 11, 0 (pre-dose)
26	11	240.5	Day 11, 0.5
27	11	241	Day 11, 1
28	11	241.5	Day 11, 1.5
29	11	242	Day 11, 2 (end of infusion)
30	11	242.25	Day 11, 2.25
31	11	242.5	Day 11, 2.5
32	11	242.75	Day 11, 2.75

Table 3 Part A pharmacokinetic blood sampling time points

33	11	243	Day 11, 3
34	11	243.5	Day 11, 3.5
35	11	244	Day 11, 4
36	11	246	Day 11, 6
37	11	248	Day 11, 8
38	11	252	Day 11, 12
39	12	264	Day 11, 24 (Day 12)

[a] Hours indicated are relative to the time of start of infusion of the most recent dose. Pre-dose on Days 2, 4, 7, and 11 refer to the morning doses on those days.

Part B

Part B is an open-label, randomised, 3-way cross-over study designed to investigate the effect on the PK of avibactam alone, ceftazidime alone, and CAZ104 following single and multiple investigational product administrations in healthy male and female subjects at steady-state. Approximately 27 subjects will be enrolled to ensure 24 evaluable subjects. Subjects participating in Part A will not be allowed in Part B.

All subjects will receive all 3 treatments over 3 periods (Period 1, Period 2, and Period 3).

- Treatment A: 2-hour infusion of 500 mg avibactam on the morning of Day 1, every 8 hours from Day 2 to Day 3 (inclusive) (3 infusions per day), and another single infusion on Day 4
- Treatment B: 2-hour infusion of 2000 mg ceftazidime on the morning of Day 1, every 8 hours from Day 2 to Day 3 (inclusive) (3 infusions per day), and another single infusion on Day 4
- Treatment C: 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime (CAZ104) on the morning of Day 1, every 8 hours from Day 2 to Day 3 (inclusive) (3 infusions per day), and another single infusion on Day 4

Subjects will be randomised to 1 of 3 treatment sequences on Day 1 of Visit 2 as presented in Table 4.

Table 4 Part B treatment periods and sequences

	Period 1	Period 2	Period 3
Sequence ABC	A	B	C
Sequence BCA	B	C	A
Sequence CAB	C	A	B

The study will comprise 5 visits:

Visit 1: subjects will be screened for eligibility within 28 days of Visit 2

Visits 2, 3, and 4: subjects will be admitted to the study centre on Day -1 of each visit and receive treatment in the randomised treatment sequence from Day 1 to Day 4. All subjects will receive a total of 8 infusions with a volume of 100 mL per period. Subjects will be discharged on Day 5 after the last PK blood sampling, 24 hours after the last infusion of each period on Day 4. Each visit will be separated by a wash-out period of at least 2 days.

Visit 5: follow-up assessments will be performed 7 to 10 days after the last investigational product administration at Visit 4.

A flow chart for Part B is presented in Figure 2, the study plan in Table 5, the dECG time points in Table 6, and the PK blood sampling time points in Table 7.

Figure 2 Part B flow chart (treatment sequence ABC is illustrated)

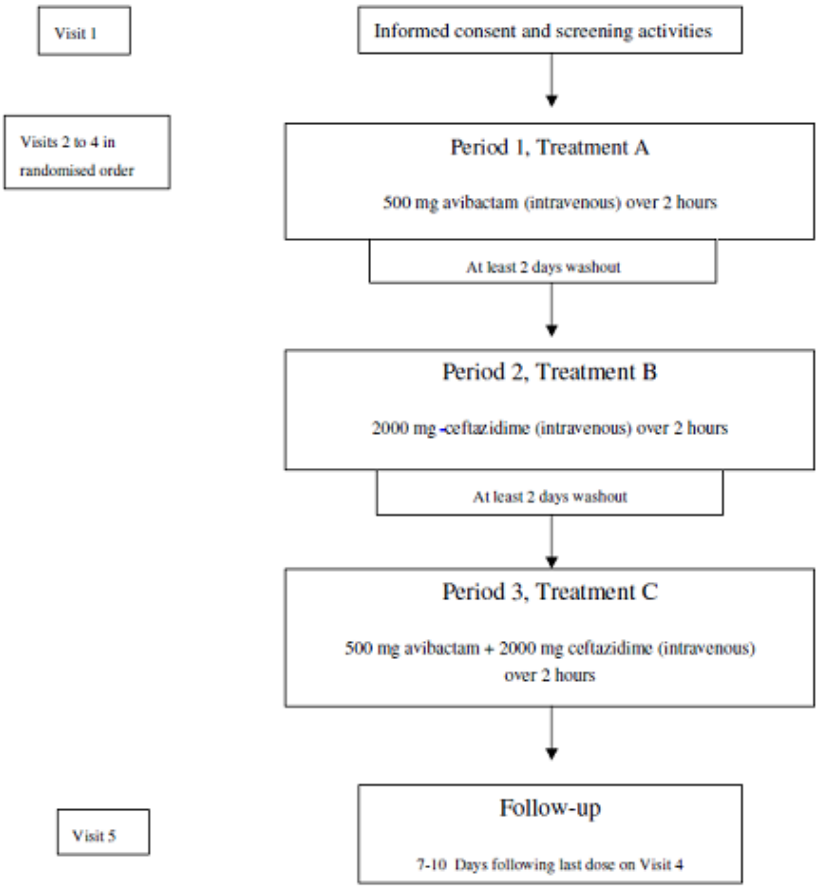

Table 5 Part B study plan

Study Assessments	Visit 1[a] Screening ≤28 days prior to Visit 2	Visit 2, 3 and 4 Treatment Days -1 to 5 (residential)	Visit 5 Follow-up 7 to 10 days after Visit 4
Informed consent	X		
Demographics	X		
Medical/surgical history	X		
Physical examination	X	X[b]	X
Inclusion/exclusion criteria	X	X[c]	
Follicle-stimulating hormone (female subjects only)	X		
Pregnancy test (female subjects only)	X	X	X
Weight and height	X		
Vital signs[d]	X	X[b]	X
Safety paper ECG[e]	X	X[b]	X
Safety laboratory sampling (clinical chemistry, haematology, and urinalysis)	X	X[b]	X
Urine drugs of abuse, smoking, and alcohol screen	X	X[k]	
HIV antibody/hepatitis B and C screen	X		
Randomisation[f]		X	
Investigational product administration		X	
Blood sampling for PK analysis		X[g]	
Urine sampling for PK and metabolite identification		X[h]	
Digital ECG		X[i]	
Concomitant medication	X	X	X
Adverse event questioning[j]	X	X	X

[a] Screening can occur up to 28 days prior to Visit 2 and may be divided into 2 separate occasions.
[b] Safety laboratory measurements, vital signs, physical examination, and paper ECG will be performed at Day -1 and before discharge from the study centre.
[c] Only on Day -1 and on Day 1 before administration of the investigational product.
[d] Vital signs will include resting supine blood pressure and pulse rate. Blood pressure will be measured after the paper ECG.
[e] A paper ECG for safety review by the Investigator will be performed as required.
[f] Subjects will be randomised to a treatment sequence at Visit 2.
[g] Time points for the measurement of ceftazidime and avibactam concentrations are presented in Table 7.
[h] Urine will be collected for 24 hours on Days 1 and 4 to estimate renal clearance of ceftazidime and avibactam and for metabolite identification at pre-dose and during the following intervals: 0-2 hours, 2-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours post dose.

[i] Time points for digital ECGs are presented in Table 6.

[j] All adverse events and serious adverse events will be collected daily from the time of obtaining informed consent through follow-up.

[k] Day -1 of each treatment period.

ECG: electrocardiogram; HIV: human immunodeficiency virus; PK: pharmacokinetics.

Table 6 Part B time schedule for digital electrocardiogram assessments

Study day	ECG Number	ECG Number	Time Start hour:min[d]	Dose	Stop time	dECG cont.[a,c,d]	Other
1,4			-01:00				Apply the electrodes[b]
1,4	1	8	-00:30		-00:20	10 minutes	Pre-dose ECG
1,4			-00:20		-00:10		Toilet use recommended
			00:00	Administration of CAZ104/ avibactam/ ceftazidine			
1,4	2	9	00:55		01:00	5 minutes	
1,4	3	10	01:55		02:00	5 minutes	
1,4	4	11	02:55		03:00	5 minutes	
1,4	5	12	05:55		06:00	5 minutes	
1,4	6	13	11:55		12:00	5 minutes	
2,5	7	14	23:55		24:00	5 minutes	

[a] The subject must be in same supine (max. 30 degrees flexion in the hip) body position at each time point and in all visits and feet not in contact with footboard.

[b] Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied 30 minutes before first recording.

[c] Time points for dECG may be adjusted according to emerging PK data.

[d] All ECG recordings will be preceded by a 10 minute controlled rest period.

dECG: Digitial electrocardiogram; ECG: Electrocardiogram; PK: Pharmacokinetics.

Table 7 Part B pharmacokinetic blood sampling time points

Sample number	Study day	Protocol time (hours post start of first dose on Day 1)	Protocol time (days and hours)[a]
1	1	0 (pre-dose)	Day 1, 0 (pre-dose)
2	1	0.5	Day 1, 0.5
3	1	1	Day 1, 1
4	1	1.5	Day 1, 1.5
5	1	2	Day 1, 2 (end of infusion)
6	1	2.25	Day 1, 2.25
7	1	2.5	Day 1, 2.5
8	1	2.75	Day 1, 2.75
9	1	3	Day 1, 3
10	1	3.5	Day 1, 3.5
11	1	4	Day 1, 4
12	1	6	Day 1, 6
13	1	8	Day 1, 8
14	1	12	Day 1, 12
15	2	24	Day 1, 24 (Day 2, pre-dose)
16	4	72	Day 4, 0 (pre-dose)
17	4	72.5	Day 4, 0.5
18	4	73	Day 4, 1
19	4	73.5	Day 4, 1.5
20	4	74	Day 4, 2 (end of infusion)
21	4	74.25	Day 4, 2.25
22	4	74.5	Day 4, 2.5
23	4	74.75	Day 4, 2.75
24	4	75	Day 4, 3
25	4	75.5	Day 4, 3.5

Table 7 Part B pharmacokinetic blood sampling time points

26	4	76	Day 4, 4
27	4	78	Day 4, 6
28	4	80	Day 4, 8
29	4	84	Day 4, 12
30	4	96	Day 4, 24 (Day 5)

[a] Hours indicated are relative to the time of start of infusion of the most recent dose.

3.2 Rationale for study design, doses and control groups

The dose levels administered in this study are the same dose levels that will be used in the Phase III programme.

This study will be conducted in healthy male and female subjects in order to avoid interference with the study results from disease processes and other drugs. The inclusion and exclusion criteria are chosen in order to select healthy subjects who are known to be free from any significant illness relevant to the proposed study. For safety reasons, only post-menopausal or surgically sterile women will be included.

A multiple dose period of 10 days was selected for Part A as this represents how CAZ104 may be administered in clinical practice and to observe the exposure to clarify results from an earlier study.

A cross-over design where each subject acts as his/her own control is used in Part B. Inter-individual variability is thereby eliminated. The risk of carry-over has been addressed by a wash-out period between the administrations of the investigational product.

The primary objectives of this study are avibactam and ceftazidime concentration-time profiles and the resulting PK parameters, which are objective measurements. The risk of bias in this study is therefore minimal and both parts can be conducted open-label.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the subject screening log, of subjects who entered pre-study screening.

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

4.1 Inclusion criteria

For inclusion in either Part A or Part B subjects must fulfil the following criteria:

1. Provision of signed and dated, written informed consent prior to any study-specific procedures

2. Healthy male and female subjects aged 18 to 50 years (inclusive) with suitable veins for cannulation or repeated venipuncture; female subjects must be post-menopausal or surgically sterile. Female subjects must have a negative pregnancy test at screening and on admission to the study centre, must not be lactating, and must be of non-child-bearing potential, confirmed at screening by fulfilling 1 of the following criteria:

- Post-menopausal defined as amenorrhoea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone (FSH) levels in the laboratory defined post-menopausal range

- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation

3. Male subjects should be willing to use barrier contraception ie, condoms, from the first day of the investigational product administration until 3 months after the last administration of the investigational product

4. Have a body mass index (BMI) between 19 and 30 kg/m2

5. Be able to understand and willing to comply with study procedures, restrictions, and requirements, as judged by the Investigator

4.2 Exclusion criteria

Subjects must not enter either Part A or Part B if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study

2. History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs

3. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to avibactam, ceftazidime, and/or excipients

4. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks prior to the first administration of investigational product

5. Any clinically significant abnormalities in physical examination, ECG, clinical chemistry, haematology, or urinalysis results, as judged by the Investigator

6. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

   - Systolic blood pressure >140 mmHg

   - Diastolic blood pressure >90 mmHg

   - Heart rate <40 or >85 beats per minute

7. Prolonged QTcF (>450 ms) or shortened QTcF (<350 ms) or a family history of long QT syndrome

8. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or the human immunodeficiency virus (HIV)

9. Known or suspected history of drug abuse, as judged by the Investigator

10. History of alcohol abuse or excessive intake of alcohol, as judged by the Investigator

11. Positive screen for drugs of abuse or cotinine (nicotine) at screening or on admission to the study centre or positive screen for alcohol on admission to the study centre prior to the first administration of the investigational product

12. Current smokers or ex-smokers who have smoked or used nicotine products within the previous 3 months and/or have smoked more than 10 pack years [number of pack years = (number of cigarettes smoked x number of years)/20]

13. Use of any prescribed or non-prescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins, and minerals during the 2 weeks prior to the first administration of investigational product or longer if the medication has a long half-life. Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache

14. Plasma donation within 1 month of screening or any blood donation/blood loss during the 3 months prior to screening

15. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 3 months of the first administration of investigational product in this study. The period of exclusion begins at the time of the last visit of the prior study. Note: subjects consented and screened, but not dosed in this study or a previous Phase I study, are not excluded

16. Involvement in the planning and/or conduct of the study (applies to AstraZeneca, , and personnel, and any other personnel involved in the study)

17. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the investigational product

18. Excessive intake of caffeine-containing drinks eg, coffee (more than 5 cups of coffee or the equivalent per day), tea, caffeine-containing energy drinks, and cola

19. Judgement by the Investigator that the subject should not participate in the study if he/she is considered unlikely to comply with study procedures, restrictions, and requirements

20. Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. The following restrictions apply for the specified times in Part A and Part B:

2. Eat and drink only the standardised meals and drinks provided (apart from water) during the residential period in the study centre

3. Abstain from consuming any of the following:

   - Alcohol from 72 hours before admission, during the residential periods, and for 72 hours before follow-up

   - Energy drinks containing taurine or glucuronolactone eg, Red Bull from 72 hours before admission, during the residential periods, and for 72 hours before follow-up

   - Poppy seeds found in speciality bread from the time of consent until after the final assessment at follow-up

   - Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges from 7 days before admission until after the final assessment at follow-up

4. Limit caffeine intake to 5 cups per day from enrolment and limit to 3 cups per day at meal times from admission to the study centre and during the study visits

5. Abstain from nicotine use, smoking, and drugs of abuse from the time of consent until after the final assessment at follow-up

6. Abstain from taking any prescribed or non-prescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins, and minerals during the 2 weeks prior to the first administration of investigational product or longer if the medication has a long half-life until after the final assessment at follow-up. Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache. However, this should not obviate necessary medical treatment

7. Refrain from strenuous physical activity, which is not within the subject's normal daily routine, from 7 days prior to admission to the study centre until after the final assessment at follow-up

8. Abstain from blood or plasma donation until 3 months after the final assessment at follow-up

9. Abstain from scheduled in-patient surgery or hospitalisation during the course of the study

10. Male subjects should use a condom to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm or fathering a child from the first investigational product administration until 3 months after the last administration of the investigational product

5.2 Subject enrolment and randomisation and initiation of investigational product

The Investigator will:

1. Obtain signed informed consent from the potential subject before any study-specific procedures are performed

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

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign each eligible subject in Part A a unique subject number and each eligible subject in Part B a unique randomisation code

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be re-used. Additional randomisation numbers will be included in the randomisation schedule to use for replacement subjects. Subject numbers and replacement subject numbers will have the same number of digits.

5.2.1 Procedures for randomisation

A randomisation scheme will be produced by using the AstraZeneca global randomisation system (GRAND) for Part B. Subjects in Part B will be randomised to 1 of 3 treatment sequences in a 1:1:1 ratio on the morning of Day 1 of Visit 2. Part A uses a single treatment and therefore no randomisation is required.

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

5.3 Procedures for handling subjects incorrectly enrolled or randomised or initiated on investigational product

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled in Part A or randomised in Part B. There can be no exceptions to this rule.

Where subjects that do not meet the selection criteria and are incorrectly started on treatment, randomised, or where subjects subsequently fail to meet the study criteria after initiation, a discussion should occur between the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

The AstraZeneca CPA Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, further administration of the investigational product should be stopped.

5.4 Blinding and procedures for unblinding the study

Both parts of this study will be open-label.

5.5 Treatments

5.5.1 Identity of investigational products

AstraZeneca, or a company acting on its behalf, will supply the investigational products to the study centre. The investigational products used in this study are presented in Table 8.

Table 8 Identity of the investigational products

Investigational product	Dosage form (strength)	Manufacturer
Avibactam	Lyophilisate for concentrate for solution for infusion (600 mg vial)	
Ceftazidime	Sterile crystalline powder (2 g vial)	

Avibactam will be packaged and labelled in accordance with current Good Manufacturing Practice (GMP) and supplied to the study centre. Commercially available ceftazidime will be sourced and supplied to the study centre. The investigational products will be administered intravenously.

Part A

Avibactam and ceftazidime will be reconstituted and added to the same infusion bag.

Part B

Treatment A: avibactam will be reconstituted and added to an infusion bag.

Treatment B: ceftazdime will be reconstituted and added to an infusion bag.

Treatment C: avibactam and ceftazidime will be reconstituted and added to the same infusion bag.

Handling instructions detailing how the infusions are to be prepared will be provided to the study centre by AstraZeneca.

5.5.2 Doses and treatment regimens

Part A

Subjects in Part A will each receive 29 infusions of 500 mg avibactam and 2000 mg ceftazidime (CAZ104) intravenously over 2 hours from Day 1 to Day 11. A single administration on Day 1, multiple administrations every 8 hours from Day 2 to Day 10 (inclusive), and a single administration on Day 11.

Subjects may eat normally without a fasting period and can be fed before the infusions. Specific food restrictions are listed in Section 5.1.

Part B

Subjects in Part B will each receive 8 infusions of each treatment:

- Treatment A: 500 mg avibactam intravenously over 2 hours from Day 1 to Day 4 (a single administration on Day 1, multiple administrations every 8 hours from Day 2 to Day 3 [inclusive], and a single administration on Day 4)
- Treatment B: 2000 mg ceftazidime intravenously over 2 hours from Day 1 to Day 4 (a single administration on Day 1, multiple administrations every 8 hours from Day 2 to Day 3 [inclusive], and a single administration on Day 4)
- Treatment C: 500 mg avibactam and 2000 mg ceftazidime (CAZ104) intravenously over 2 hours from Day 1 to Day 4 (a single administration on Day 1, multiple administrations every 8 hours from Day 2 to Day 3 [inclusive], and a single administration on Day 4)

A wash-out period of at least 2 days will separate the treatment periods.

Subjects may eat normally without a fasting period and can be fed before the infusions. Specific food restrictions are listed in Section 5.1.

5.5.3 Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be in English.

5.5.4 Storage

All investigational products should be kept in a secure place under appropriate storage conditions in the pack provided. Descriptions of the appropriate storage are specified on the investigational product label and in the IB.

5.6 Concomitant and post-study treatment(s)

Subjects must abstain from taking any prescribed or non-prescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins, and minerals during the 2 weeks prior to the first administration of investigational product or longer if the medication has a long half-life until after the final assessment at follow-up. Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache.

Medication, considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the electronic Case Report Form (eCRF).

5.7 Treatment compliance

The administration of all investigational products should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by supervised administration of the investigational product by the Investigator or qualified representative. The dose, date, and time of administration of the investigational product will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

The investigational product provided for this study will be used only as directed in this CSP.

The study centre personnel will account for all investigational products administered to the subject.

The study centre personnel will account for all investigational products received at the study centre, unused investigational product, and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of investigational product

Subjects must be discontinued from the investigational product in the following situations:

- Any risk to the subject, as judged by the Investigator and/or AstraZeneca

- Eligibility criteria not fulfilled
- Subject lost to follow-up
- Death
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, blood pressure, pulse rate, laboratory measurements, and AEs) causing continuation of the investigational product administration to be unjustified
- A QTc prolongation defined as QTcF >500 ms or an increase in QTcF >60 ms above baseline confirmed (persistent for ≥5 minutes) and determined post-dose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG

Subjects may be discontinued from the investigational product in the following situations:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Severe non-compliance to the CSP, as judged by the Investigator and/or AstraZeneca
- AEs

Study stopping criteria

The study should be stopped in the following situations:

- **3** or more subjects have >**3** x the upper limit of normal (ULN) of ALT or 3 subjects have >2 x ULN of alkaline phosphatase (ALP) or 3 subjects have elevations of total bilirubin >2 x ULN
- 1 or more subjects, who fulfill Hy's law defined as ALT >3 x ULN and total bilirubin >2 x ULN in the absence of significant increase in ALP and in the absence of an alternative diagnosis that explains the increase in total bilirubin (see Appendix D for follow up procedures)
- 2 or more subjects have a QTc prolongation defined as QTcF >500 ms or an increase in QTcF >60 ms above baseline confirmed (persistent for ≥5 minutes) and determined post-dose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG

Individual subject stopping criteria

The following individual subject withdrawal and intensified monitoring criteria will apply:

Liver chemistry variable	Intensified monitoring criteria	Individual subject withdrawal criteria
ALT	Level >2 x ULN: monitor at least every 48 hours until the levels return to within the normal limits or are stable, as judged by the Investigator	Level >3 x ULN
ALP	An increase of >100%: check GGT, monitor at least every 48 hours until the levels return to within the normal limits or are stable, as judged by the Investigator	Level >2 x ULN
Bilirubin	Level >1.5 x ULN: monitor at least every 48 hours until the levels return to within the normal limits or are stable, as judged by the Investigator	Level >2 x ULN

Any subject who meets the individual subject withdrawal criteria will be withdrawn from the study and advised to continue assessments to ensure his/her safety.

The following study review criteria will apply:

- If any 2 subjects meet any of the withdrawal criteria of the study, the Investigator will contact the CPA Physician to initiate a review process that will, at minimum, include the Medical Science Director and the Global Safety Physician. The review process will consider study and subject information and determine the subsequent necessary actions

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject who decides to discontinue the investigational product administration will always be asked about the reason(s) and the presence of any AEs. If possible, he/she will be seen and assessed by the Investigator. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

If a subject is withdrawn from the study, see Section 5.9.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from the study (investigational product and study assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, he/she will be seen and assessed by the Investigator. Withdrawn subjects will undergo follow-up assessments 7 to 10 days after the last investigational product administration. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

Withdrawn subjects will be replaced to ensure 12 evaluable subjects in Part A and 24 evaluable subjects in Part B.

6. COLLECTION OF STUDY VARIABLES

Refer to Table 1 and Table 5 for the study assessments to be performed in Part A and Part B, respectively.

When more than 1 assessment is required at a particular time point, PK samples should take precedence.

6.1 Recording of data

Subject data will be collected by using the Phase I electronic data capture (EDC) system. The Investigator will ensure that data are recorded in the eCRF as specified in the CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study centre.

Procedures for data editing, entry, and handling of the data query process will be described in the Data Management Plan.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

Each subject will undergo screening to confirm eligibility. This will consist of the following:

- Obtaining informed consent before starting any study-specific procedures
- Review of the inclusion/exclusion criteria with the subject
- Recording of demographic data (date of birth, gender, and race)

- A standard recording of medical and surgical history
- A complete physical examination
- Height, weight, and calculation of BMI
- Vital signs (resting supine systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate) (after ECG)
- Blood sampling for routine clinical chemistry and haematology measurements, a HBsAg, HCV antibody, and HIV screen, and FSH (female subjects only)
- Pregnancy test (female subjects only)
- Urine sampling for routine urinalysis
- Urine will be tested for cotinine and alcohol ( ) or smokerlyzer and breathalyzer tests ( )
- Drugs of abuse screen in urine
- Paper ECG
- AE questioning
- Concomitant medication recording

6.2.2 Follow-up procedures

Follow-up procedures will be performed 7 to 10 days after the last investigational product administration at Visit 2 for Part A and Visit 4 for Part B. These assessments will include a complete physical examination, vital signs, paper ECG, safety laboratory assessments, AE questioning, and concomitant medication recording.

6.3 Safety

The Investigator is responsible for ensuring that all personnel 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 pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or wash-out periods, even if no investigational product has been administered.

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

6.3.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix B to this CSP

6.3.3 Recording of adverse events

Time period for collection of adverse events

All AEs (including SAEs) will be collected from the time of signing the informed consent and throughout the study, including the follow-up period.

Follow-up of unresolved adverse events

Any AEs that are unresolved at follow-up will be monitored by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date and time when the AE started and stopped
- Intensity, rated according to the following scale:
  - Mild (awareness of sign or symptom, but easily tolerated)
  - Moderate (discomfort sufficient to cause interference with normal activities)

  - Severe (incapacitating, with inability to perform normal activities)

- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to the investigational product
- Whether the AE caused the subject's withdrawal from study (yes or no)
- Outcome

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

- Date the AE met the SAE criteria
- Date the Investigator became aware of the SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to the study procedure(s)
- Causality assessment in relation to other medication
- Description of the 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 an 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.

Causality collection

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

For SAEs, the causal relationship will also be assessed for other medication and study procedures and additional investigational product. 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 to this CSP.

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in the CSP-mandated laboratory values, vital signs, or ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Subjects with ALT >2 x ULN or 80 U/L or with total bilirubin >1.5 x ULN or 38 µmol/L will qualify for intensified monitoring. Detailed liver chemistry sampling aimed at identifying the cause of changes observed during routine monitoring should be done for all subjects fulfilling intensified monitoring criteria. Detailed liver chemistry sampling should also be made in subjects with liver clinical chemistry values that are repeatedly close to fulfilling discontinuation criteria and for whom it is considered important to evaluate the cause of the observed changes. See Section 5.8 for individual subject study drug discontinuation criteria.

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.

NB. Cases where a subject shows an AST **or** ALT value ≥3 x ULN **or** total bilirubin ≥ 2 x ULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.4 Reporting of serious adverse events

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

If any SAE occurs during the course of the study, then the Investigator or other study centre personnel will inform the appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he/she becomes aware of it.

The designated AstraZeneca representative works 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 is undertaken immediately. The Investigator or other study centre personnel will inform the AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than the end of the next business day** of when he/she becomes aware of it.

The reference document for definition of expectedness/listedness is the CAZ104 IB.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be collected at the time points specified in the study plans (Table 1 and Table 5).

The safety laboratory variables are presented in Table 9.

Table 9 Safety laboratory variables

Clinical chemistry (serum)	**Haematology (blood)**
Alkaline phosphatase	Haemoglobin[a]
Aspartate aminotransferase[a]	Platelet count
Alanine aminotransferase[a]	Leukocyte count[a]
Albumin	Leukocyte differential count[a]
Total bilirubin	Neutrophils
Creatinine	Eosinophils
Total calcium	Basophils
Potassium	Lymphocytes
Sodium	Monocytes
Glucose (preferably fasting)	
Thyroid stimulating hormone[b]	**Urinalysis**
Urea	Blood
	Protein
Endocrinology	Glucose
Free thyroxine[a]	Creatinine

Serology	**Other**
HIV and Hepatitis B and C[b]	Follicle-stimulating hormone (female subjects only)[a]
	Pregnancy test (female subjects only)[b]

[a] At screening only.
[b] Serum at screening, urine or serum at all other time points.

HIV: human immunodeficiency virus.

NB. In case a subject shows an AST **or** ALT of ≥3 x ULN **or** total bilirubin ≥2 x ULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Urine will be tested for the following drugs of abuse at screening and Day -1 of each visit: amphetamines, barbiturates, tricyclic anti-depressants, cocaine, methadone, morphine, phencyclidine, tetrahydrocannabinol, and opiates.

Urine will be tested for cotinine and alcohol ( ) or smokerlyzer and breathalyzer tests ( ) will be conducted at screening and Day -1 of each visit.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Subjects in whom suspected clinical significance is confirmed, will either not be included in the study or if already enrolled, will be monitored until normalisation or for as long as the Investigator considers necessary. Additional laboratory assessments may be performed for safety reasons if judged necessary by the Investigator.

The safety laboratory samples will be analysed using routine methods at the Pathology Laboratory of the clinical unit.

For blood volume see Section 7.1.

6.3.6 Physical examination

A full physical examination, according to normal clinical routines, will be performed at the time points specified in the study plans (Table 1 and Table 5) and will include an examination of general appearance, skin, lymph nodes, thyroid, musculo-skeletal/extremities, neurological condition, mouth, teeth, throat, cardiovascular system, lungs, and abdomen. The outcome of the examination is to be recorded as normal/abnormal in the eCRF, with any abnormalities specified. 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.

Only a brief physical examination is required at follow-up. Only information on whether the assessment was performed or not and any AEs are to be recorded in the study database.

Height will be measured in centimeters and weight in kilograms. Measurements should be taken without shoes and the same scale used for all measurements. The BMI will be calculated from the height and weight measurements.

6.3.7 ECG

6.3.7.1 Resting 12-lead ECG

12-lead ECG recordings will be obtained at the time points specified in the study plans (Table 1 and Table 5), after 10 minutes' rest in the supine position. Paper ECGs for safety review by the Investigator will be performed at additional intervals if required. The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities specified. The print-out of the ECG is to be signed, dated, and filed in the Investigator's Study File, along with a signed and dated copy (if the print-outs are not on archive-quality paper).

6.3.7.2 Digital ECG

The AstraZeneca ECG Centre will perform the dECG analysis in this study, using the EClysis© system, Version 3.2, or higher.

At protocol-indicated time points (Table 2 and Table 6), 12-lead continuous dECG will be recorded over at least 5 minutes with the Schiller Cardiovit CS-200 recorder ( ) and transmitted to the AZ central dECG repository, according to the

AstraZeneca ECG Centre's standard procedures for settings, recording, and transmission of dECGs.

The same recorder will be used for each subject at all time points, when possible. Date and time settings must be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead ECG placement. Electrode positions for dECG take precedence over telemetry electrodes. Electrode positions will be marked with an indelible pen at the start of each study day to ensure exact reposition. Permanent electrodes will be applied at least 30 minutes before the first study recording and left in place for the duration of each relevant study day.

Subjects will rest in a supine position for at least 10 minutes before the start of each recording. The subject should be in the same supine body position (maximum 30 degrees flexion of the hip and feet not in contact with the footboard) at each recording time point during the study.

The metadata for all dECG files will be checked and approved by the responsible personnel at the study centre to ensure that the files transferred to the AstraZeneca central dECG files repository are made accessible to the ECG Scientific Advisors for analysis.

As standard, 10-second ECGs are extracted by the EClysis© system twice per minute from the continuous recording and initially automatically analysed by the software.

Lead V2 will be analysed and reported as primary. Lead V5 will be analysed, for all visits, as backup for the individual where analysis in lead V2 is not deemed possible for pre-dose, for significant parts of whole visits or for whole visits. The analysis is performed blinded to treatment.

The ECG Scientific Advisor(s) will perform a preliminary analysis of the first 24 hours (as a minimum) of dECG recordings, in lead V2, with main focus on QT changes, wave morphology changes, and dysrhythmia. The AstraZeneca ECG Centre Cardiologist will review the data, perform an evaluation and interpretation of findings, and will provide a safety report.

The ECG Scientific Advisor will perform all required manual adjustments to the ECG annotations provided automatically by EClysis©. Finally, an external expert cardiologist will review the totality of data and perform all necessary adjustments before locking the EClysis© data into a read-only state.

The numerical values for ECG intervals and amplitudes will be exported and made accessible on the AstraZeneca central dECG repository to accredited data management specialists for conversion into SAS files. The following variables will be reported by the AstraZeneca ECG Centre: RR, PR, QRS, and QT intervals from the lead defined as primary in the protocol. Derived parameters (QTcF, heart rate, and others, as applicable) are calculated by the study statistician or designee.

6.3.8 Vital signs

6.3.8.1 Pulse rate and blood pressure

Supine pulse rate (bpm) and blood pressure (mmHg) will be measured at the time points specified in the study plans (Table 1 and Table 5). Measurements will be performed according to local procedures after 10 minutes' rest. Blood pressure, SBP and DBP, will be measured using the same cuff size, appropriate for arm circumference, throughout the study.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (4 mL) for the determination of avibactam and ceftazidime in plasma will be taken at the times presented in Table 3 and Table 7.

The volumes of urine collected over the time intervals presented in Table 1 and Table 5 will be recorded, and 10 mL aliquots from each collection interval will be stored for the determination of avibactam and ceftazidime in urine.

Blood samples (5 mL) for metabolite identification will be collected in Part A at the time points presented in Table 1.

Blood and urine samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of avibactam and ceftazidime concentrations in plasma and urine will be analysed by under the supervision of , , AstraZeneca.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be collected from each subject in Part A and Part B is presented in Table 10 and Table 11, respectively.

Table 10 Volume of blood to be drawn from each subject in Part A

Assessment		Sample volume (mL)[a]		No. of samples	Total volume (mL)	
Safety	Clinical chemistry	5	2.5	6	30	15
	Haematology	2	2	6	12	12
	Serology	3.5	2.5	1	3.5	2.5
	Endocrinology[c]	3.5	0	1	3.5	0
Follicle-stimulating hormone[b,c]		3.5	0	1	3.5	0
Metabolite identification		5	5	6	30	30
Pharmacokinetics		4	4	39	156	156
Total					**238.5**	**215.5**

[a] If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula at each sample time point.

[b] Female subjects only.

[C`] At analysis will be done with blood from the serology sample. Additional blood samples (2) may be collected for a pregnancy test.

Table 11 Volume of blood to be drawn from each subject in Part B

Assessment		Sample volume (mL)[a]		No. of samples	Total volume (mL)	
Safety	Clinical chemistry	5	2.5	8	40	20
	Haematology	2	2	8	16	16
	Serology	3.5	2.5	1	3.5	2.5
	Endocrinology[c]	3.5	0	1	3.5	3.5
Follicle-stimulating hormone[b,c]		3.5	0	1	3.5	3.5
Pharmacokinetics		4	4	90 (30 x 3)	360	360
Total					**426.5**	**405.5**

[a] If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula at each sample time point.

[b] Female subjects only.

C` At analysis will be done with blood from the serology sample. Additional blood samples (4) may be collected for a pregnancy test.

The number of samples collected and the volume required for each analysis may be changed during the study (ie, if additional samples are collected for repeated safety assessments). However, the maximum volume to be collected from each subject will not exceed 500 mL.

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 in this section.

7.2.1 Safety samples

Safety samples will be disposed of after analysis.

7.2.2 Pharmacokinetic samples

Samples will be disposed of after the CSR has been finalised, unless retained for future analyses.

Selected PK samples may be used for metabolite identification and/or quantification. These samples will be retained by, or on behalf of, AstraZeneca for a maximum of 5 years following the finalisation of the CSR. The results from any metabolite investigation will not be reported in the CSR, but separately in a metabolism report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

7.3 Labelling and shipment of biohazard samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C International Air Transport Association (IATA) 6.2 Guidance Document.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, 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 life cycle.

The Investigator keeps full traceability of collected biological samples from the subjects while in storage at the study centre until shipment or disposal (where appropriate) and keeps 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.

AstraZeneca oversees the entire life cycle through internal procedures, monitoring of the study centre, and auditing of external laboratory providers.

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

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, the subject will then be withdrawn from further study participation.

The Investigator will:

- Ensure that the subject's withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensure that biological samples from that subject, if stored at the study centre, are immediately identified, disposed of or destroyed, and the action documented
- Ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented, and the signed document returned to the study centre
- Ensure that the subject and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or destroyed and the action documented and returned to the study centre.

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 the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

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

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC and to the study centre personnel.

The opinion of the EC should be provided in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the EC annually.

Before enrolment of any subject into the study, the final CSP, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide regulatory authorities, the EC, and the Investigator with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

8.4 Informed consent

The Investigator will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an EC

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 CSP, then these changes will be documented in an Amendment and where required in a new version of the CSP (Revised CSP).

The Amendment should be approved by an EC and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised CSPs.

AstraZeneca will distribute any subsequent Amendments and Revised CSPs to the Investigator. For distribution to the EC see Section 8.3.

If an Amendment requires a change to the Informed Consent Form, AstraZeneca, and the EC should approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the study centre to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the Investigator (and other personnel involved with the study) their responsibilities with regard to CSP adherence and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator

9.2 Training of study centre personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of this CSP and related documents with the study centre personnel and also train them in any study-specific procedures and system(s) utilised.

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

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

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contact with the study centre, including visits to:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the study centre personnel is adhering to the CSP, 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 investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of or destroyed accordingly and the action is documented and reported to the subject

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

9.3.1 Source data

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

9.4 Study agreements

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

Agreements between AstraZeneca and the Investigator should be in place before any study-related procedures can take place or subjects are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

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

The study is expected to start in and to end by .

The study may be terminated at the study centre 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 CAZ104 or avibactam and ceftazidime alone.

10. DATA MANAGEMENT

Procedures applicable to :

A 21 CFR part 11 compliant electronic data capture (EDC) system will be used at this site. Electronic CRFs will be produced by for each subject. The majority of study data collected will be either directly entered by clinical research staff or directly captured from devices onto the electronic CRF. Data will be available for AstraZeneca review via pre-defined reports extracted from the database at agreed intervals. The electronic CRFs must be

kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

When direct data entry onto the electronic CRF is inappropriate or impractical data will be collected on paper source documents and subsequently transcribed, where necessary, onto the electronic CRFs by the clinical research staff of . All source documents will be retained by . Photocopies of completed source documents will be provided only if essential (ie, for regulatory purposes) at the request of the AstraZeneca.

All electronic CRF entries, corrections, and alterations must be made by the Investigator or other, authorised, study-site personnel and only by individuals who have received training on the EDC system. Site staff may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

Procedures applicable to :

Data collected at will be captured on a paper CRF designed to be compatible with the EDC system used at . Paper CRFs will be transferred electronically, as PDF files, to the Data Management department at only when complete, fully monitored and signed by the Investigator. Data from the paper CRF will be entered into the EDC system by the data management team and will be subject to verification by an independent operator as defined in the Data Management Plan. Once the data is in the EDC system it will be subject to the same validation and consistency checks as directly captured data. Data clarification forms (DCFs) will be generated for any discrepancies found and sent to the site for resolution.

The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the electronic CRFs are accurate and correct.

Procedures applicable to both clinical sites:

Only the date and time of laboratory sampling are recorded in the CRF. Data that are not directly captured eg, safety laboratory results and AE coding, are managed externally from the main study database. These data will be merged with the data from the main study database in post-production. Datasets supplied to AstraZeneca will contain all study data.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

The Data Management Plan will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the

course of the study. After completion of the study and when all collected data is validated, the database will be locked. Final data will be extracted from the EDC system and delivered to AstraZeneca in the form of SAS® datasets in accordance with defined project standards. For subjects dosed at a PDF copy of the electronic CRF will be produced for each study subject and included in the final delivery.

AE and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the Dictionary coding.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database. External data reconciliation will be done with the clinical database as applicable.

SAE/AE Reconciliation

Serious Adverse Event Reconciliation Reports are produced and reconciled with the Patient Safety database and/or the Investigational Site.

Data verification and validation

The source data verification will be carried out by a site monitor comparing database entered data to source documents (ie, ECG print-outs, laboratory results and other health records at the study site). Questions and corrections will be noted and verified by the Investigator.

11. EVALUATION AND CALCULATION OF VARIABLES BY

11.1 Calculation or derivation of safety variable(s)

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 and AEs leading to premature discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory, vital signs, and ECG data will be performed for identification of OAEs.

Examples of these are marked haematological 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 pharmacokinetic variables

The PK analyses of the plasma and urine concentration data for avibactam and ceftazidime will be performed at . Standard Operation Procedures and Work Instructions will be used as the default methodology, unless otherwise specified.

The actual sampling times will be used in the plasma PK parameter calculations. Pharmacokinetic parameters will be derived using non-compartmental methods with WinNonlin® Professional Version 5.2, or higher, ( ), or SAS® Version 9.1, or higher (SAS Institute, Inc., Cary, North Carolina). All PK computations will be performed using WinNonlin® Professional 5.2, or higher; or SAS® Version 9.1, or higher. Graphics may be prepared with SAS® Version 9.1, or higher; SigmaPlot® 9.0, or higher ( ); Excel 2007, or higher ( ); or WinNonlin® Professional 5.2, or higher.

Where possible, the following PK parameters will be determined for avibactam and ceftazidime when applicable:

- Maximum plasma concentration (C_{max}, μg/mL), obtained directly from the observed concentration versus time data
- Time of maximum plasma concentration (t_{max}, hr), obtained directly from the observed concentration versus time data
- Minimum plasma concentration during a dosing interval (C_{min}, μg/mL) on Days 4 and 11 in Part A and Day 4 in Part B, obtained directly from the observed concentration versus time data
- Time of minimum plasma concentration during a dosing interval (t_{min}, hr), obtained directly from the observed concentration versus time data
- Last quantifiable plasma concentration (C_{last}, μg/mL), obtained directly from the observed concentration versus time data
- Time of last quantifiable plasma concentration (t_{last}, hr), obtained directly from the observed concentration versus time data
- Calculated average plasma concentration during a dosing interval (C_{avg}, μg/mL) on Days 4 and 11 in Part A and Day 4 in Part B

- Fluctuation index during a dosing interval (FI, %) on Days 4 and 11 in Part A and Day 4 in Part B, calculated as $100*(C_{max}-C_{min})/C_{avg}$

- Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration [$AUC_{(0-t)}$, µg.hr/mL], calculated by linear up/log down trapezoidal summation

- Area under the plasma concentration time curve from zero (pre-dose) extrapolated to infinity (AUC, µg.hr/mL) on Day 1 only, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-t)} + C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 20% of AUC, then AUC and related parameters will not be reported

- Area under the plasma concentration-time curve during the dosing interval [$AUC_{(0-\tau)}$, µg.hr/mL], calculated by linear up/log down trapezoidal summation

- Terminal half-life ($t_{1/2}$, hr). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination

- Systemic plasma clearance (CL, L/hr)

- Volume of distribution at steady-state (V_{ss}, L), calculated as Mean Residence Time*CL

- Volume of distribution at the terminal phase (V_z, L), calculated as CL/λ_z

- Accumulation ratio for C_{max} (RC_{max})

- Accumulation ratio for $AUC_{(0-\tau)}$ [$RAUC_{(0-\tau)}$]

- Linearity index will be determined as the ratio of Day 11 $AUC_{(0-\tau)}$ to Day 1 AUC in Part A and as the ratio of Day 4 $AUC_{(0-\tau)}$ to Day 1 AUC in Part B

- Amount of drug excreted unchanged into urine, calculated as the product of the urine volume and the urine concentration. The amount will be calculated and reported for each collection interval and cumulatively [$A_{e(0-t)}$, mg]

- Fraction of dose excreted as unchanged drug into urine (f_e; % dose). The fraction will be calculated and reported for each collection interval and cumulatively

- Renal clearance (CL_R, L/hr), calculated as $A_{e(0-t)}$ divided by $AUC_{(0-t)}$ on Day 1 or as $A_{e(0-\tau)}$ divided by $AUC_{(0-\tau)}$ at steady-state

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

- The time interval (hr) of the log-linear regression to determine $t_{1/2}$ ($t_{1/2}$, Interval)
- Number of data points ($t_{1/2}$, N) included in the log-linear regression analysis to determine $t_{1/2}$
- Coefficient of determination (Rsq) for calculation of λ_z. If Rsq is less than or equal to 0.800, λ_z and related parameters will not be reported
- Percentage of AUC obtained by extrapolation (%AUCex)

Additional PK parameters may be determined if deemed appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY

12.1 Description of analysis sets

12.1.1 Safety analysis set

All subjects who receive at least 1 dose of investigational product and for whom any post-dose data are available will be included in the safety analysis set.

12.1.2 PK analysis set

The PK analysis set will include all subjects who receive at least 1 dose of avibactam or ceftazidime and have at least 1 scheduled post-dose PK measurement without important protocol deviations, violations, or events thought to significantly affect the PK of the investigational product. Subjects will be analysed according to the treatment they actually received.

12.2 Methods of statistical analyses

12.2.1 General principles

The PK, PD, and safety summaries, individual figures and data listings as well as the statistical analysis of the PK variables will be the responsibility of the study biostatistician at (using SAS® Version 9.1 or higher and, where appropriate, additional validated software).

In general, descriptive statistics will follow the rounding convention in the Global Standard Operating Procedures.

12.2.2 Subject characteristics

Continuous variables will be summarised by study part using descriptive statistics (n, mean, standard deviation [SD], minimum [min], median, and maximum [max]) in total. Categorical variables will be summarised by study part in frequency tables (frequency and proportion) in total.

12.2.3 Safety analyses

All safety data will be listed in subject listings. Continuous variables (haematology, clinical chemistry, and vital signs) will be summarised using descriptive statistics (n, mean, SD, min, median, and max) by study part, treatment and/or each scheduled assessment point, both as absolute values and as change from baseline. Categorical variables (urinalysis, ECG interpretation) will be summarised in frequency tables (frequency and proportion) by scheduled assessment point. Laboratory values and vital signs outside reference limits will be marked high and low where appropriate.

Adverse events will be summarised by study part, Preferred Term and System Organ Class using the MedDRA.

The number of subjects who had any AEs, SAEs, discontinuation due to AEs, OAEs, AEs with severe intensity, and AEs judged causally related to the investigational product by the Investigator will be summarized by study part. Any SAEs and DAEs will be listed separately.

12.2.4 Pharmacokinetic analyses

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A subject listing of all concentration-time data by study part for each treatment will be presented.

Pharmacokinetic variables (avibactam and ceftazidime plasma concentrations, urine amounts, and PK parameters) will be summarised by study part, study day/measurement time, and treatment using appropriate descriptive statistics (eg, n, arithmetic mean, SD, min, median, max, geometric mean, and geometric coefficient of variation [CV%]). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, geometric mean, and CV% will not be calculated for t_{max}.

For descriptive statistics, concentrations below lower limit of quantification (LLOQ) values will be handled as follows:

- At a time point where less than or equal to 50% of the values are below the LLOQ (BLQ), all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated

- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to not determined (ND). The max value will be reported from the individual data, and the min and median will be set to BLQ

- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV%, and BLQ will be written in fields for mean, geometric mean, min, median, and max

- The number of BLQ values (n below LLOQ) will be reported for each time point

Figures of mean (±SD) concentration-time data will be presented on linear and semi-logarithmic scales by study part and treatment. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales. Figures of individual and geometric mean AUC (Day 1), $AUC_{(0-\tau)}$ (Day 4), and C_{max} by treatment in Part B will be presented. Additional graphical presentations of PK data may be added at the discretion of the PK scientist.

An exploratory evaluation of achievement of steady-state will be performed graphically. Figures of mean plasma trough concentrations of avibactam and ceftazidime versus study days will be presented on linear scale by study part and treatment.

For Part B only, treatments will be compared between test and reference (Treatment C vs A for avibactam PK parameters, Treatment C vs B for ceftazidime PK parameters). Analyses will be performed by day (1 and 4) with a linear mixed-effects model using the logarithm of AUC (Day 1 only), $AUC_{(0-\tau)}$, (Day 4 only), and C_{max} (both Day 1 and Day 4) as the response variables, sequence, period, and treatment as fixed effects, and subject nested within sequence as random effect. Transformed back from the logarithmic scale, geometric means together with 95% confidence intervals (CIs) will be estimated and presented. Also, ratios of geometric means together with 90% CIs will be estimated and presented.

12.3 Determination of sample size

Twenty-four evaluable subjects will provide approximately 90% power to correctly conclude that the combined treatment has no effect on the PK of each of the individual treatment components. The power calculation was based on equivalence testing using standard equivalence limits of (0.8, 1.25), to compare the C_{max} of avibactam after Treatment A versus C_{max} of avibactam after Treatment C, and the C_{max} of ceftazadime after Treatment B versus C_{max} of ceftazidime after Treatment C. The within-subject SD of log(avibactam C_{max}) and log(ceftazidime C_{max}) were estimated as 0.2088 and 0.2171 respectively, using data from study avibactam/1002.

The estimates of within-subject variability for the AUC parameters were lower than for C_{max}, therefore the sample size will also provide sufficient power for comparisons involving AUC. Furthermore, in another recent study in Japanese healthy volunteers (D4280C00010), the observed within-subject variability was considerably lower.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca 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 a medical emergency the Investigator may contact the CPA Physician. If the CPA Physician is not available, contact the CPA Programme Director at AstraZeneca.

Name	**Role in the study**	**Address & telephone number**
	AstraZeneca CPA Programme Director	
	AstraZeneca CPA Physician	
Serious adverse event reporting	24-hour emergency cover at central R&D site	
	Chief Investigator	
	Principal Investigator	
	24 hour emergency telephone number	

Name	Role in the study	Address & telephone number
	Project Manager	

13.2 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca investigational product occurs during the course of the study, then the Investigator or other study centre personnel will inform the appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **the end of the next business day** of when he/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 timelines 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.

13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

13.3.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last administration of the investigational product.

Pregnancy of a subject'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 monitored and documented from the first administration until 3 months after the last administration of the investigational product.

14. LIST OF REFERENCES

Livermore 2008
Livermore DM, Mushtaq S, Warner M, Miossec C, Woodford N. NXL104 combinations versus *Enterobacteriaceae* with CTX-M extended-spectrum beta-lactamases and carbapenemases. J Antimicrob Chemother. 2008;62(5):1053-1056.

Louie et al 2010
Louie A, Bied A, Fregeau C, Van Scoy B, Brown D, Liu Q, et al. Impact of different carbapenems and regimens of administration on resistance emergence for three isogenic *Pseudomonas aeruginosa* strains with differing mechanisms of resistance. Antimicrob Agents Chemother. 2010;54(6):2638-2645.

Rossolini and Docquier 2006
Rossolini GM and Docquier JD. New β-lactamases: A paradigm for the rapid response of bacterial evolution in the clinical setting. Future Microbiol. 2006;1:295-308.

Schwaber and Carmeli 2008
Schwaber MJ and Carmeli Y. Carbapenem-resistant *Enterobacteriaceae*: a potential threat. J Am Med Assoc. 2008;300:2911-2913.

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Clinical Study Protocol Appendix B

Drug Substance	CAZ104
Study Code	D4280C00011
Edition Number	1
Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	CAZ104
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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Clinical Study Protocol Appendix D

Drug Substance	CAZ104
Study Code	D4280C00011
Edition Number	1
Date	

Appendix D

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

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory date into the laboratory CRF.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central ST

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP

- Completes the Liver CRF Modules.

- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP,

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

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

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

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

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

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

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

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

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

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

2. REFERENCES

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

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm