AstraZeneca

Clinical Study Report Synopsis

Drug Substance	CAZ-AVI/CXL
Study Code	D4280C00023
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A Phase 1, Open-label, Multiple-dose, Single Centre Study to Investigate the Effect of Administration of CAZ-AVI and CXL on the Intestinal Flora of Healthy Volunteers

Study dates:	First volunteer enrolled: 28 August 2013 Last volunteer last visit: 5 March 2014
Phase of development:	Clinical pharmacology and Clinical Microbiology (1)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre

This study was conducted at 1 study centre in the Clinical Pharmacology Trial Unit.

Publications

None at the time of writing this Clinical Study Report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Microbiological	To investigate the effect of administration of CAZ-AVI on the intestinal flora of healthy volunteers	The number and types of microorganisms in faeces; CAZ-AVI susceptibility testing
Primary	Microbiological	To investigate the effect of administration of CXL on the intestinal flora of healthy volunteers	The number and types of microorganisms in faeces; CXL susceptibility testing
Secondary	Safety	To investigate the safety, and tolerability of CAZ-AVI and CXL in healthy volunteers	Adverse events, 12-lead ECGs, safety laboratory assessments, physical examinations, and vital signs
Secondary	PK	To investigate the pharmacokinetics of CAZ-AVI and CXL in healthy volunteers[1]	C_{max}, t_{max}, t_{last}, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, $t_{½}$, CL, CL/F, V_{ss}, and V_z/F
Secondary	PK	To measure CAZ-AVI in plasma and faeces using bioactivity techniques	
Secondary	PK	To measure CXL in plasma and faeces using bioactivity techniques	

[1] In this report in the context of bioanalysis by LC/MS-MS or of characterizing pharmacokinetics, CXL may be taken to represent Ceftaroline, Ceftaroline fosamil, Ceftaroline M-1 and/or Avibactam, (ie, the individual components found in plasma after intravenous administration of CXL

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Microbiological	To describe the in vitro susceptibility of new colonising bacteria in the intestinal microflora to CAZ-AVI during and after CAZ-AVI administration	CAZ-AVI MIC
Secondary	Microbiological	To describe the in vitro susceptibility of new colonising bacteria in the intestinal microflora to CXL during and after CXL administration	CXL MIC

$AUC_{(0-\tau)}$: Area under the plasma concentration-time curve during the dosing interval; $AUC_{(0-t)}$: Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CAZ-AVI: Ceftazidime-avibactam; CL: Systemic plasma clearance; CL/F: Apparent plasma clearance; C_{max}: Maximum plasma concentration; CXL: Ceftaroline fosamil-avibactam; ECG: Electrocardiogram; MIC: Minimal inhibitory concentration; PK: Pharmacokinetic; $t_{½}$: Half-life; t_{last}: Time of last quantifiable plasma concentration; t_{max}: Time of C_{max}; V_{ss}: Volume of distribution at steady state; V_z/F: Apparent volume of distribution

Study design

This was an open-label, multiple-dose study in healthy volunteers designed to investigate the effect of multiple administrations of ceftazidime-avibactam (CAZ-AVI) or ceftaroline fosamil-avibactam (CXL) multiple administrations over 7 days on intestinal flora. A total of 28 volunteers (13 volunteers in Cohort 1 and 15 volunteers in Cohort 2) were enrolled at a single study centre in Sweden.

Cohort 1 received CAZ-AVI (2000 mg CAZ and 500 mg AVI) by intravenous infusion over 2 hours, every 8 hours on Days 1 to 6 (inclusive) and a single dose on Day 7.

Cohort 2 received CXL (600 mg ceftaroline fosamil and 600 mg AVI) by intravenous infusion over 1 hour, every 8 hours on Days 1 to 6 (inclusive) and a single dose on Day 7.

In each cohort, each volunteer was to receive a total of 19 infusions.

Due to the potential impact on the intestinal flora, volunteers were not to use regular medications or to receive any antimicrobial drug in the 3 months prior to this study.

The duration of the study for each volunteer was approximately 7 weeks. For both cohorts, the study comprised 4 visits:

- Visit 1 (screening): Screening evaluations occurred within 28 days prior to Visit 2

- Visit 2 (treatment period): Eligible volunteers were admitted to the study centre on Day -1 (within 24 hours prior to the first infusion on Day 1) for baseline assessments to be performed. The volunteers remained resident at the study centre until the completion of assessments on Day 8. Intravenous infusions of either CAZ-AVI (Cohort 1) or CXL (Cohort 2) every 8 hours on Days 1 to 6 (inclusive) and a single dose on Day 7 were administered to the volunteers

- Visit 3 (Day 10): was an outpatient visit

- Visit 4 (follow-up): A post-study follow-up visit took place on Day 14

- Visit 5 (end of study assessment): The end of study assessment took place on Day 21

Target subject population and sample size

A total of 28 volunteers were enrolled (13 volunteers in Cohort 1 and 15 volunteers in Cohort 2) to ensure 24 evaluable volunteers (ie, 12 volunteers in the microbiological analysis set for each cohort).

In Cohort 1, a total of 13 male and female volunteers with a mean age of 25 years and body mass index (BMI) within the protocol-specified range of 19 kg/m^2 to 30 kg/m^2 received at least 1 dose of the investigational product.

In Cohort 2, a total of 15 male and female volunteers with a mean age of 27 years and BMI within the protocol-specified range of 19 kg/m^2 to 30 kg/m^2 received at least 1 dose of the investigational product.

Investigational products: dosage, mode of administration and batch numbers

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
Avibactam (AVI)[a]	Sterile lyophilisate for concentrate for solution for infusion; 600 mg vial	Patheon	12-001986AZ
Ceftaroline fosamil[a]	Sterile crystalline powder for concentrate for solution for infusion; 600 mg vial	Facta Farmaceutici S.p.A	13-000538AZ
Ceftazidime-avibactam (CAZ-AVI)[b]	Sterile ceftazidime avibactam powder for concentrate for solution for infusion; 2000 mg/500 mg vial	GlaxoSmithKline	12-003109AZ

[a] Administered to subjects in Cohort 2 only
[b] Administered to subjects in Cohort 1 only

Duration of treatment

In both cohorts, a total of 19 doses were to be administered to each volunteer.

Volunteers in Cohort 1 were to receive CAZ-AVI (2000 mg CAZ and 500 mg AVI) by intravenous infusion given over 2 hours, every 8 hours on Days 1 to 6 (inclusive) and a single dose on Day 7.

Volunteers in Cohort 2 were to receive CXL (600 mg ceftaroline fosamil and 600 mg AVI) by intravenous infusion given over 1 hour, every 8 hours on Days 1 to 6 (inclusive) and a single dose on Day 7.

Statistical methods

Pharmacokinetic parameters were only calculated for plasma concentrations determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS). Pharmacokinetic concentrations and parameters were summarised using appropriate descriptive statistics.

The effect of CAZ-AVI and CXL on the intestinal microflora was assessed using the log number of microorganisms (log CFU) per gram faeces, before, during and after dosing, both as absolute values and changes from baseline. The 95% confidence intervals (CIs) for the median change from baseline in log CFU at each scheduled assessment (Days 2, 5, 7, 10, 14, and 21) were tabulated by organism and day. The changes from baseline at Day 7 (end of treatment) and Day 21 (end of study) were analysed using Wilcoxon signed rank tests.

Subject population

Cohort 1

In Cohort 1 a total of 13 subjects were enrolled and all received at least 1 dose of CAZ-AVI. Subject E0001007 withdrew from the study due to social reasons after receiving 6 doses (2 days) of CAZ-AVI and did not complete the study or treatment.

Cohort 2

In Cohort 2, a total of 15 subjects were enrolled and all received at least 1 dose of CXL. Subject E0001041 was discontinued from the treatment and study on Day 3 due to an AE of Rash maculo-papular.

Summary of pharmacokinetic results

Cohort 1

Plasma PK parameters of avibactam and ceftazidime by LC-MS/MS method were well characterised and in line with previous PK results at a therapeutic dose level (CAZ-AVI Investigator's Brochure: Edition 12).

CAZ-AVI was detected in the plasma in all volunteers during treatment by the bioactivity method. CAZ-AVI was detected in the faeces up to 2 days after the last dose by the bioactivity method.

Cohort 2

Plasma PK parameters of avibactam, ceftaroline, ceftaroline fosamil, and ceftaroline M-1 by LC-MS/MS method were well characterised and in line with previous PK results at a therapeutic dose level (CXL Investigator's Brochure: Edition 3).

CXL was detected in the plasma in all volunteers during treatment by the bioactivity method. CXL was detected in the faeces by the bioactivity method in 4 volunteers during treatment. CXL was not detected in any sample pre- or post-treatment.

Summary of pharmacodynamic (microbiological) results

Cohort 1

Disturbances in the intestinal microflora were observed. For aerobic intestinal microflora, on average, the number of *E. coli* decreased significantly during the administration of CAZ-AVI and the number of *Enterococci* increased. In some subjects, a reduction in other *Enterobacteria* was also observed. Except for *Enterococci*, the aerobic microflora colony counts were not significantly different from baseline on Day 21. For anaerobic intestinal microflora, *Lactobacilli*, *Bifidobacteria*, *Clostridia*, and *Bacteroides* decreased significantly on average during administration of CAZ-AVI. All the anaerobic microflora colony counts were not significantly different from baseline on Day 21. Aerobic and anaerobic Gram-positive bacteria with elevated CAZ-AVI MIC values present in the normal flora were recovered before, during, and following treatment. *Enterobacteriaceae* with elevated CAZ-AVI MIC values were not isolated before, during, and following treatment from the faecal flora. Five of 12 volunteers were positive for *C. difficile* (Days 14 and/or 21). Four of these volunteers reported gastrointestinal AEs. These AEs were of short duration and mild intensity, and resolved without specific treatment.

Cohort 2

Disturbances in the intestinal microflora were observed. For aerobic intestinal microflora, on average, the number of *E. coli* decreased significantly during the administration of CXL. In some subjects, *Enterococci* decreased on Day 7 and increased significantly on Day 21. *Candida* increased significantly on Day 7. With the exception of *Enterococci*, the aerobic microflora colony counts were not significantly different from baseline on Day 21. For anaerobic intestinal microflora, *Lactobacilli* and *Bifidobacteria* decreased significantly on average during administration of CXL. *Clostridia* decreased in some subjects. No changes in the *Bacteroides* population were seen. All the anaerobic microflora colony counts were not significantly different from baseline on Day 21. Aerobic and anaerobic bacteria with elevated MIC values for CXL were recovered in the normal flora before, during, and following

treatment without a predominant pathogen or temporal pattern. One volunteer was positive for *C. difficile* (Day 21). No gastrointestinal AE was reported for this volunteer.

Summary of safety results

Cohort 1

- Twelve subjects in Cohort 1 reported at least 1 AE. No deaths, SAEs, or DAEs were reported in Cohort 1

- The most commonly reported AE belonged to the SOC Gastrointestinal disorders (84.6% of the subjects; 11/13). Diarrhoea was reported by 8 (61.5%), and Flatulence by 5 (38.5%) subjects. Headache and Rash maculo-papular were reported by 3 (23.1%) subjects. One subject each reported an AE of Rash, Rash pruritic, Vesiculopapular rash, and Rash papular (7.7% each). Diarrhoea, Headache, maculopapular or urticarial rash, and Pruritus are expected events for the ceftazidime portion of CAZ-AVI. Overall 10 (76.9%) subjects reported at least 1 AE considered to be causally related to the investigational product by the Investigator

- All the AEs reported in Cohort 1 were considered to be of mild intensity by the Investigator, except for 2 AEs, which were of moderate intensity. Subject E0001002 had a moderate AE of diarrhoea and Subject E0001010 had a moderate AE of headache. Both these AEs resolved by the end of the study

- No trends were observed in haematology, biochemistry, and urinalysis parameters over time or in mean or median vital signs values for any subject during the study. Although abnormal 12-lead ECG results were reported for Cohort 1 during the study, none of the values were considered clinically significant by the Investigator

Cohort 2

- All the subjects in Cohort 2 reported at least 1 AE. No SAEs or deaths were reported in Cohort 2. Subject E0001041 was permanently discontinued from the study due to an AE of Rash maculo-papular

- The most commonly reported AEs belonged to the SOCs Skin and subcutaneous tissue disorders (80% of the subjects; 12/15) and Gastrointestinal disorders (66.7% of the subjects; 10/15). Flatulence was reported by 5 (33.3%), and Diarrhoea by 3 (20.0%) subjects. At least 1 rash event was reported by 12 subjects and at least 1 pruritus event by 5 subjects. These are expected events for the ceftaroline portion of CXL

  - Rash maculo-papular was reported by 6 (40%), Pruritus and Rash each by 4 (26.7%), Rash papular by 2 (13.3%) subjects. One subject each reported an

AE of Papulae, Pruritus generalised, Rash erythematous and Skin fissures (6.7% each)

- All the AEs reported in Cohort 2 were considered to be of mild intensity by the Investigator, except for 5 AEs reported by 4 subjects which were of moderate intensity. A total of 9 mild and 2 moderate AEs reported by 7 subjects were ongoing at the end of the study
- No clinically significant trends were observed in mean and median biochemistry and haematology laboratory values
- A total of 5 subjects had physical examination findings, all of which were reported as AEs
- One subject tested positive for the serum pregnancy test at Visit 4 (follow-up). The outcome of the pregnancy was elective termination which was not due to a medical reason