Original Article

Ceftazidime-avibactam plus metronidazole *vs*. meropenem in complicated intra-abdominal infections: Indian subset from RECLAIM

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Abstract

Introduction: This study analyzes the safety and efficacy results of the Indian population subset from the RECLAIM trial investigating the non-inferiority of Ceftazidime-Avibactam (CAZ-AVI) plus metronidazole to meropenem and interprets its relevance.

Methodology: The study design, subjects inclusion criteria, dosage, safety and efficacy evaluations in Indian patients have been followed as per the RECLAIM trial protocol.

Results: A total of 142 Indian patients with complicated intra-abdominal infection were enrolled across eight centers in India, 125 of them were randomized to either CAZ-AVI + metronidazole (n = 62) or meropenem (n = 63) group. the clinical cure rates in modified intention-to-treat (MITT; all randomized patients who met minimum disease requirements and received any amount of study drug) and clinically evaluable (CE, patients who had an evaluable assessment and no protocol deviations) analysis sets, was numerically comparable to the results of overall population for CAZ-AVI + metronidazole [MITT: 82.5% (Overall, n = 429/520) versus 89.3% (Indian, n = 50/56); CE: 91.7% (Overall, n = 376/410) versus 97.8% (Indian, n = 45/46)] and meropenem [MITT: 84.9% (Overall, n = 444/523) versus 84.7% (Indian, n = 50/59); CE: 92.5% (Overall, n = 385/416) versus 95.5% (Indian, n = 42/44)]. No new safety findings were reported in the Indian population.

Conclusions: CAZ-AVI + metronidazole proved to be an effective option for critical patients with complicated intra-abdominal infection and can be considered as an alternative to carbapenems in the ICU setting for the treatment of resistant pathogens.

Key words: Ceftazidime; avibactam; meropenem; intra-abdominal infections; RECLAIM.

Introduction

Complicated intra-abdominal infections (cIAIs) are local or systemic infections that occur as a result of a perforation in the gastrointestinal tract or by a necrotic gut wall spilling bacteria into the peritoneal space, leading to abscess formation and/or generalized peritonitis. These infections require operative intervention or percutaneous drainage in conjunction with antibacterial therapy [1]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) reported *E. coli* to be the most commonly isolated strain (351/588; 60%) followed by *Klebsiella spp*. (114/588; 19%); of which 79% of *E. coli* and 70% of *Klebsiella spp*. were extended spectrum beta-lactamase (ESBL)-producers [2]. As per the Indian Council of Medical Research (ICMR) 2019 guidelines, up to 30% of isolated *E. coli* and 50% of isolated *K. pnuemoniae* are carbapenemase producers [3]. Molecular studies across India have demonstrated a rise in oxacillinase (OXA) - 48 producing microbes with incidence ranging from 28 - 32% to as high as 50%. About 10 – 15% of OXA-48

producers were reported to co-produce New Delhi metallo-beta-lactamase (NDM) [4-7].

The Surgical Infection Society (SIS) 2017 guidelines and the World Society of Emergency Surgery (WSES) 2017 guidelines emphasize the need to consider local antimicrobial susceptibility patterns when opting for an appropriate initial regimen. The Infectious Diseases Society of America (IDSA) guideline 2010 on intra-abdominal infections also recommends this practice [8-10]. The pathogens implicated in cIAI are frequently resistant to commonly used antibiotics leading to a severe limitation in the treatment options for these infections. Specifically, the emerging problem of carbapenem-resistant Enterobacterales in the Indian hospital setting points towards an urgent need for alternative treatment options to effectively tackle these difficult-to-treat, multi-drug resistant (MDR) organisms related infections. Ceftazidime-avibactam (CAZ-AVI) is a novel ß lactam-ß lactamase inhibitor (BL-BLI) which targets resistant, difficult-to-treat Gram-negative infections [11]. Avibactam restores the *in vitro* activity of the

established extended-spectrum anti-pseudomonal cephalosporin, ceftazidime, against Ambler class A, class C, and some class D β-lactamase–producing pathogens, thus proposing CAZ-AVI as an effective antibiotic option for the treatment of MDR Gram-negative infections including cIAI [12].

Efficacy and safety of CAZ-AVI plus metronidazole were compared with meropenem in the RECLAIM study which was a multi-center, randomized, double-blind, non-inferiority clinical trial. In the RECLAIM study, CAZ-AVI plus metronidazole was demonstrated to be non-inferior to meropenem [1]. In the study, a total of 1066 adults with cIAI were enrolled from 136 centres across 23 countries globally, of which, 142 patients were from 8 centers in India.

Currently, there is limited published data available that has demonstrated the efficacy of CAZ-AVI in Indian patients with complicated intra-abdominal infections. This article focuses on the analysis of clinical outcomes of Indian patients enrolled in the RECLAIM trial and the relevance of the results in the Indian context. The aim of this subgroup analysis was to assess whether the results in the Indian population are in line with the results of the overall study (overall population) and whether the conclusions from the overall study could be considered applicable to the Indian population.

Methodology
Design
In line with the global RECLAIM study protocol, data of Indian patients from prospective, randomized, multicenter, double-dummy, double-blind, comparative, global studies (RECLAIM 1 and RECLAIM 2) was analysed [1]. The studies were funded by Astra Zeneca.

In India, the study was conducted at eight centers across the country. The centers were: MS Ramaiah Medical College & Hospital, Bangalore; KEM Hospital Research Center, Pune; Inamdar Multispeciality Hospital, Nagpur; Sir Sayajirao General Hospital, Baroda; Noorul Islam Institute of Medical Sciences & Research Foundation, Trivandrum; Sahyadri Hospital, Pune; Bangalore Medical College and Research Institute, Victoria Hospital, Bangalore; and Indraprastha Apollo Hospital, New Delhi.

The study was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6 (R1) for Good Clinical Practice, and local regulatory requirements. The study protocol and amendments were approved by local institutional ethics committees or institutional review boards.

Eligibility
Adult patients (aged 18-65 years from India) who were diagnosed with cIAI and requiring surgical intervention or percutaneous drainage within 24 hours before or after randomization were included in the study. Patients with traumatic bowel perforation managed operatively within 12 hours; perforation of gastroduodenal ulcers managed operatively within 24 hours; intra-abdominal processes in which the primary cause was unlikely to be infectious; abdominal wall abscess, bowel obstruction, or ischemic bowel without perforation; simple cholecystitis or gangrenous cholecystitis without rupture; simple appendicitis; acute suppurative cholangitis; and infected necrotizing pancreatitis or pancreatic abscess, were excluded. The detailed inclusion and exclusion criteria have been published in Mazuski *et al.* [1].

Randomization
As per the RECLAIM study protocol, eligible patients were randomly assigned (1:1) to receive either CAZ-AVI (2000 mg of ceftazidime and 500 mg of avibactam as a 2-hour intravenous infusion every 8 hours), followed by metronidazole (500 mg as a 60-minute intravenous infusion every 8 hours); or meropenem (1,000 mg as a 30-minute intravenous infusion every 8 hours). The interventions were administered for 5 -14 days.

Analysis Plan
The results obtained from the subset of the Indian patients enrolled in the RECLAIM study were analyzed using descriptive statistics.

The analyses set included in the study were modified intention-to-treat (MITT; all randomized patients who met minimum disease requirements and received any amount of study drug) population, microbiological modified intention-to-treat (mMITT; All patients in the MITT analysis set who had ≥1 baseline Gram-negative pathogen) population, and clinically evaluable (CE, Patients who had an evaluable assessment and no protocol deviations) population.

Outcomes
The primary outcome of the study was to assess and compare clinical cure rates of CAZ-AVI plus metronidazole, and meropenem at the test-of-cure (TOC) visit, which was 28 - 35 days after

randomization in the mMITT and CE populations. 'Clinical cure' was defined as complete resolution or significant improvement of signs and symptoms of the index infection, such that no further antibacterial therapy, drainage, or surgical intervention was necessary. A patient was considered to have 'clinical failure' for one of the following reasons: death related to cIAI, persisting or recurring abdominal infection, postsurgical wound infection requiring additional antibiotics, ongoing cIAI symptoms requiring additional antibiotics, or any previously met criteria for failure. Patients determined to be clinical failure by the investigator were reclassified as indeterminate by the surgical review panel for those with inadequate source control.

Key secondary endpoints were clinical response at end-of-treatment (EOT; up to 24 hours after the last infusion) and at late-follow-up (LFU; 42–49 days after randomization) visits; microbiological response

at EOT, TOC, LFU visits; and evaluation of the efficacy of ceftazidime-avibactam plus metronidazole or meropenem against ceftazidime-resistant pathogens.

A ceftazidime-resistant organism was defined based on Clinical and Laboratory Standards Institute (CLSI) as 'a pathogen with a minimum inhibitory concentration (MIC) greater than or equal to the resistant MIC breakpoints: Ceftazidime - ≥ 8 µg/mL for Enterobacterales and ≥ 16 µg/mL for *P. aeruginosa*' when central microbiology reference laboratory result was used and as 'a pathogen with disk diffusion diameter (from a 30µg ceftazidime disk) less than the resistant disk diffusion breakpoints, namely, ≤ 20 mm for Enterobacterales and ≤ 17 mm for *P. aeruginosa*' when the local laboratory results were used.

This study also analyzed the safety of CAZ-AVI with metronidazole in comparison with meropenem in Indian patients. The safety analysis included monitoring the number of adverse events (AEs) and their severity during the study including the LFU visit.
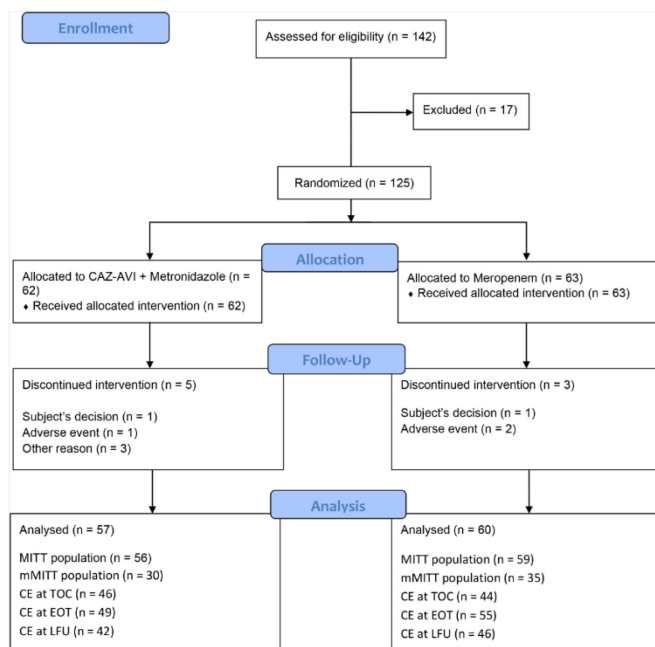
Statistical Analyses

The data of the Indian population included in the RECLAIM study was analyzed using descriptive statistics The results were compared with the results of the overall RECLAIM study.

In the overall study, non-inferiority of CAZ-AVI was considered met if the lower limit of the 95% confidence interval (CI) for the between-group difference was above least -12.5%, although it was recognized that the FDA required a lower limit of above -10% for the mMITT population. However, the non-inferiority could not be analyzed in this study, as it is a subset analysis.

Ethics Approval

The study was initiated at all the study centers after obtaining ethics committee approval at the respective sites. The names of the committees are as follows: Ethical Review Board, M S Ramaiah Medical, Bangalore; Ethics committee of Bangalore Medical College and Research Institute, Bangalore; Ethics committee of Inamdar Multispecialty Hospital, Pune; Ethics committee of KEM Hospital Research Center, Pune; Ethics committee of Noorul Islam Institute of Medical Sciences, Trivandrum; Ethics committee of Sahyadri Hospitals Ltd., Pune; Institutional ethics committee for human research, Medical college & SSG Hospital, Baroda; and Institutional ethics committee for clinical studies (IECCS) of Indraprastha Apollo Hospital, New Delhi.

Results

A total of 142 Indian patients with cIAI were enrolled across eight centers in India, of these 125 were randomized to one of the two study treatment arms: 62 to CAZ-AVI + metronidazole group and 63 to Meropenem group (Please refer to Figure 1 for patient disposition). Fifty-seven patients from CAZ-AVI + metronidazole group and 60 patients from the meropenem group completed the study.

Baseline demographic and patient characteristics were generally well balanced between the treatment

Figure 1. Patient Disposition.

groups (Table 1). No patients above 65 years of age were enrolled in India (per local requirements).

The mean age of Indian patients was 36.6 years, which was lower compared to the overall population (50 years).

In the MITT analyses set, the most common primary diagnoses were appendiceal perforation (41.7%) and acute gastric & duodenal perforation (36.5%). A lower proportion (6.1%) of subjects had cholecystitis. The proportion of patients with

appendicitis in the Indian population (41.7%) was similar to that of the overall population (41.3%) (Table 1). Majority of the patients in each treatment group were enrolled post-operatively (64.3% in the CAZ-AVI plus metronidazole group and 59.3% in the meropenem group). Overall, 86.1% of patients underwent laparotomy (with fascial and skin closure) as initial surgical intervention. About 41.1% of patients from CAZ-AVI plus metronidazole group and 45.8% of patients from the meropenem group reported prior

Table1. Demographics and disease characteristics of Indian patients at baseline (MITT Analysis Set).

		CAZ-AVI + Metronidazole (N = 56)	Meropenem (N = 59)	Total (N = 115)
Age (years)	Median	34.5	35.0	35.0
Sex n (%)	Female	17 (30.4)	42 (71.2)	85 (73.9)
	Male	39 (69.6)	17 (28.8)	30 (26.1)
APACHE Ii[a]; n (%)	≤ 10	51 (91.1)	54 (91.5)	105 (91.3)
	> 10 to ≤ 30	5 (8.9)	5 (8.5)	10 (8.7)
	Total	56 (100)	59 (100)	115 (100)
Prior treatment failure; n (%)	Yes	3 (5.4)	2 (3.4)	5 (4.3)
	No	53 (94.6)	57 (96.6)	110 (95.7)
Prior systemic antibiotics use in the previous 72 hours before randomization; n (%)	Yes	23 (41.1)	27 (45.8)	50 (43.5)
	≤ 24 hours	21 (37.5)	26 (44.1)	47 (40.9)
	≥ 24 hours	2 (3.6)	1 (1.7)	3 (2.6)
	No	33 (58.9)	32 (54.2)	65 (56.5)
Renal status; n (%)	Normal renal function/mild; impairment (CrCl > 50 mL/min)	51 (91.1)	54 (91.5)	105 (91.3)
	Moderate impairment (CrCl ≥ 30 to ≤ 50 mL/min)	4 (7.1)	5 (8.5)	9 (7.8)
Bacteremia; n (%)	Yes	4 (7.1)	2 (3.4)	6 (5.2)
	No	52 (92.0)	57 (96.6)	109 (94.8)
Primary diagnosis; n (%)	Cholecystitis	4 (7.1)	3 (5.1)	7 (6.1)
	Diverticular disease	1 (1.8)	0	1 (0.9)
	Appendiceal perforation or peri-appendiceal abscess	23 (41.1)	25 (42.4)	48 (41.7)
	Acute gastric and duodenal perforations	20 (35.7)	22 (37.3)	42 (36.5)
	Traumatic perforation	1 (1.8)	2 (3.4)	3 (2.6)
	Secondary peritonitis	3 (5.4)	6 (10.2)	9 (7.8)
	Intra-abdominal abscess	4 (7.1)	1 (1.7)	5 (4.3)
Anatomic location of infection[b]; n (%)	Stomach	12 (21.4)	15 (25.4)	27 (23.5)
	Liver	2 (3.6)	0	2 (1.7)
	Pancreas	0	0	0
	Gall bladder	4 (7.1)	3 (5.1)	7 (6.1)
	Small intestine	14 (25.0)	15 (25.4)	29 (25.2)
	Large intestine	2 (3.6)	2 (3.4)	4 (3.5)
	Spleen	0	0	0
	Appendix	24 (42.9)	25 (42.4)	49 (42.6)
	Other	14 (25.0)	19 (32.2)	33 (28.7)
Infection type; n (%)	Monomicrobial	21 (37.5)	24 (40.7)	45 (39.1)
	Polymicrobial	11 (19.6)	13 (22.0)	24 (20.9)

Percentages were based on the total number of patients in the treatment group (N). APACHE II: Acute Physiology and Chronic Health Evaluation II; CAZ-AVI: ceftazidime-avibactam; CrCl: creatinine clearance; eCRF: electronic case report form; MITT-modified intent-to-treat; N: total number of patients in the treatment group; n: number of patients in category or analysis. [a]APACHE II score was calculated programmatically using data obtained at the site and reported in the eCRF. [b]Patients with > 1 diagnosis at the same location were counted only once for that location.

antibiotic use in the 72 hours before randomization. The prior systemic antibiotic medications most commonly taken by patients in both treatment groups were metronidazole (21 patients [37.5%] in the CAZ-AVI plus metronidazole group and 18 patients [30.5%] in the meropenem group) and piperacillin + tazobactam (14 patients [25.0%] in the CAZ-AVI plus metronidazole group and 18 patients [30.5%] in the meropenem group). Majority of the patients (99.1%) had no complications from previous abdominal surgery. Six patients (5.2%) were bacteremic.

Monomicrobial infection was present in ~40% of total patients (similar to the overall population), and 20.9% had a polymicrobial infection. The remaining 40% of patients did not have a study qualifying pathogen. The majority of patients (91.3% in the Indian subset; 91.5% in the overall population) had normal renal function or mild renal impairment (CrCl >50 mL/min). APACHE II score of <10 was reported in 91.3% of the patients. The history of medical conditions was lower as compared to the overall population.[1]

The baseline microbiology showed that 80.0% of patients were infected with *E. coli*, 16.9% infected with *K. pneumoniae* and 10.8% infected with *P. aeruginosa*.

In the overall population, for all Enterobacterales isolated (no. of pathogens = 794) at baseline (mMITT analysis set), the MIC_{90} for ceftazidime was 8 μg/mL and for CAZ-AVI was 0.25 μg/mL, a 32-fold reduction. In the Indian population, for all Enterobacterales isolated (no. of pathogens = 69) at baseline (mMITT analysis set), the ceftazidime MIC_{90} was > 64 μg/mL and the CAZ-AVI MIC_{90} was 2 μg/mL, a reduction of at least 32-fold. This reduction in MIC_{90} demonstrates the impact of avibactam on the antimicrobial activity of ceftazidime. The CAZ-AVI MIC range, for all Enterobacterales isolates (n = 69), was 0.015 μg/mL to > 256 μg/mL with an MIC_{90} of 2 μg/mL. Three (3) isolates (2 in CAZ-AVI plus metronidazole group and 1 in meropenem group) were non-susceptible to CAZ-AVI with an MIC > 32 μg/mL.

The mean duration of treatment for the CAZ-AVI plus metronidazole group was 10.8 days and that for the meropenem group was 10.9 days.

The primary efficacy outcome measure was the clinical cure rate at TOC in mMITT and CE populations.

The clinical cure rate at TOC for the mMITT analysis set of the Indian population for CAZ-AVI plus metronidazole group and in the meropenem group were 83.3% and 77.1%, respectively (Table 2).

In the Indian sub-group for the CE analysis set, the clinical cure rates at TOC in the CAZ-AVI plus metronidazole group and in the meropenem group were 97.8% and 95.5%, respectively (difference 2.4%; 95% CI: -7.41 to 13.33). The results in Indian subset were thus consistent with the overall RECLAIM study findings (Table 2).

Table 2. Clinical response by visit – (MITT, mMITT, CE Analysis Sets).

Visit	Number (%) of Patients		Difference (%) (95% CI[a] for Percent Difference)
	CAZ-AVI + Metronidazole	Meropenem	
MITT Analysis Set			
	(N = 56)	(N = 59)	
TOC	50 (89.3)	50 (84.7)	4.5 (-8.41, 17.50)[b]
EOT	51 (91.1)	55 (93.2)	-2.1 (-13.51, 8.64)
LFU	50 (89.3)	50 (84.7)	4.5 (-8.41, 17.50)
CE Analysis Set			
	(N = 46)	(N = 44)	
TOC	45 (97.8)	42 (95.5)	2.4 (-7.41, 13.33)[b]
EOT	48 (98.0)	53 (96.4)	1.6 (-7.50, 10.62)
LFU	41 (97.6)	44 (95.7)	2.0 (-8.55, 12.57)
mMITT Analysis Set			
	(N = 30)	(N = 35)	
TOC	25 (83.3)	27 (77.1)	6.2 (-14.31, 25.65)[c]
EOT	26 (86.7)	32 (91.4)	-4.8 (-22.63, 11.52)
LFU	26 (86.7)	28 (80.0)	6.7 (-12.85, 25.23)

Difference: difference in clinical cure rates (CAZ-AVI + metronidazole group minus meropenem group). For subjects reviewed by the SRP, the clinical response was based on surgical review evaluation if it was different from the investigator's assessment. Percentages were based on the total number of patients in the treatment group (N). [a]CIs for group differences were calculated using the unstratified Miettinen and Nurminen method. [b]The MITT and CE populations were the co-primary populations for the ROW. Consistent with the SAP, the sponsor concluded non-inferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) was greater than -12.5% for both the MITT and CE analysis sets. [c]The mMITT population was the primary analysis population for the FDA. Consistent with the protocol, the sponsor concluded non-inferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) at TOC was greater than -12.5%. The sponsor accepted that FDA concluded non-inferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) was greater than -10%. CAZ-AVI: ceftazidime-avibactam; mMITT: microbiologically modified intent-to-treat; CE: clinically evaluable; CI: confidence interval; MITT: modified intent-to-treat; EOT: end of treatment; TOC: test-of-cure; LFU: late follow up; N: number of patients in treatment group; ROW: rest of the world; SAP: statistical analysis plan; SRP: Surgical Review Panel.

Table 3. AE up to EOT and LFU visit in any category (Safety Analysis Set) at LFU visit.

AE Category	Number (%) of Patients[a]	
	CAZ-AVI + Metronidazole (N = 62)	Meropenem (N = 63)
Any AE	44 (71.0)	35 (55.6)
Any AE with outcome = death[b]	1 (1.6)	0
Any SAE	1 (1.6)	1 (1.6)
Any AE leading to discontinuation of IP[c]	1 (1.6)	2 (3.2)
Any AE of severe intensity	1 (1.6)	1 (1.6)
AEs up to LFU in ≥ 2% of patients		
Infections and infestations		
Purulent discharge	2 (3.2)	0(0)
Blood and lymphatic system disorders		
Anaemia	1 (1.6)	2 (3.2)
Metabolism and nutrition disorders		
Decreased appetite	2 (3.2)	4 (6.3)
Nervous system disorders		
Dizziness	3 (4.8)	2 (3.2)
Headache	4 (6.5)	4 (6.3)
Vascular disorders		
Hypotension	9 (14.5)	8 (12.7)
Thrombophlebitis	7 (11.3)	6 (9.5)
Respiratory, thoracic and mediastinal disorders		
Cough	7 (11.3)	7 (11.1)
Dyspnoea	1 (1.6)	3 (4.8)
Lung consolidation	0(0)	2 (3.2)
Oropharyngeal pain	1 (1.6)	2 (3.2)
Throat irritation	0(0)	2 (3.2)
Gastrointestinal disorders		
Abdominal distention	7 (11.3)	7 (11.1)
Abdominal pain	2 (3.2)	2 (3.2)
Abdominal pain upper	3 (4.8)	3 (4.8)
Constipation	6 (9.7)	12 (19.0)
Diarrhoea	7 (11.3)	4 (6.3)
Dry mouth	2 (3.2)	1 (1.6)
Dyspepsia	1 (1.6)	3 (4.8)
Gastroesophageal reflux disease	0 (0)	2 (3.2)
Nausea	14 (22.6)	13 (20.6)
Tongue dry	1 (1.6)	2 (3.2)
Vomiting	11 (17.7)	2 (3.2)
Skin and subcutaneous tissues disorders		
Hyperhidrosis	0 (0)	2 (3.2)
Musculoskeletal and connective tissue disorders		
Back pain	2 (3.2)	1 (1.6)
Renal and urinary disorders		
Dysuria	1 (1.6)	3 (4.8)
Urinary retention	5 (8.1)	3 (4.8)
General disorders and administration site conditions		
Asthenia	9 (14.5)	11 (17.5)
Oedema peripheral	2 (3.2)	2 (3.2)
Pyrexia	14 (22.6)	11 (17.5)
Injury, poisoning and procedural complications		
Wound dehiscence	2 (3.2)	0 (0)
Wound secretion	2 (3.2)	3 (4.8)

Percentages were based on the total number of patients in the treatment group (N). AEs: adverse events; CAZ-AVI: ceftazidime avibactam; IP: investigational product; EOT: end of treatment; LFU: late follow-up; N: number of patients in the treatment group; PT: preferred term; SAE: serious adverse events; SOC: system organ class. [a]Patients with multiple AEs were counted once for each SOC and/or PT. [b]Deaths due to disease progression were not presented here. [c]Action taken, IP permanently stopped. Included AEs and SAEs with an onset date and time on or after the date and time of first dose and up to and including the EOT/LFU visit.

For the Indian population, the observed difference in cure rates between the CAZ-AVI and meropenem treatment groups at EOT ranged from -4.8% (95% CI: -22.63, 11.52) in the mMITT analysis set to 1.6% (95% CI: -7.50, 10.62) in the CE analysis set at EOT (Table 2).

Clinical cure rates in the CAZ-AVI treatment group in the India subset (mMITT analysis set) were similar to those observed in the overall population for the most common Enterobacterales isolates, (84.0% for *E. coli* and 75.0% for *K. pneumoniae*) as well as for *P. aeruginosa* (100%). Per-pathogen favorable microbiological response rates in the India subset was 84.0% for *E. coli,* 75.0% for *K. pneumoniae,* and 100% for *P. aeruginosa*. These results were in line with the overall population. In both the overall population as well as the Indian subset, CAZ-AVI demonstrated efficacy at TOC against ceftazidime-resistant Enterobacterales and against Gram-negative pathogens other than Enterobacterales with clinical cure rates being 69.2% and 100% respectively.

There were no emergent infections reported in the India subset. One patient in the CAZ-AVI plus metronidazole group (mMITT analysis set) was considered clinical failure due to persistence of infection (incomplete clinical resolution) at the EOT visit. The TOC and LFU visits had no cases of clinical failure due to persistence.

The safety analysis set included 125 Indian patients. In the overall population, the rates of adverse events (AEs), including AEs with a fatal outcome, serious adverse events (SAEs), and discontinuation of investigational product due to an AE (DAEs) were similar across the two treatment groups (Table 3). A comparable percentage of patients in both treatment groups experienced at least one AE up to the EOT visit. The most commonly reported AEs were pyrexia, nausea, vomiting, hypotension, and thrombophlebitis. No new safety findings were reported in the Indian population. The safety outcomes of Indian subset were comparable to the outcomes of the overall RECLAIM study.

Discussion

The overall objective of the global RECLAIM study was met by demonstrating the noninferiority of CAZ-AVI plus metronidazole to meropenem in the treatment of cIAI (against 12.5% non-inferiority margin and 10% non-inferiority margin) [1]. The results from the analysis of the Indian subset were consistent with those of the overall population. Hence, the conclusions made for the overall study could be applied to the Indian subset.

The rationale for combining avibactam with ceftazidime is to provide a therapeutic option for the treatment of multidrug resistant Gram-negative bacteria like Enterobacterales and *P. aeruginosa*. Avibactam expands the spectrum of inhibition of class A and C β-lactamases including extended-spectrum β-lactamase, AmpC, and *K. pneumoniae* carbapenemase (KPC) enzymes, and certain class D β-lactamases such as OXA-48 [11, 12]. The spectrum includes organisms that are resistant to cephalosporins and carbapenems due to the production of extended-spectrum β-lactamases, AmpC cephalosporinases, and serine carbapenemases.

The mean age in the Indian patients (36.6 years) was lower compared to the overall population (50 years). This was reflected in the demographics, as there were fewer co-morbidities in the Indian population. The cIAI diagnoses were adequately represented. The proportion of patients with appendicitis in the Indian population (41.7%) was similar to that of the overall population (41.3%). Appendicitis has been reported to be the most common source of cIAI which can further complicate to either peritonitis or intra-abdominal abscess formation [13]. Overall, longer treatment duration was observed in the Indian patients than in the overall population. Most patients in the Indian population were treated for 11 to 14 days compared to 5 to 10 days in the overall population.

Meropenem was the comparator used in the study as it is one of the standard treatment options for the management of cIAI [3]. Ceftazidime-avibactam does not cover anaerobes and hence metronidazole was added to provide anaerobic coverage since anaerobes are frequently implicated in cIAI [12].

The baseline microbiology of the Indian subset was similar to that of the overall population. The most frequently isolated causative agents for cIAI infection are Enterobacterales and other Gram-negative bacteria. This was reflected in the baseline microbiology in the overall study population (mMITT), in which 67.6% of patients were infected with *E. coli*, 12.2% were infected with *K. pneumoniae* and 8.6% were infected with *P. aeruginosa*. β-lactamase-producing Enterobacterales are an important clinical problem seen in cIAI. Hence, cIAI was an appropriate infection to investigate the efficacy and safety of CAZ-AVI [14-16].

In the 2012-2014 global International Network for Optimal Resistance Monitoring (INFORM) surveillance report, the MIC_{90} of ceftazidime alone against extended spectrum beta-lactamase (ESBL) -

producing, plasmid-mediated AmpC - producing, and ESBL- plus AmpC - producing isolates of *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* was reported to be higher than the MIC_{90} of ceftazidime-avibactam (>128μg/mL vs. 0.5μg/mL for AmpC - producing isolates and >128μg/mL vs. 1μg/mL for ESBL - plus AmpC – producing isolates) [17]. The 2015-2017 INFORM program conducted for the Asia-Pacific region reported similar findings for ESBL-positive, carbapenemase-negative and carbapenemase-positive, MBL-negative isolates of *E. coli, K. pneumoniae,* and *P. aeruginosa* [18].

In the overall population, for all Enterobacterales isolated at baseline (mMITT analysis set), the ceftazidime MIC_{90} was 8 μg/mL and the CAZ-AVI MIC_{90} was 0.25 μg/mL, a 32-fold reduction. In the Indian population, for all Enterobacterales isolated at baseline (mMITT analysis set), the ceftazidime MIC_{90} was > 64 μg/mL and the CAZ-AVI MIC_{90} was 2 μg/mL, a reduction of at least 32-fold. This reduction in MIC_{90} demonstrates the impact of avibactam on the antimicrobial activity of ceftazidime.

Clinical cure rates at the TOC visit in the overall population for mMITT set were 81.6% vs 85.1% in the CAZ-AVI group and in the meropenem group, respectively. The cure rates at the TOC visit in the Indian population for mMITT set were 83.3% vs 77.1% in the CAZ-AVI group and in the meropenem group, respectively. The clinical cure rate for the CE set at TOC were 97.8% vs 95.5% in the CAZ-AVI group and in the meropenem group, respectively. These results were in line with the results of the overall population. The lower cure rate in the meropenem group in the Indian subset appeared to be driven mainly by a higher proportion of indeterminate responses in the meropenem group (20%) vs the India CAZ-AVI plus metronidazole group (6.7%) and the overall population, meropenem group (7.6%).

In both the overall population as well as the India subset, CAZ-AVI demonstrated efficacy at TOC against ceftazidime-resistant Enterobacterales and against Gram-negative pathogens other than Enterobacterales, although the small numbers in the India subset limit interpretation.

The safety evaluation showed no new safety concerns in the Indian population. The safety findings were in line with the previously known effects of ceftazidime and cephalosporins in general. The study also confirmed that the safety profile of CAZ-AVI is similar to that of ceftazidime.

CAZ-AVI has been demonstrated to be non-inferior to meropenem for the treatment of cIAI, and the real-world evidence (RWE) has also demonstrated its efficacy in the management of carbapenem resistant Enterobacterales in patients of cIAI [1, 19]. The SIS guidelines recommend the use of CAZ-AVI plus metronidazole for 'empiric therapy of adults with cIAI, but reserve this regimen primarily for higher-risk patients strongly suspected or proven to be infected with *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae, for which other agents are not suitable'. The SIS guidelines recommend CAZ-AVI as an alternative for 'empiric therapy of patients at risk for infection with ESBL-producing Enterobacteriaceae' and as 'empiric therapy of patients at risk for infection with Amp C-βlactamase–producing Enterobacteriaceae' [9]. The WSES guidelines of 2017 recommend the use of CAZ-AVI in patients with 'suspected or proven infection with carbapenemase-producing *K. pneunomiae*' [10].

Conclusions

The safety and efficacy outcomes in the Indian population treated with CAZ-AVI as a part of the RECLAIM study were in line with the global RECLAIM trial. CAZ-AVI plus metronidazole proved to be an effective option for critical patients with cIAI and can be considered as an alternative to carbapenems in the ICU setting for the treatment of resistant pathogens.

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