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# A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia

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## ABSTRACT

Ceftazidime/avibactam comprises the broad-spectrum cephalosporin ceftazidime and the non- $\beta$ -lactam  $\beta$ -lactamase inhibitor avibactam. This phase 3, randomised, double-blind study (NCT01726023) assessed the efficacy and safety of ceftazidime/avibactam plus metronidazole compared with meropenem in patients with complicated intra-abdominal infection (cIAI) in Asian countries. Subjects aged 18–90 years and hospitalised with cIAI requiring surgical intervention were randomised 1:1 to receive every 8 h either: ceftazidime/avibactam (2000/500 mg, 2-h infusion) followed by metronidazole (500 mg, 60-min infusion); or meropenem (1000 mg, 30-min infusion). Non-inferiority of ceftazidime/avibactam plus metronidazole to meropenem was concluded if the lower limit of the 95% confidence interval (CI) for the between-group difference in clinical cure rate was greater than  $-12.5\%$  at the test-of-cure (TOC) visit (28–35 days after randomisation) in the clinically evaluable (CE) population. Safety was also evaluated. Of 441 subjects randomised, 432 received at least one dose of study medication (ceftazidime/avibactam plus metronidazole,  $n = 215$ ; meropenem,  $n = 217$ ). In the CE population at the TOC visit, non-inferiority of ceftazidime/avibactam plus metronidazole to meropenem was demonstrated, with clinical cure reported for 93.8% (166/177) and 94.0% (173/184) of subjects, respectively (between-group difference,  $-0.2$ , 95% CI  $-5.53$  to 4.97). The clinical cure rate with ceftazidime/avibactam plus metronidazole was comparable in subjects with ceftazidime-non-susceptible and ceftazidime-susceptible isolates (95.7% vs. 92.1%, respectively). Adverse events were similar between the study groups. Ceftazidime/avibactam plus metronidazole was non-inferior to meropenem in the treatment of cIAIs in Asian populations and was effective against ceftazidime-non-susceptible pathogens. No new safety concerns were identified.

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The RECLAIM 3 clinical study protocol will be available at <http://www.astrazenecaclinicaltrials.com> upon publication of the manuscript.

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## 1. Introduction

The prevalence and diversity of enteric bacteria producing extended-spectrum  $\beta$ -lactamases (ESBLs) conferring resistance to  $\beta$ -lactam antibiotics has become a global concern [1–3]. Complicated intra-abdominal infections (cIAIs) are localised or diffuse infections of the peritoneum caused by various conditions,

including gastrointestinal perforation, necrosis of the gut wall spilling bacteria, or dehiscence of bowel anastomoses [4]. Effective treatment of cIAls therefore requires both adequate source control and empirical antimicrobial therapy that includes agents with an extended spectrum of activity against Gram-negative as well as anaerobic pathogens [5,6].

The Study for Monitoring Antimicrobial Resistance Trends (SMART) showed that ESBL-positive rates for Enterobacteriaceae isolated from cIAls were consistently highest in the Asia-Pacific region compared with the rest of the world from 2002 to 2011 [7]. Carbapenems have been used increasingly as a treatment option. However, this trend has its own implications, with a notable increase in carbapenemase-producing Enterobacteriaceae observed across Asia [8,9].

Ceftazidime/avibactam comprises ceftazidime, an established antipseudomonal cephalosporin, and avibactam, a first-in-class non- $\beta$ -lactam  $\beta$ -lactamase inhibitor with activity against Ambler class A [including ESBLs such as SHV, TEM and CTX-M, and *Klebsiella pneumoniae* carbapenemase (KPC)], class C (AmpC) and some class D (OXA-48) enzymes [10,11]. When tested in vitro, avibactam restores the antimicrobial activity of ceftazidime, with ceftazidime/avibactam demonstrating reduced minimum inhibitory concentrations (MICs) against various populations of ceftazidime-non-susceptible Gram-negative bacteria, including some carbapenem-resistant Enterobacteriaceae [11–14].

Ceftazidime/avibactam was approved in 2015 by the US Food and Drug Administration (FDA) for the treatment of cIAI (in combination with metronidazole) and complicated urinary tract infection (cUTI), including acute pyelonephritis, in adults who have limited or no alternative treatment options [15]. Approval was based in part on data from two phase 2 trials in Western subjects (NCT00690378; NCT00752219) [16,17] and has been subsequently supported by data from phase 3 trials in subjects in Western hospitals with cIAI (NCT01499290; NCT01500239) [18], cUTI (NCT01595438; NCT01599806) [19], or those with either cIAI or cUTI with ceftazidime-non-susceptible Gram-negative infections (NCT01644643) [20]. An additional phase 3 study in subjects with nosocomial pneumonia, including ventilator-associated pneumonia (VAP), has recently been completed (NCT01808092). Data from these phase 3 programmes contributed towards the recent approval by the European Medicines Agency (EMA) of ceftazidime/avibactam for the treatment of adults with cIAI, cUTI (including pyelonephritis), hospital-acquired pneumonia (including VAP) and infections due to Gram-negative organisms in patients with limited treatment options [21].

Potential pharmacokinetic and pharmacodynamic variation in different ethnic groups owing to genetic and environmental factors may affect the efficacy and safety of a drug [22,23]. This is especially relevant when considering combination therapies, such as ceftazidime/avibactam, in which it is essential that effective drug concentrations of both elements are maintained. This phase 3 study (NCT01726023) assessed the efficacy and safety of ceftazidime/avibactam plus metronidazole in patients hospitalised with cIAI in a sample of Asian countries (China, Republic of Korea and Vietnam) by determining the proportion of subjects assessed as clinical cure after receiving ceftazidime/avibactam plus metronidazole compared with those receiving meropenem.

## 2. Methods

### 2.1. Study design

RECLAIM 3 was a phase 3, multicentre, randomised, double-blind, double-dummy, comparative study performed in China, the Republic of Korea and Vietnam between January 2013 and March 2015. The study was conducted in accordance with Good Clinical Practice guidelines and with the ethical principles that have their

origin in the Declaration of Helsinki. For each participating centre, protocols (including all amendments) and informed consent documents were approved by an independent ethics committee and/or institutional review board. To be eligible, all subjects or their legal representatives had to provide informed written consent.

Subjects were randomised 1:1 to receive either ceftazidime/avibactam 2000/500 mg as a 2-h intravenous (i.v.) infusion followed by metronidazole 500 mg as a 60-min i.v. infusion every 8 h, or meropenem 1000 mg as a 30-min i.v. infusion every 8 h. Matching placebo infusions were used to maintain blinding. For subjects with moderate renal impairment [creatinine clearance (CrCL) 31–50 mL/min calculated using the Cockcroft–Gault method], dose regimen adjustments were made to ceftazidime/avibactam 1000/250 mg every 12 h and to meropenem 1000 mg every 12 h. No adjustment for renal impairment was required for metronidazole.

Subjects were treated for a minimum of 5 days and for up to 14 days with i.v. study therapy. After 5 days, i.v. study therapy could be stopped if clinical improvement was observed as judged by the study investigator. Use of other systemic antibacterial treatments was prohibited unless *Enterococcus* spp. or methicillin-resistant *Staphylococcus aureus* (MRSA) were among the pathogens suspected or isolated. In this case, where available, subjects were permitted to receive vancomycin, linezolid or daptomycin.

### 2.2. Subjects

This study included subjects aged 18–90 years and hospitalised with cIAI requiring surgical intervention. Diagnosis was based on clinical assessment, including intra-operative/laparoscopic findings within 24 h either side of randomisation (further details of cIAI diagnosis are detailed in the Supplementary material). Microbiological confirmation was not a prerequisite.

Key exclusion criteria were diagnosis with traumatic bowel perforation undergoing surgery within 12 h; perforation of gastroduodenal ulcers undergoing surgery within 24 h; abdominal wall abscess, bowel obstruction or ischaemic bowel without perforation; intra-abdominal processes in which the primary aetiology was not likely to be infective; simple cholecystitis or gangrenous cholecystitis without rupture; simple appendicitis or acute suppurative cholangitis; necrotizing pancreatitis or pancreatic abscess; cIAI considered unlikely to respond to 5–14 days of antibiotic treatment; known history of serious allergy to  $\beta$ -lactam antibiotics or metronidazole; and CrCL  $\leq$  30 mL/min. Further inclusion and exclusion criteria are provided in the Supplementary material.

### 2.3. Procedures

After assessment for eligibility, patients were enrolled by the lead investigator at each study centre. Randomisation to each treatment group was performed according to a central randomisation schedule, and computer-generated randomisation codes were assigned sequentially to eligible patients. These codes were assigned by the unblinded pharmacist/designee of each centre using the interactive voice response system/interactive web response system. The same unblinded designee at each site prepared all of the blinded i.v. study therapy according to the handling instructions. All other personnel remained blinded to study therapy until final unlocking of the database, or in the case of a medical emergency.

Blood samples and specimens taken from the site of abdominal infection during surgery were collected for culture during screening within 24 h prior to the first dose of i.v. study therapy. Susceptibility testing of the isolates against study drugs was performed by the local laboratory using disk diffusion methodology and by the central laboratory using broth microdilution and disk diffusion according to Clinical Laboratory Standards Institute (CLSI) methodology and interpretive criteria where they exist [24]. Sub-

**Table 1**  
Analysis populations and associated endpoints reported in the present study.

Population	Definition	Assessment
Modified intention-to-treat (MITT)	Subjects met the disease definition of cIAI.	Baseline demographics and subject characteristics.
Clinically evaluable (CE)	Subjects received at least one dose of study drug.	
	Subjects met the disease definition of cIAI. Subjects with a bacterial species not expected to respond to both study drugs were excluded.	Primary endpoint: clinical cure rate at the TOC visit. Secondary endpoints: clinical cure rate at the EOT and LFU visits.
	Subjects either received therapy for $\geq 48$ h with 80% of the scheduled drug administered; or received therapy for $< 48$ h before discontinuing due to an AE.	
	Subjects were evaluated at the EOT, TOC or LFU visit with a clinical response of cure or failure.	
	Subjects had no deviations from the protocol that would affect the assessment of efficacy.	
	Subjects did not receive any prior antibiotics other than protocol-specified antibiotics with specified duration (see Supplementary material).	
	With the exception of metronidazole and protocol-specified antibiotics for the coverage of <i>Enterococcus</i> spp. and MRSA (see exclusion criteria 3, Supplementary material), subjects did not receive any concomitant antibiotic therapy from the time of randomisation to the time of each assessment visit. This did not include subjects with a response of clinical failure who required additional antibiotic therapy. Topical antibacterials and antifungals were permitted as long as not applied to the surgical site.	Secondary endpoints: clinical cure rate at the EOT, TOC and LFU visits.
	Subjects were considered to have received adequate initial source control of the infection.	
Microbiologically modified intention-to-treat (mMITT)	Subjects met the disease definition of cIAI.	
	Subjects had at least one aetiological pathogen identified at study entry. Those with a bacterial species typically not expected to respond to both study drugs (e.g. <i>Acinetobacter</i> spp., <i>Stenotrophomonas</i> spp.) were excluded.	
Microbiologically evaluable (ME)	Subjects met the criteria for the CE population.	
	Subjects had at least one Gram-negative pathogen in the pre-study culture that was susceptible to both groups of study drugs.	Secondary endpoints: clinical cure rate at the EOT, TOC and LFU visits.
Extended microbiologically evaluable (eME)	Subjects met the criteria for the CE population.	
	Subjects had at least one Gram-negative pathogen in the pre-study culture regardless of susceptibility.	Secondary endpoints: clinical cure rate at the EOT, TOC and LFU visits; and clinical cure rate at the TOC visit in patients with infections caused by ceftazidime-non-susceptible or ceftazidime-susceptible isolates.
Safety	Subjects who received any amount of either study drug.	
		Secondary endpoint: safety profile of ceftazidime/avibactam plus metronidazole compared with meropenem.

cIAI, complicated intra-abdominal infection; AE, adverse event; EOT, end-of-treatment; TOC, test-of-cure; LFU, late-follow-up; MRSA, methicillin-resistant *Staphylococcus aureus*.

CE, eME, ME and safety populations were analysed according to treatment received; MITT and mMITT were analysed according to randomisation group.

jects with isolates typically not expected to respond to either study drug (e.g. *Acinetobacter* spp. and *Stenotrophomonas* spp.) were excluded from the study.

Clinical response was determined by the investigators as clinical cure, failure or indeterminate at the end-of-treatment (EOT) (within 24 h following the last i.v. infusion of study therapy), test-of-cure (TOC) (28–35 days after randomisation) and late follow-up (LFU) (42–49 days after randomisation) visits. Clinical cure was defined as resolution or improvement in signs and symptoms of the index infection so that no further treatment was required. Clinical failure was defined as any patients meeting the following criteria: death related to IAI; persisting or recurrent infection within the abdomen found at re-intervention either percutaneously or operatively; post-surgical wound infections that required additional antibiotics and/or non-routine wound care; additional antibiotics for ongoing symptoms of IAI; and previously meeting criteria for failure. Patients were classified as indeterminate if study data were not available for evaluation of study drug efficacy for any reason. Adequacy of source control was assessed by an independent surgical review panel (SRP) blinded to the study therapy. Clinical failures with inadequate source control as assessed by the SRP were reclassified as indeterminate.

#### 2.4. Endpoints

Efficacy endpoints were assessed in the analysis populations shown in Table 1. The primary efficacy endpoint was the clinical cure rate at the TOC visit in clinically evaluable (CE) subjects. Key secondary efficacy endpoints reported here include clinical cure rate

in the CE population at the EOT and LFU visits; clinical cure rate at the EOT, TOC and LFU visits in the microbiologically modified intention-to-treat (mMITT), microbiologically evaluable (ME) and extended ME (eME) populations; and clinical cure rate in subjects with ceftazidime-non-susceptible pathogens (defined by CLSI interpretive criteria for both the resistant and intermediate categories: ceftazidime MIC  $\geq 8$  mg/L for Enterobacteriaceae and MIC  $\geq 16$  mg/L for *Pseudomonas aeruginosa*) in the eME population.

Adverse events (AEs) were assessed from time of screening up to and including the LFU visit in the safety population. AEs were summarised by preferred term and system organ class using MedDRA vocabulary (version 18.0).

At screening, baseline and throughout the study up to the LFU visit, blood and urine samples were collected and were sent to a central laboratory for haematology, clinical chemistry and urinalysis; vital signs were monitored; and 12-lead electrocardiograms (ECGs) were performed. CrCL was calculated at screening using serum creatinine levels from the local laboratory.

#### 2.5. Statistical analyses

For the primary endpoint of clinical cure rate in the CE population at the TOC visit, non-inferiority of ceftazidime/avibactam plus metronidazole compared with meropenem was concluded if the lower limit of the 95% confidence interval (CI) for the between-group difference was greater than  $-12.5\%$ . Between-group differences and two-sided 95% CIs were determined using the unstratified Miettinen & Nurminen method [25]. Sensitivity analyses with subjects stratified by baseline severity of disease [Acute Physiology and

Chronic Health Evaluation (APACHE) II score  $\leq 10$  or  $>10$  and  $\leq 30$ ] and country (China and non-China) were performed for the primary efficacy variable. Clinical outcome at the TOC visit in the CE population was also analysed by patient and disease baseline characteristic subgroups. SAS® software v.9.1 or higher (SAS Institute, Inc., Cary, NC) was used to conduct all statistical analyses.

Study population size was designed to provide 80% power for a  $-12.5\%$  non-inferiority margin. Assuming that both treatment groups had an underlying cure rate of 80% in the CE population, and that 80% of randomised subjects were included in the CE population, this required 404 subjects (202 per treatment group) to be randomised, with a minimum of 250 eligible subjects from China to adhere to Chinese State Food and Drug Administration requirements.

### 3. Results

#### 3.1. Patient disposition and baseline characteristics

Of the 486 subjects enrolled into the study, 441 subjects from 43 centres were randomised from 14 January 2013 to 30 January 2015. Of these, 270 (61.2%) were randomised in China, 105 (23.8%) in the Republic of Korea and 66 (15.0%) in Vietnam. Overall, 432 subjects received at least one dose of i.v. study medication (ceftazidime/avibactam plus metronidazole,  $n = 215$ ; meropenem,  $n = 217$ ) and 398 subjects completed treatment (ceftazidime/avibactam plus metronidazole,  $n = 196$ ; meropenem,  $n = 202$ ). The primary analysis population (the CE population) comprised 177 and 184 subjects in

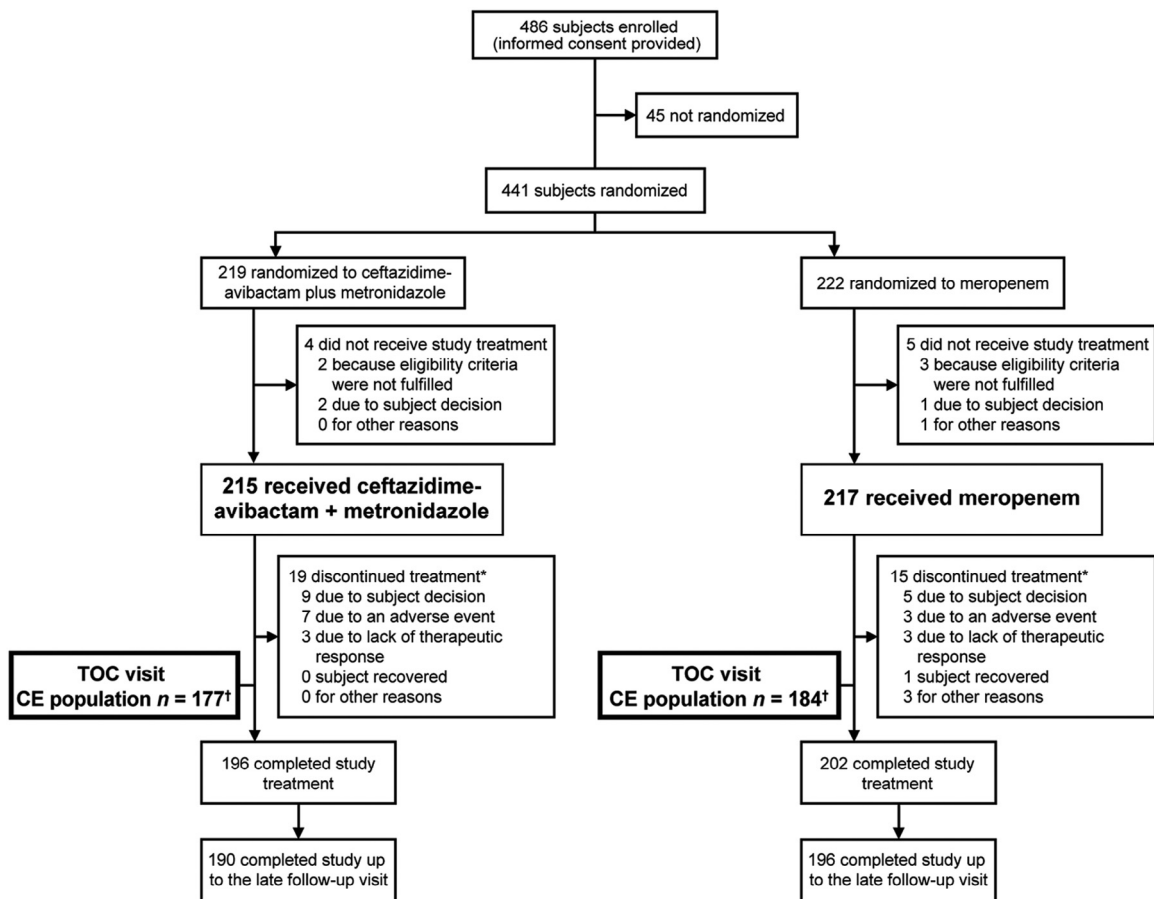
the ceftazidime/avibactam plus metronidazole group and meropenem group, respectively (Fig. 1).

Baseline demographics and clinical characteristics in the modified intention-to-treat (MITT) population (comprising subjects who met the disease definition of cIAI and received at least one dose of study drug) were generally balanced between treatment groups (Table 2). The mean  $\pm$  standard deviation duration of exposure to i.v. study therapy in the safety population was  $6.9 \pm 2.9$  days in the ceftazidime/avibactam plus metronidazole group and  $7.3 \pm 2.8$  days in the meropenem group. Across both groups, 21.3% of subjects had not received any systemic antimicrobial therapy in the 72 h prior to randomisation. A further 65.4% had received  $<24$  h of prior systemic antimicrobial therapy (Table 2). Baseline characteristics in the primary analysis population (the CE population) were generally comparable with those observed in the MITT population.

#### 3.2. Pathogens at baseline

Baseline pathogens isolated from blood and/or the site of IAI were similar across treatment arms. The proportions of patients with monomicrobial and polymicrobial infections are summarised in Table 2.

The mMITT population comprised 295 subjects, of whom 239 (81.0%) had one or more Enterobacteriaceae isolate identified from the blood and/or intra-abdominal site. The most frequently reported Enterobacteriaceae were *Escherichia coli* (173 subjects; 58.6%) and *K. pneumoniae* (63 subjects; 21.4%). Of the 47 subjects (15.9%)



**Fig. 1.** Patient flow. \*Study treatment was stopped before receiving the minimum 5 days of treatment for any reason, or at any time and for any reason before the complicated intra-abdominal infection was considered resolved or cured and a non-study antibiotic was required to complete treatment. †Primary analysis population comprising all subjects who met the clinical disease criteria and who had an evaluable assessment and no deviations from the protocol that affected the assessment of efficacy.



**Table 2**  
Baseline patient and disease characteristics (modified intention-to-treat population)<sup>a</sup>.

Parameter	Ceftazidime/avibactam + metronidazole (n = 214)	Meropenem (n = 217)
Age (years) (mean ± S.D.)	48.5 ± 16.8	48.5 ± 17.4
Sex male	141 (65.9)	153 (70.5)
Asian	214 (100)	217 (100)
Chinese	127 (59.3)	135 (62.2)
BMI (kg/m <sup>2</sup> ) (mean ± S.D.)	22.7 ± 3.5	22.4 ± 3.5
APACHE II score		
≤10	201 (93.9)	201 (92.6)
>10 to ≤30	13 (6.1)	16 (7.4)
Primary diagnosis		
Appendiceal perforation or periappendiceal abscess	83 (38.8)	79 (36.4)
Secondary peritonitis	36 (16.8)	38 (17.5)
Cholecystitis	33 (15.4)	27 (12.4)
Intra-abdominal abscess	22 (10.3)	24 (11.1)
Acute gastric and duodenal perforations	22 (10.3)	23 (10.6)
Traumatic perforations	13 (6.1)	17 (7.8)
Diverticular disease	5 (2.3)	9 (4.1)
Prior treatment failure	26 (12.1)	27 (12.4)
Systemic antimicrobial therapy in the previous 72 h before randomisation	167 (78.0)	172 (79.3)
≤24 h exposure	139 (65.0)	143 (65.9)
Infection type		
Monomicrobial infection	84 (39.3)	101 (46.5)
Polymicrobial infection	58 (27.1)	52 (24.0)
No study-qualifying pathogen identified	72 (33.6)	64 (29.5)
Bacteraemia	5 (2.3)	10 (4.6)
Renal status		
Normal renal function/mild impairment (CrCL >50 mL/min)	201 (93.9)	201 (92.6)
Moderate impairment (CrCL >30 to ≤50 mL/min)	13 (6.1)	16 (7.4)

S.D., standard deviation; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; CrCL, creatinine clearance.

<sup>a</sup> Data are n (%) unless otherwise stated.

with non-Enterobacteriaceae Gram-negative pathogens, *P. aeruginosa* was the most frequently reported (37 subjects; 12.5%).

In the mMITT population, 58 subjects (19.7%) split evenly between the two treatment groups had an infection with a ceftazidime-non-susceptible aerobic Gram-negative pathogen (ceftazidime MIC ≥ 8 mg/L for Enterobacteriaceae and MIC ≥ 16 mg/L for *P. aeruginosa*). Of these, 55 (18.6%) had ceftazidime-non-susceptible Enterobacteriaceae isolates, including *E. coli* in 44 subjects (ceftazidime/avibactam plus metronidazole, 19; meropenem, 25) and *K. pneumoniae* in 4 (ceftazidime/avibactam plus metronidazole, 3; meropenem, 1). In addition, one *P. aeruginosa* isolate in the ceftazidime/avibactam plus metronidazole group was non-susceptible to ceftazidime.

For the 55 ceftazidime-non-susceptible Enterobacteriaceae, the ceftazidime/avibactam MIC range was 0.03–4 mg/L, with an MIC<sub>90</sub> of 1 mg/L. The single ceftazidime-non-susceptible *P. aeruginosa* isolate had a ceftazidime/avibactam MIC of 8 mg/L. Thus, among the ceftazidime-non-susceptible isolates in the mMITT population, the distribution of the ceftazidime/avibactam MICs was left-shifted to a lower MIC compared with that of ceftazidime alone. In vitro, all ceftazidime-non-susceptible isolates were within the susceptible range for ceftazidime/avibactam.

In the mMITT population overall, one *E. coli* isolate in the meropenem group had a meropenem MIC of 4 mg/L (meropenem resistance defined as MIC ≥ 2 mg/L for Enterobacteriaceae and MIC ≥ 4 mg/L for *P. aeruginosa*). In addition, one *K. pneumoniae* isolate in the meropenem group and three *P. aeruginosa* isolates (ceftazidime/avibactam plus metronidazole, 1; meropenem, 2) were resistant to meropenem. All four isolates that were resistant to meropenem were within the susceptible range for ceftazidime/avibactam.

Overall, Gram-positive aerobes were isolated in 73 subjects (24.7%) in the mMITT population. The most frequent were *Streptococcus anginosus* (15 subjects; 5.1%), *Enterococcus faecalis* (12 subjects; 4.1%), and *Enterococcus faecium* and *Streptococcus mitis* (11 sub-

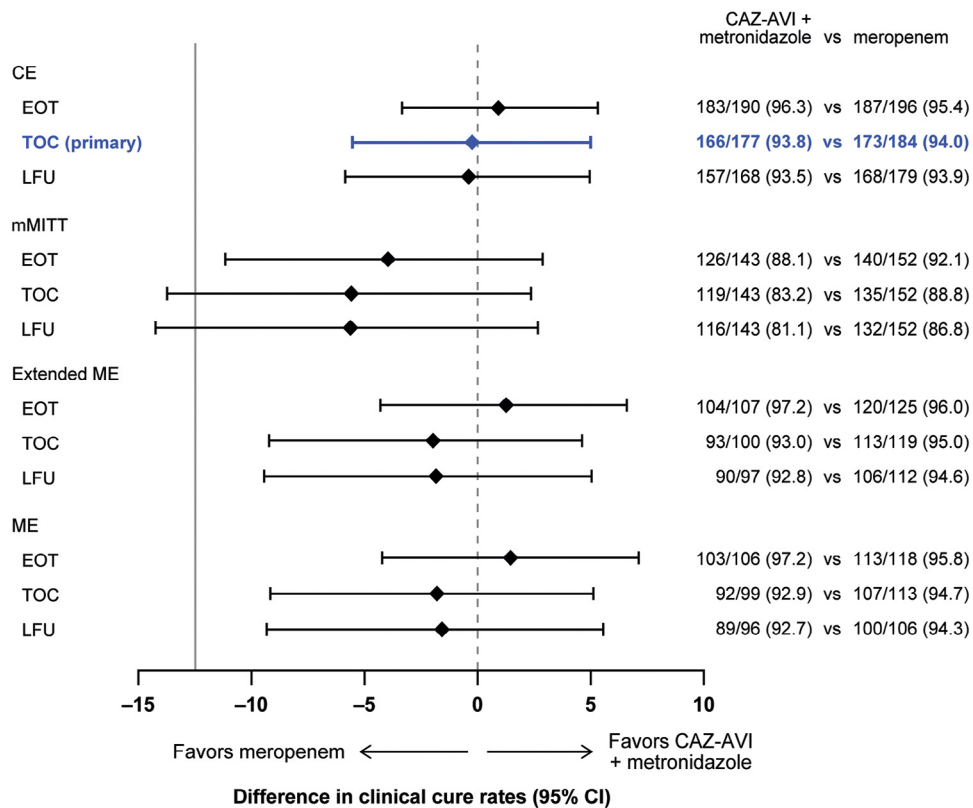
jects each; 3.7%). At least one anaerobic pathogen was reported in 31 subjects (10.5%) in the mMITT population, the most frequent being *Bacteroides fragilis* (8 subjects; 2.7%).

### 3.3. Endpoints

Clinical cure at the TOC visit in the CE population was reported in 166/177 (93.8%) of subjects receiving ceftazidime/avibactam plus metronidazole and 173/184 (94.0%) of those receiving meropenem (between-group difference, -0.2, 95% CI -5.53 to 4.97; *P* < 0.001) (Fig. 2). This confirmed the non-inferiority of ceftazidime/avibactam versus meropenem. Sensitivity analyses confirmed the robustness of the primary analysis, with a difference in clinical cure rate in the CE population at the TOC visit of 0.4% (95% CI -4.97 to 5.69), demonstrating a consistent result with the primary efficacy outcome when stratified by baseline severity of disease and country. In the CE population at the TOC visit, 11 patients in each treatment arm were considered clinical failures. Reasons for clinical failure are summarised in Supplementary Table S1.

Secondary endpoints were not formally assessed against a non-inferiority margin; however, clinical cure rate at the EOT and LFU visits in the CE population, as well as the EOT, TOC and LFU visits in the ME and eME populations, and the EOT visit in the mMITT population were all similar to the primary analysis result, with the lower limit of the 95% CI for the between-group difference numerically above -12.5% (Fig. 2). The differences in clinical cure rates between the two treatment groups were consistent with the overall results when analysed by patient demographics and clinical characteristics (Fig. 3).

The treatment difference observed for clinical cure rate at TOC and LFU visits in the mMITT population was greater than that in the ME and eME populations (Fig. 2). Subjects in the mMITT population could be assessed as having an indeterminate response, which was treated as a negative outcome. To confirm this, a sensitivity analysis was performed to explore the impact of the indeterminate outcomes by treating all subjects with indeterminate responses in



**Fig. 2.** Difference in clinical cure rate with ceftazidime/avibactam (CAZ-AVI) plus metronidazole compared with meropenem by visit and analysis population. CE, clinically evaluable; EOT, end-of-treatment; TOC, test-of-cure; LFU, late follow-up; mMITT, microbiologically modified intention-to-treat; ME, microbiologically evaluable; CI, confidence interval. Data listed are  $n/N$  (%). Solid vertical line represents  $-12.5\%$  non-inferiority margin.

the mMITT population as clinical cure. This resulted in similar response rates between groups at the TOC visit [ceftazidime/avibactam plus metronidazole, 133 (93.0%); meropenem, 143 (94.1%); difference,  $-1.1\%$ , 95% CI  $-7.21$  to  $4.82$ ].

Intra-abdominal culture requires an invasive procedure, which was not performed during the follow-up period of the study. Therefore, microbiological responses were presumed from clinical responses for all subjects. In the ME and eME populations, the most common Enterobacteriaceae species isolated in subjects in both treatment groups was *E. coli*, and of these  $>90\%$  of subjects in both groups were assessed as clinical cure at the TOC visit.

There was no statistical evidence of a difference between treatment groups in time to defervescence; however, the number of patients in this analysis was small. No subjects in the ME, eME or mMITT populations had emergent infections at the TOC visit.

Based on data from the eME population, ceftazidime/avibactam was effective in treating infections caused by ceftazidime-non-susceptible Gram-negative pathogens, with clinical cure rates similar to those seen with ceftazidime-susceptible isolates [22/23 (95.7%) vs. 70/76 (92.1%) subjects, respectively] (Table 3).

### 3.4. Surgical review panel findings

The SRP reviewed 34 subjects (ceftazidime/avibactam plus metronidazole, 20; meropenem, 14) assessed by the investigator as clinical failure. Six were considered to have inadequate source control and were reassigned as indeterminate (ceftazidime/avibactam plus metronidazole, 4; meropenem, 2). Furthermore, one patient in the ceftazidime/avibactam plus metronidazole group who was assessed by the investigator as clinical cure with a second procedure was reassigned as indeterminate.

### 3.5. Safety

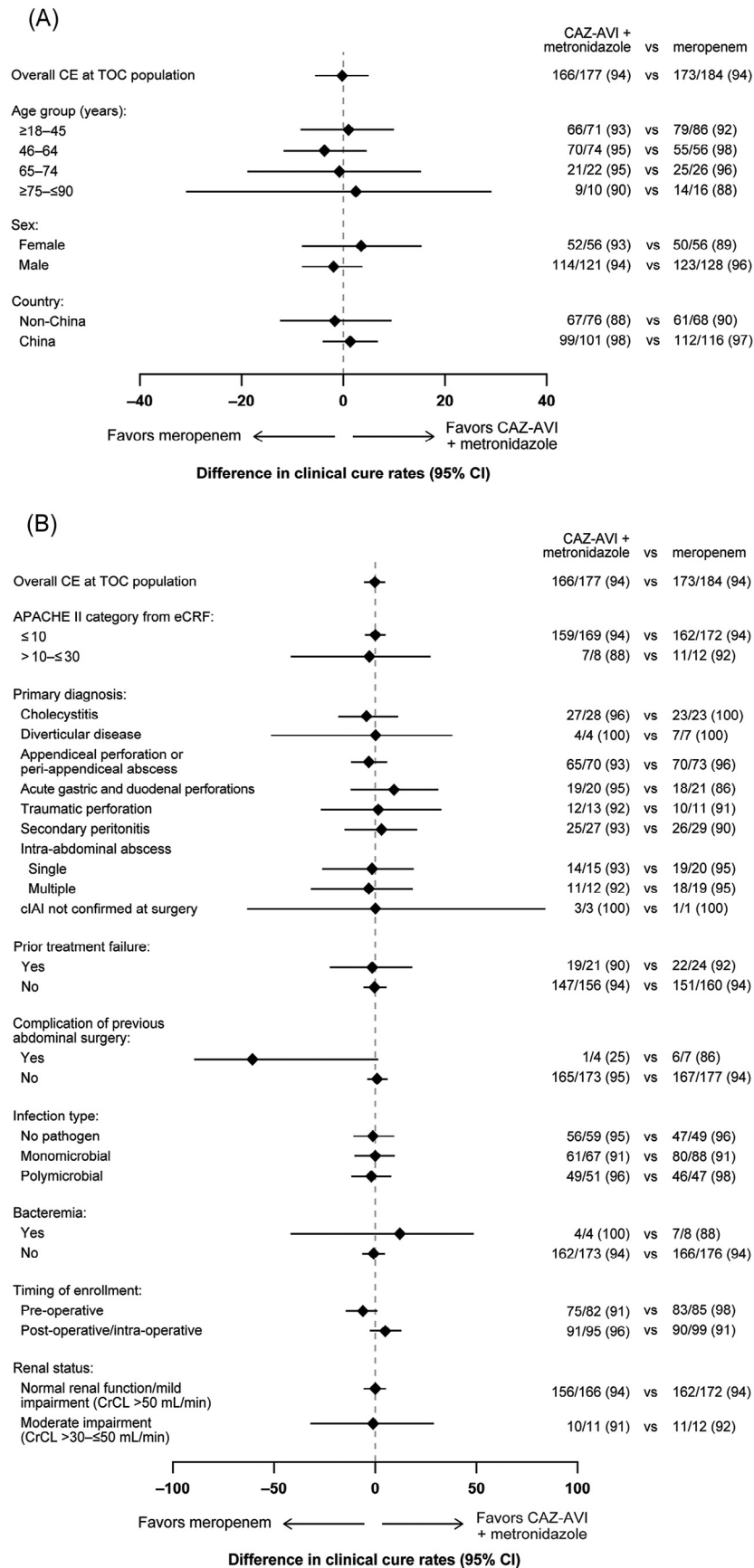
In the safety population, 82/215 (38.1%) and 83/217 (38.2%) subjects in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively, experienced at least one AE up to the LFU visit. In both groups, five AEs (2.3%) were considered severe in intensity. There were 9 (4.2%) and 11 (5.1%) serious AEs reported in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively. None of these were reported in more than one patient in either treatment group. The most frequently reported AEs were in the system organ class gastrointestinal disorders [ceftazidime/avibactam plus metronidazole, 41 (19.1%); meropenem, 26 (12.0%)], including nausea, diarrhoea, constipation and vomiting (Table 4).

The number of discontinuations due to AEs was low in both treatment groups [ceftazidime/avibactam plus metronidazole, 7 (3.3%); meropenem, 3 (1.4%)]. In the meropenem group, there was one AE of aspiration pneumonia that commenced 28 days after the start of treatment and resulted in death. This death was not considered related to disease progression or to the study drug. There were also two deaths due to disease progression in the ceftazidime/avibactam plus metronidazole group, the primary causes of which were septic shock and multi-organ failure. Neither were considered to be related to the study drug.

There were no clinically meaningful trends or concerns in vital signs, ECGs, laboratory values or coagulation results.

## 4. Discussion

The data presented here contribute to the body of evidence supporting the use of ceftazidime/avibactam in the treatment of patients



**Fig. 3.** Difference in clinical cure rates with ceftazidime/avibactam (CAZ-AVI) plus metronidazole compared with meropenem at test-of cure (TOC) visit in the clinically evaluable (CE) population by (A) baseline demographics and (B) baseline clinical characteristics. CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; eCRF, electronic case report form; cIAI, complicated intra-abdominal infection; CrCL, creatinine clearance. Data listed are n/N (%).

**Table 3**  
Clinical response at the test-of-cure visit for subjects with ceftazidime-non-susceptible (CAZ-NS) and ceftazidime-susceptible (CAZ-S) Gram-negative pathogens [extended microbiologically evaluable (eME) population].

Isolates	Susceptibility	Ceftazidime/avibactam + metronidazole (N = 100)		Meropenem (N = 119)		Comparison between groups [difference <sup>a</sup> , % (95% CI <sup>b</sup> )]
		n	Clinical cure [n (%)]	n	Clinical cure [n (%)]	
All isolates	CAZ-NS	23	22 (95.7)	26	25 (96.2)	-0.5 (-17.93, 15.43)
	CAZ-S	76	70 (92.1)	89	84 (94.4)	-2.3 (-11.30, 5.82)
Enterobacteriaceae	CAZ-NS	21	20 (95.2)	25	24 (96.0)	-0.8 (-19.51, 15.78)
	CAZ-S	70	64 (91.4)	81	78 (96.3)	-4.9 (-14.28, 3.08)
<i>Escherichia coli</i>	CAZ-NS	14	13 (92.9)	23	22 (95.7)	-2.8 (-28.19, 15.54)
	CAZ-S	54	50 (92.6)	53	51 (96.2)	-3.6 (-14.40, 6.40)
<i>Klebsiella pneumoniae</i>	CAZ-NS	3	3 (100)	1	1 (100)	0.0 (-63.06, 83.67)
	CAZ-S	16	15 (93.8)	26	25 (96.2)	-2.4 (-25.36, 14.04)
Non-Enterobacteriaceae	CAZ-NS	2	2 (100)	1	1 (100)	0.0 (-74.23, 85.21)
	CAZ-S	15	15 (100)	15	13 (86.7)	13.3 (-9.08, 38.36)
<i>Pseudomonas aeruginosa</i>	CAZ-NS	1	1 (100)	0	0	-
	CAZ-S	10	10 (100)	14	12 (85.7)	14.3 (-16.23, 40.56)

<sup>a</sup> Difference in clinical cure rates (%).

<sup>b</sup> 95% confidence interval (CI) for group differences was calculated using the unstratified Miettinen & Nurminen method. Clinical cure rate for the eME population was defined as the number of subjects with a response of clinical cure at the test-of-cure visit divided by the number of subjects with clinical cure + clinical failure. Clinical response was based on surgical review evaluation if it was different from the investigator's assessment. Ceftazidime resistance includes both the Clinical and Laboratory Standards Institute breakpoint-defined non-susceptible and intermediate categories [24]. Percentages are based on the total number of subjects in the subgroup (n).

with cIAI by demonstrating that ceftazidime/avibactam in combination with metronidazole has equivalent efficacy to meropenem in patients hospitalised in China, the Republic of Korea and Vietnam. Non-inferiority of ceftazidime/avibactam plus metronidazole was demonstrated versus meropenem for the primary endpoint of clinical cure at the TOC visit in the CE population, with the lower limit of the 95% CI for the between-group difference being higher than the pre-defined margin of -12.5%. These findings are in line with previous randomised controlled trials of other antimicrobials in

**Table 4**  
Safety evaluation up to late-follow-up visit (42–49 days after randomisation) (safety population) [n (%)]<sup>a</sup>.

	Ceftazidime/ avibactam + metronidazole (n = 215)	Meropenem (n = 217)
AEs in ≥2% subjects in either treatment group by system organ class/preferred term <sup>b</sup> [n (%)]		
Nervous system disorders	7 (3.3)	6 (2.8)
Headache	3 (1.4)	5 (2.3)
Respiratory disorders	13 (6.0)	16 (7.4)
Productive cough	5 (2.3)	6 (2.8)
Cough	3 (1.4)	8 (3.7)
Gastrointestinal disorders	41 (19.1)	26 (12.0)
Nausea	18 (8.4)	4 (1.8)
Diarrhoea <sup>c</sup>	13 (6.0)	16 (7.4)
Constipation	5 (2.3)	3 (1.4)
Vomiting	5 (2.3)	4 (1.8)
General disorders	15 (7.0)	17 (7.8)
Pyrexia	9 (4.2)	13 (6.0)
Safety topics <sup>d</sup>		
Liver disorder	6 (2.8)	10 (4.6)
Diarrhoea	13 (6.0)	16 (7.4)
Hypersensitivity/anaphylaxis disorder	7 (3.3)	8 (3.7)
Haematological disorder	2 (0.9)	1 (0.5)
Renal disorder	1 (0.5)	1 (0.5)

AE, adverse event.

<sup>a</sup> Subjects with multiple AEs are counted once for each system organ class and/or preferred term.

<sup>b</sup> AEs are sorted by system organ class in international order and by preferred term in decreasing order of frequency in subjects treated with ceftazidime/avibactam + metronidazole.

<sup>c</sup> No cases of *Clostridium difficile* enterocolitis reported.

<sup>d</sup> Each safety topic represents the aggregate of a group of pre-identified relevant AE preferred terms based on those from previous a phase 2 study of ceftazidime/avibactam in complicated intra-abdominal infection.

subjects with cIAI where non-inferiority to a 'gold-standard' comparator such as meropenem has been used to demonstrate antimicrobial efficacy [26–29].

To date, two phase 1 studies have shown the safety and pharmacokinetics of ceftazidime/avibactam in healthy Chinese or Japanese subjects to be comparable with that in healthy Western subjects [30,31]. However, there has been little other clinical evaluation of ceftazidime/avibactam in an Asian-focused population. In particular, there are no studies assessing the use of ceftazidime/avibactam in the treatment of patients with cIAIs in Asian countries. Interethnic differences in genotypic factors such as the expression of metabolic enzymes and drug transporters as well as environmental factors such as diet have the potential to affect the metabolic profile of a drug [22,23]. There is also the potential for variation in clinical efficacy due to regional differences in antimicrobial susceptibility [7]. The present study provides evidence that the efficacy and safety profile of ceftazidime/avibactam in a distinct subset of patients from the Asian region is consistent with previous data in patients with cIAI from outside of Asia [18].

The differences in clinical cure rates between the two treatment groups across patient demographic and clinical characteristic subgroups, including age, APACHE II score and renal function, were generally consistent with the primary results. The lower limit of the 95% CI for the between-group difference of clinical cure rate was numerically greater than -12.5% at all time points assessed in each of the secondary analysis populations, except for the mMITT population at the TOC and LFU visits. Here there was an observed treatment difference in favour of meropenem that may be explained by the higher proportion of indeterminate responses in the ceftazidime/avibactam plus metronidazole group compared with the meropenem group (Supplementary Table S2). This treatment difference was reflected in all subgroup analyses of the mMITT population.

The pathogens isolated at baseline in the present study were comparable with those isolated in the SMART surveillance study in 2008–2009 in the Asia-Pacific region and in other recent clinical studies of cIAI, where the leading pathogens isolated from IAIs were *E. coli* and *K. pneumoniae* [2,18,32]. The prevalence of *P. aeruginosa* in the present study of patients enrolled in China, the Republic of Korea and Vietnam was also consistent with that seen in subjects from outside Asia [18]. In total, 19.7% of patients in the mMITT population in the present study had a ceftazidime-non-susceptible aerobic Gram-negative pathogen compared with 13.5% of patients in the



mMITT population in a previous study carried out in Western subjects [18]. Whilst this discrepancy compared with Western subjects may be seen as a potential limitation of the study, we believe the conclusions are still valid, and the overall susceptibility profile of the study population allowed for the assessment of the utility of ceftazidime/avibactam both against ceftazidime-non-susceptible and ceftazidime-susceptible pathogens.

In the present study, there were lower MICs for ceftazidime/avibactam against ceftazidime-non-susceptible isolates compared with ceftazidime alone, and all ceftazidime-non-susceptible Enterobacteriaceae and *P. aeruginosa* isolates had a ceftazidime/avibactam MIC  $\leq$  8 mg/L, indicating that avibactam effectively restored the in vitro activity of ceftazidime against ceftazidime-non-susceptible isolates in line with previous data [11–13]. With regard to clinical outcome in the ceftazidime/avibactam plus metronidazole treatment group, the proportion of subjects who had ceftazidime-non-susceptible Enterobacteriaceae infections and were recorded as clinical cure at the TOC visit in the eME population was comparable with that of subjects with ceftazidime-susceptible Enterobacteriaceae infections (95.2% vs. 91.4%, respectively), providing further evidence for the clinical utility of ceftazidime/avibactam against ceftazidime-non-susceptible pathogens.

No new safety concerns were identified for ceftazidime/avibactam in this study. The majority of AEs were mild or moderate in intensity with a low incidence of discontinuations due to AEs, and there were no deaths that were considered related to the study drugs. Although these data only represent a subset of patients from Asia, they add to the overall safety database of the use of ceftazidime/avibactam in patients with cIAI. Furthermore, taking into account the known safety profile of metronidazole, safety findings for ceftazidime/avibactam in this study were in line with other populations and the known profiles of ceftazidime and cephalosporins in general [33].

To conclude, ceftazidime/avibactam plus metronidazole was non-inferior to meropenem in the treatment of patients with cIAI in China, the Republic of Korea and Vietnam, with a safety profile reflective of ceftazidime alone. In addition, ceftazidime/avibactam plus metronidazole was effective against ceftazidime-non-susceptible Enterobacteriaceae. These data support the use of ceftazidime/avibactam plus metronidazole as a potential treatment option for subjects in Asia with cIAI, including those infected with ceftazidime-non-susceptible pathogens.

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**Competing interests:** JWC and JS are employees of AstraZeneca; JWC is a shareholder in AstraZeneca; GGS was an employee of and shareholder in AstraZeneca at the time of the study, and is currently an employee of Pfizer Inc.; PJJ is contracted to AstraZeneca from the Statistical Services Unit at the University of Sheffield (Sheffield, UK), which received institutional funding from AstraZeneca for the current study; XQ is an employee of Zhongshan Hospital affiliated to Fudan University (Shanghai, China), which received institutional funding for the conduct of the study and to support travel to investigator meetings; BGT is an employee of Viet-Duc Hospital (Hanoi, Vietnam), which received institutional funding for the conduct of the study; MJK is an employee of Korea University Anam Hospital (Seoul, Republic of Korea), which received institutional funding for the conduct of the study and to support travel to investigator meetings; LW is an employee of Fuzhou General Hospital of Nanjing Military Region (Fuzhou, China), which received institutional funding for the conduct of the study and to support travel to investigator meetings; DAN is an employee of Gia Dinh People Hospital (Ho Chi Minh, Vietnam), which received institutional funding for the conduct of the study; QC is an employee of the Affiliated Hospital of Guilin Medical University (Guangxi, China), which received institutional funding for the conduct of the study and to support travel to investigator meetings.

**Ethical approval:** This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The final study protocol, including the final version of the informed consent form and any other written information or materials provided to the patients, was approved by the independent Ethics Committee (EC) and/or Institutional Review Board (IRB) for each study centre. The investigator ensured the distribution of these documents to the applicable EC/IRB and to the study centre personnel. If there were any substantial changes to the study protocol, these changes were documented in a study protocol amendment and, where required, in a revised version of the clinical study protocol. The amendment was approved by the relevant EC/IRB and, if applicable, national regulatory authority approval was obtained before implementation. Local requirements were followed for revised protocols. AstraZeneca distributed any subsequent amendments and new versions of the protocol to each investigator.

## Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ijantimicag.2017.01.010](https://doi.org/10.1016/j.ijantimicag.2017.01.010).

## References

- [1] Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant Gram-negative organisms: extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clin Proc* 2011;86:250–9.
- [2] Sheng WH, Badal RE, Hsueh PR. Distribution of extended-spectrum  $\beta$ -lactamases, AmpC  $\beta$ -lactamases, and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal infections in the Asia-Pacific region: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob Agents Chemother* 2013;57:2981–8.
- [3] Bush K. Bench-to-bedside review: the role of  $\beta$ -lactamases in antibiotic-resistant Gram-negative infections. *Crit Care* 2010;14:224.
- [4] Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M, et al. 2013 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg* 2013;8:3.
- [5] Solomkin J, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50:133–64.

- [6] Solomkin J, Ristagno RL, Das AF, Cone JB, Wilson SE, Rotstein OD, et al. Source control review in clinical trials of anti-infective agents in complicated intra-abdominal infections. *Clin Infect Dis* 2013;56:1765–73.
- [7] Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. *Pharmaceuticals (Basel)* 2013;6:1335–46.
- [8] Jean SS, Hsueh PR, SMART Asia-Pacific Group. Distribution of ESBLs, AmpC  $\beta$ -lactamases and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal and urinary tract infections in the Asia-Pacific region during 2008–14: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *J Antimicrob Chemother* 2017;72:166–71.
- [9] Tzouveleki LS, Markogiannakis A, Psychogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev* 2012;25:682–707.
- [10] Ehmann DE, Jahic H, Ross PL, Gu RF, Hu J, Durand-Reville TF, et al. Kinetics of avibactam inhibition against class A, C, and D  $\beta$ -lactamases. *J Biol Chem* 2013;288:27960–71.
- [11] Lagace-Wiens PR, Tailor F, Simner P, DeCorby M, Karlowsky JA, Walkty A, et al. Activity of NXL104 in combination with  $\beta$ -lactams against genetically characterized *Escherichia coli* and *Klebsiella pneumoniae* isolates producing class A extended-spectrum  $\beta$ -lactamases and class C  $\beta$ -lactamases. *Antimicrob Agents Chemother* 2011;55:2434–7.
- [12] Aktas Z, Kayacan C, Oncul O. In vitro activity of avibactam (NXL104) in combination with  $\beta$ -lactams against Gram-negative bacteria, including OXA-48  $\beta$ -lactamase-producing *Klebsiella pneumoniae*. *Int J Antimicrob Agents* 2012;39:86–9.
- [13] Levasseur P, Girard AM, Miossec C, Pace J, Coleman K. In vitro antibacterial activity of the ceftazidime-avibactam combination against Enterobacteriaceae, including strains with well-characterized  $\beta$ -lactamases. *Antimicrob Agents Chemother* 2015;59:1931–4.
- [14] MacVane SH, Crandon JL, Nichols WW, Nicolau DP. In vivo efficacy of humanized exposures of ceftazidime-avibactam in comparison with ceftazidime against contemporary Enterobacteriaceae isolates. *Antimicrob Agents Chemother* 2014;58:6913–19.
- [15] Actavis Inc. Prescribing information: AVYCAZ (ceftazidime-avibactam) for injection, for intravenous use, 2015. Available from: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/2064941bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/2064941bl.pdf). [Accessed 20 August 2016].
- [16] Vazquez JA, Gonzalez Patzan LD, Stricklin D, Duttaroy DD, Kreidly Z, Lipka J, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin* 2012;28:1921–31.
- [17] Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. *J Antimicrob Chemother* 2013;68:1183–92.
- [18] Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection—results from a randomised, controlled, double-blind, phase 3 program. *Clin Infect Dis* 2016;62:1380–9.
- [19] Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016;63:754–62.
- [20] Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Results from REPRIZE, a randomised, pathogen-directed phase 3 study of ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant complicated urinary tract infections or complicated intra-abdominal infections. *Lancet Infect Dis* 2016;16:661–73.
- [21] AstraZeneca Ltd. Summary of product characteristics: Zavicefta, 2016. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/004027/WC500210234.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf). [Accessed 20 August 2016].
- [22] Baietto L, Corcione S, Pacini G, Perri GD, D'Avolio A, De Rosa FG. A 30-years review on pharmacokinetics of antibiotics: is the right time for pharmacogenetics? *Curr Drug Metab* 2014;15:581–98.
- [23] Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. *Clin Pharmacol Ther* 2008;84:417–23.
- [24] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty-second informational supplement. Wayne, PA: CLSI; 2012 Document M100-S22.
- [25] Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985;4:213–26.
- [26] Lucasti C, Jasovich A, Umeh O, Jiang J, Kaniga K, Friedland I. Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin Ther* 2008;30:868–83.
- [27] Qvist N, Warren B, Leister-Tebbe H, Zito ET, Pedersen R, McGovern PC, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. *Surg Infect (Larchmt)* 2012;13:102–9.
- [28] Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenberg J, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-clAI). *Clin Infect Dis* 2015;60:1462–71.
- [29] Solomkin J, Zhao YP, Ma EL, Chen MJ, Hampel B. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. *Int J Antimicrob Agents* 2009;34:439–45.
- [30] Li J, Learoyd M, Qiu F, Zhu L, Edeki T. A randomized, phase I study to assess the safety, tolerability and pharmacokinetics of ceftazidime-avibactam in healthy Chinese subjects. *Clin Drug Investig* 2016;36:119–26.
- [31] Tominaga N, Edeki T, Li J, Learoyd M, Bouw MR, Das S. Phase I study assessing the safety, tolerability, and pharmacokinetics of avibactam and ceftazidime-avibactam in healthy Japanese volunteers. *J Infect Chemother* 2015;21:551–8.
- [32] Lucasti C, Hershberger E, Miller B, Yankelev S, Steenberg J, Friedland I, et al. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. *Antimicrob Agents Chemother* 2014;58:5350–7.
- [33] GlaxoSmithKline. Fortum® 1g injection SPC, 2016. Available from: <http://www.medicines.org.uk/emc/document.aspx?documentid=19176&docType=SPC>. [Accessed 20 August 2016].