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MECHANISMS OF RESISTANCE

Characterization of β-Lactamase Content of Ceftazidime-Resistant Pathogens Recovered during the Pathogen-Directed Phase 3 REPRISE Trial for Ceftazidime-Avibactam: Correlation of Efficacy against β-Lactamase Producers

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ABSTRACT REPRISE was a pathogen-directed (ceftazidime-resistant) phase 3 prospective, open-label, randomized, multicenter trial that evaluated the efficacy, safety, and tolerability of ceftazidime-avibactam (CAZ-AVI) and best available therapy (BAT) in the treatment of hospitalized adults with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). This study characterized the β-lactamase content of ceftazidime-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* recovered during the baseline visits of patients enrolled in REPRISE. Ceftazidime had MIC_{90} results of >64 μg/ml against baseline *Enterobacteriaceae* and *P. aeruginosa*. bla_{CTX-M} variants were the most common β-lactamases found in *Escherichia coli* (detected in 94.3% of all *E. coli* isolates) and *Klebsiella pneumoniae* (91.2%), whereas *Proteus mirabilis* often carried plasmid AmpC (pAmpC) (66.7%). bla_{KPC} (6 isolates), bla_{NDM-1} (3), bla_{OXA-48} (3), and bla_{VIM} (2) were detected in 4.9% (14/284) of *Enterobacteriaceae*. Overall, clinical cure rates against the *Enterobacteriaceae* were 91.2% and 90.8% for the CAZ-AVI and BAT groups, respectively, or 92.5% and 92.9% in the subset of patients infected with isolates harboring bla_{CTX-M}. Patients with baseline isolates carrying AmpC genes (pAmpC and/or overexpression of intrinsic AmpC) showed clinical cure rates of 80.0% and 89.5% for CAZ-AVI and BAT arms, respectively. Favorable microbiological responses were generally lower than clinical cure rates in both arms, but CAZ-AVI (80.0 to 85.0%) showed microbiological response rates consistently higher than those for BAT (57.9 to 64.3%) among patients with non-carbapenemase-producing *Enterobacteriaceae*. Lower microbiological response rates (50.0%) were found in patients with carbapenemase producers from both arms. This study expands on efficacy data analysis of CAZ-AVI among patients infected with ceftazidime-resistant pathogens, especially bla_{CTX-M}-carrying isolates, and although clinical cure rates for CAZ-AVI and BAT were similar, eradication rates for CAZ-AVI were higher than those for BAT. (This study has been registered at ClinicalTrials.gov under identifier NCT01644643.)

KEYWORDS CTX-M-15, ESBL, carbapenemase, clinical efficacy

Antimicrobial resistance is recognized as one of the most serious public health threats worldwide, and failure to address it could compromise modern medical advances (1). Currently, great concern is focused on emerging multidrug resistance in Gram-negative pathogens (2, 3). This concern relates to the increased prevalence of multidrug resistance among Gram-negative pathogens, including those producing extended-spectrum β-lactamase (ESBL) (4, 5), which led to a concomitant increase in carbapenem agent use and, consequently, increased selective pressure (6). The latter has led to the global emergence and dissemination of Gram-negative organisms

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producing class A *Klebsiella pneumoniae* carbapenemase (KPC), class B metallo-β-lactamase (MBL), and/or class D carbapenemases (OXA-48-like), challenging antimicrobial therapy and increasing mortality (7–10).

Ceftazidime-avibactam (CAZ-AVI) was approved for complicated urinary tract infections (cUTI), including acute pyelonephritis; complicated intra-abdominal infections (cIAI); and hospital-acquired pneumonia, including ventilator-associated pneumonia (11, 12). Several phase 3 trials investigated the safety and efficacy of CAZ-AVI against standard clinical comparator agents (13–15). The molecular characterization of CAZ-AVI isolates from various clinical trials was previously reported (16, 17). The study presented here describes the characterization of the β-lactamase content of baseline pathogens recovered from a phase 3 prospective, open-label, randomized, multicenter trial to evaluate the efficacy, safety, and tolerability of CAZ-AVI and the best available therapy (BAT) in the treatment of hospitalized adults with cIAI and cUTI caused by ceftazidime-resistant Gram-negative pathogens, described here as those with MIC results of ≥8 μg/ml (15). Moreover, the efficacy results for CAZ-AVI and BAT were evaluated against subsets of molecularly characterized pathogens.

RESULTS

Bacterial pathogens and β-lactamase profiles. Isolates included in this study resulted in elevated ceftazidime MIC_{50} and MIC_{90} values ($MIC_{50/90}$ of 64/>64 μg/ml for *Enterobacteriaceae* and $MIC_{50/90}$ of >64/>64 μg/ml for *Pseudomonas aeruginosa*) (15). Overall, CTX-M-encoding genes alone or combined with other β-lactamase genes were the most prevalent resistance determinants (89.4%; 254/284) among *Enterobacteriaceae* (Table 1). bla_{CTX-M} variants were most commonly detected among *Escherichia coli* (94.3%) and *K. pneumoniae* (91.2%) isolates, followed by *Enterobacter* species (76.5%) and *Citrobacter freundii* (71.4%) isolates. In contrast, *Proteus mirabilis* often (66.7%) carried plasmid AmpC (pAmpC) (Table 1). Other species, such as *Klebsiella oxytoca*, *Providencia* spp., and *Serratia marcescens*, were isolated in numbers too small to provide any valuable analysis. bla_{OXA} noncarbapenemase genes (2 bla_{OXA-2}, 4 bla_{OXA-9}, 4 bla_{OXA-10}, and 175 bla_{OXA-1}) were also commonly observed (65.1%; 185/284) in *Enterobacteriaceae* isolates, whereas bla_{CTX-M} was associated with bla_{OXA-1} in 70.9% of isolates (180/254). Other ESBL genes, such as bla_{VEB-6} (1 isolate), bla_{SHV-2} (1), bla_{SHV-5} (3), bla_{SHV-12} (4), bla_{SHV-18} (2), bla_{SHV-38} (2), and bla_{TEM-15} (1), were less prevalent (4.9%; 14/284). A total of 4.9% (14/284) of *Enterobacteriaceae* isolates carried carbapenemase genes, including bla_{KPC} (6 isolates), bla_{NDM-1} (3), bla_{VIM} (2), and bla_{OXA-48} (3). These genes were mostly found in *K. pneumoniae*, except for 2 bla_{NDM-1}- and 1 bla_{VIM-1}-harboring isolate, which were detected in *Enterobacter cloacae*, *P. mirabilis*, and *Providencia rettgeri*. In addition, all carbapenemase-producing *Enterobacteriaceae* isolates were cultured from urine, except for 1 KPC-3-producing *K. pneumoniae* isolate. These isolates were collected from patients in Argentina (2 KPC-2-producing isolates), Bulgaria (1 NDM-1, 1 VIM-1, and 1 VIM-4), Israel (3 KPC-3), Romania (1 NDM-1 and 1 OXA-48), Russia (1 NDM-1), and Spain (1 KPC-3 and 2 OXA-48). *P. aeruginosa* exhibited mostly overexpression of intrinsic AmpC (44.4%; 8/18), with or without a variety of bla_{OXA}, bla_{PER}, and bla_{VEB} genes. One isolate carried bla_{VIM-2} (Table 1).

Efficacy analysis of CAZ-AVI and BAT. Similar clinical cure rates at the test-of-cure (TOC) visit were obtained for the CAZ-AVI (91.2 to 92.5%) and BAT (90.8 to 92.9%) groups that had patients infected with *Enterobacteriaceae* or patients with baseline isolates carrying only bla_{CTX-M} genes (β-lactamase genes other than AmpC and/or carbapenemase could be present with bla_{CTX-M}) (Table 2). Patients with baseline *Enterobacteriaceae* isolates carrying AmpC genes (pAmpC and/or overexpression of intrinsic AmpC) without noncarbapenemase β-lactamase genes showed clinical cure rates of 80.0% and 89.5% for CAZ-AVI and BAT arms, respectively. Patients with baseline *Enterobacteriaceae* isolates carrying carbapenemase genes were enrolled in a small number, but all patients in the CAZ-AVI arm showed clinical cure (all cUTI cases). These patients were infected with pathogens carrying bla_{KPC} ($n = 3$), bla_{VIM} ($n = 1$), bla_{NDM} ($n = 2$), and bla_{OXA-48} ($n = 2$), and the CAZ-AVI MIC results obtained against these

TABLE 1 β-Lactamase-encoding genes detected among ceftazidime-resistant baseline pathogens recovered from patients enrolled in both arms of the ceftazidime-avibactam phase 3 trial[e]

Pathogen (no.; % of total)	β-Lactam class(es)[a]	Result(s)[a]	No. of isolates
E. coli (123; 40.7)	A, D	CTX-M-15; OXA-1	44
	A	CTX-M-15; TEM-1	25
	A, D	CTX-M-15; OXA-1; TEM-1	12
	A	CTX-M-15	10
	A	CTX-M-27	5
	A, C	CMY-2; TEM-1	5
	A, C, D	CTX-M-15; CMY-2; OXA-1; TEM-1	4
	A	CTX-M-27; TEM-1	2
	A	CTX-M-55	2
	A, C, D	CTX-M-15; CMY-42; OXA-1	2
	A	CTX-M-1	1
	A	CTX-M-14	1
	A	CTX-M-15; CTX-M-3; TEM-1	1
	A	CTX-M-2	1
	A	CTX-M-32	1
	A, C	DHA-1; SHV-12; TEM-1	1
	A, D	CTX-M-14; CTX-M-15; OXA-1	1
	A, D	CTX-M-15; CTX-M-27; OXA-1; TEM-1	1
	A, D	CTX-M-15; CTX-M-3; OXA-1	1
	A, D	CTX-M-15; OXA-1; TEM-33	1
	A, D	CTX-M-3; OXA-1	1
	C	ACT-24	1
K. pneumoniae (125; 41.4)	A, D	CTX-M-15; OXA-1; SHV-1; TEM-1	37
	A, D	CTX-M-15; OXA-1; SHV-11; TEM-1	27
	A, D	CTX-M-15; OXA-1; SHV-1	7
	A	CTX-M-15; SHV-1; TEM-1	6
	A, D	CTX-M-15; OXA-1; SHV-11	5
	A, D	CTX-M-15; OXA-10; SHV-1; TEM-1	4
	A	CTX-M-15; SHV-1	3
	A	CTX-M-15; CTX-M-3; SHV-1; TEM-1	3
	A	CTX-M-15; SHV-11; TEM-1	2
	A	CTX-M-3; SHV-11	2
	A	KPC-3; SHV-11	2
	A	KPC-3; SHV-11; TEM-1	2
	A, D	CTX-M-15; OXA-1; OXA-48; SHV-11	2
	A, D	OXA-2; SHV-18	2
	A	CTX-M-15; CTX-M-3; TEM-1	1
	A	CTX-M-15; SHV-11; SHV-12; TEM-1	1
	A	CTX-M-15; SHV-38; TEM-1	1
	A	CTX-M-2; SHV-11; TEM-1	1
	A	CTX-M-3; SHV-11; SHV-2; TEM-1	1
	A	CTX-M-3; SHV-11; TEM-1	1
	A	KPC-2; SHV-11; TEM-1	1
	A	SHV-5	1
	A, B	NDM-1; SHV-11	1
	A, B	SHV-11; TEM-1; VIM-4	1
	A, C	CMY-4; CTX-M-15; SHV-1	1
	A, C, D	CMY-4; CTX-M-15; OXA-1; SHV-1	1
	A, C, D	CTX-M-15; DHA-1; OXA-1; SHV-11; TEM-1	1
	A, D	CTX-M-15; CTX-M-3; OXA-1; SHV-1; TEM-1	1
	A, D	CTX-M-15; KPC-2; OXA-1; SHV-1; TEM-1	1
	A, D	CTX-M-15; OXA-1; OXA-48; SHV-1; TEM-1	1
	A, D	CTX-M-15; OXA-1; SHV-1; SHV-11; TEM-1	1
	A, D	CTX-M-15; OXA-1; SHV-1; SHV-5; TEM-1	1
	A, D	CTX-M-15; OXA-1; SHV-38; TEM-1	1
	A, D	CTX-M-15; OXA-9; SHV-1; TEM-1	1
	A, D	OXA-9; SHV-11; TEM-1	1
Enterobacter spp. (17; 5.6)[b]	A, C, D	CTX-M-15; cAmpC; OXA-1; TEM-1	5
	C	cAmpC	3
	A	CTX-M-15	1
	A, B, D	CTX-M-15; NDM-1; OXA-1; TEM-1	1
	A, C	CTX-M-15; cAmpC	1
	A, C	CTX-M-3; cAmpC; TEM-1	1

(Continued on next page)

TABLE 1 (Continued)

Pathogen (no.; % of total)	β-Lactam class(es)[a]	Result(s)[a]	No. of isolates
	A, C, D	CTX-M-15; CTX-M-3; cAmpC; OXA-1; TEM-1	1
	A, C, D	CTX-M-15; cAmpC; OXA-1	1
	A, C, D	cAmpC; OXA-1; SHV-12; TEM-1	1
	A, D	CTX-M-15; CTX-M-3; OXA-1; TEM-1	1
	A, D	CTX-M-15; OXA-1	1
C. freundii (7; 2.3)	A, C	cAmpC; TEM-1	1
	A, C, D	CMY-86; CTX-M-15; OXA-1; TEM-1	1
	A, C, D	CTX-M-15; CTX-M-3; cAmpC; OXA-1	1
	A, C, D	CTX-M-15; cAmpC; OXA-1; TEM-1	1
	A, D	CTX-M-15; OXA-1; TEM-1	1
	A, C	CTX-M-15; cAmpC; DHA-4; TEM-1	1
	C	cAmpC	1
P. mirabilis (6; 2.0)	A	TEM-1; VEB-6	1
	A, B, C	CMY-16; SHV-12; TEM-1; VIM-1	1
	A, C	ACC-4; TEM-1	1
	A, C	CMY-16; TEM-1	1
	A, D	CTX-M-3; OXA-9; SHV-5; TEM-1	1
	C	CMY-16	1
K. oxytoca (2; 0.7)	A, D	CTX-M-15; OXA-1; TEM-1	1
	A, D	CTX-M-15; OXA-9; TEM-15	1
Providencia spp. (2; 0.7)[c]	A, B	CTX-M-3; NDM-1; TEM-1	1
	A, C	ACC-4; TEM-1	1
S. marcescens (2; 0.7)	A, C, D	CMY-4; CTX-M-15; OXA-1; TEM-1	1
	A, D	CTX-M-15; CTX-M-3; OXA-1; TEM-1	1
P. aeruginosa (18; 6.0)	C	cAmpC	5
	A, D	OXA-10; VEB-9	3
	A, D	OXA-2; OXA-74[d]; PER-1	2
	A, D	OXA-2; PER-1	2
	A, C, D	cAmpC; OXA-10; VEB-9	1
	A, D	OXA-10; VEB-1	1
	A, D	OXA-74[d]; PER-1	1
	B	VIM-2	1
	C, D	cAmpC; OXA-17[d]	1
	C, D	cAmpC; OXA-2	1

[a]Molecular class according to Bush and Jacoby (26). cAmpC represents overexpression of the intrinsic chromosomal *ampC* gene according to reverse transcription-quantitative PCR (qRT-PCR) experiments.
[b]Includes 16 *E. cloacae* and 1 *Enterobacter aerogenes* isolate.
[c]Includes 1 *P. rettgeri* and 1 *P. stuartii* isolate.
[d]OXA-10-like enzymes.
[e]Note that five patients had 2 pathogens at the baseline visit.

isolates were 0.5 to 4 μg/ml, except against bla_{NDM-1}-harboring strains (CAZ-AVI MIC, >256 μg/ml). In the BAT arm, carbapenemase-producing *Enterobacteriaceae* isolates carried bla_{KPC-3} ($n = 3$), bla_{VIM} ($n = 1$), bla_{NDM-1} ($n = 1$), and bla_{OXA-48} ($n = 1$) (Table 2). Patients with unfavorable clinical and microbiological outcomes in both study arms are described in Tables 3 and 4. Correlations were not apparent between β-lactamases present in the clinical isolates or between the CAZ-AVI MIC and the result of an unfavorable response in patients treated with CAZ-AVI; however, 4/8 patients infected with carbapenemase-producing *Enterobacteriaceae* in the CAZ-AVI arm had an unfavorable microbiological response (Tables 2 and 4). Patients infected with *P. aeruginosa* showed clinical cure rates of 84.6% and 100.0% for CAZ-AVI and BAT arms, respectively (Table 2). One patient in the CAZ-AVI arm had a VIM-2-harboring *P. aeruginosa* isolate with a CAZ-AVI MIC of 32 μg/ml, and a clinical cure as well as a favorable microbiological response were documented.

For patients enrolled in the CAZ-AVI arm (82.6%), favorable microbiological responses tended to be lower than clinical cure rates (90.6%). A similar trend was

TABLE 2 Clinical and microbiological responses at the test-of-cure visit by β-lactamase status (mMITT population)

	Cure rate at test of cure						Comparison between groups	
	CAZ-AVI (n = 149)			BAT (n = 146)				
Patient subgroup	No. of patients	No. (%) of patients with clinical cure[a]	No. (%) of patients with microbiological cure[b]	No. of patients	No. (%) of patients with clinical cure[a]	No. (%) of patients with microbiological cure[b]	% difference of clinical cure rate[c]	% difference of microbiological cure rate[d]
All	149	135 (90.6)	123 (82.6)	146	133 (91.1)	92 (63.0)	−0.5	19.6
Enterobacteriaceae[e]	136	124 (91.2)	112 (82.4)	141	128 (90.8)	89 (63.1)	+0.4	+19.3
CTX-M[f]	107	99 (92.5)	91 (85.0)	112	104 (92.9)	72 (64.3)	−0.4	+20.7
AmpC/ESBL[g]	20	16 (80.0)	16 (80.0)	19	17 (89.5)	11 (57.9)	−9.5	+22.1
Carbapenemase/ESBL	8[h]	8 (100.0)	4 (50.0)	6[i]	4 (66.7)	3 (50.0)	+33.3	0.0
P. aeruginosa	13[j]	11 (84.6)	11 (84.6)	5	5 (100.0)	3 (60.0)	−15.4	+24.6

[a]Percentages for clinical cure rates are calculated as m/n, where m is defined by the number of patients with a favorable clinical response at the test-of-cure visit and n is represented by the combined number of patients with clinical cure, clinical failure, and an indeterminate outcome.

[b]Percentages for microbiological cure rates are calculated as m/n, where m is defined by the number of patients with a favorable microbiological response at the test-of-cure visit and n is represented by the combined number of patients with microbiological cure, failure, and an indeterminate outcome.

[c]The difference of the favorable clinical cure rate is calculated as CAZ-AVI treatment group minus BAT treatment group.

[d]Difference of favorable microbiological responses is calculated as CAZ-AVI treatment group minus BAT treatment group.

[e]Two and three patients had polymicrobial infections in the CAZ-AVI and BAT groups, respectively.

[f]Includes patients with isolates carrying CTX-M-encoding genes with or without non-ESBL and/or ESBL genes (OXA-1, OXA-10, OXA-9, SHV-11, SHV-12, SHV-5, SHV-1, and TEM-1) (Table 1).

[g]Includes patients with isolates with documented overexpression of the intrinsic chromosomal AmpC gene, carrying plasmid AmpC, and/or with multiple non-ESBL and/or ESBL genes (Table 1).

[h]Includes KPC (3 isolates)-, VIM (1)-, NDM (2)-, and OXA-48 (2)-encoding genes.

[i]Includes KPC (3 isolates)-, VIM (1)-, NDM (1)-, and OXA-48 (1)-encoding genes.

[j]One patient had a polymicrobial cUTI (*P. aeruginosa* and *P. stuartii*) at the baseline visit.

TABLE 3 Patients with baseline isolates who presented clinical failure or had an indeterminate status at TOC[a]

Arm and pathogen	Country	Infection type	CAZ-AVI MIC (μg/ml)	Molecular characterization
CAZ-AVI				
K. pneumoniae	Bulgaria	cUTI	0.5	CTX-M-15; SHV-1
P. aeruginosa	Bulgaria	cUTI	16	OXA-2; OXA-74; PER-1
E. coli	Croatia	cUTI	0.12	CTX-M-15
P. mirabilis	Croatia	cUTI	0.06	CMY-16
E. coli	Israel	cUTI	0.5	CTX-M-15; OXA-1
E. coli	Romania	cUTI	0.12	CTX-M-15; TEM-1
P. mirabilis	Romania	cUTI	0.5	ACC-4; TEM-1
E. cloacae/K. pneumoniae	Russia	cIAI	1/0.25	cAmpC/CTX-M-15; OXA-1; SHV-1; TEM-1
E. coli	Russia	cIAI	0.12	CTX-M-15; TEM-1
E. coli	Russia	cUTI	0.25	CTX-M-15; OXA-1
E. coli	South Africa	cUTI	0.12	CTX-M-15; OXA-1
E. cloacae	Ukraine	cUTI	0.25	CTX-M-15; cAmpC
E. coli	Ukraine	cUTI	0.06	CTX-M-15; TEM-1
P. aeruginosa	Ukraine	cUTI	64	OXA-10; VEB-1
BAT				
K. pneumoniae	Argentina	cUTI	NA	KPC-2; SHV-11; TEM-1
E. coli	Bulgaria	cIAI	NA	CTX-M-15; OXA-1
K. pneumoniae	Bulgaria	cUTI	NA	SHV-11; TEM-1; VIM-4
E. cloacae	Croatia	cUTI	NA	CTX-M-15; cAmpC; OXA-1; TEM-1
E. cloacae	Israel	cIAI	NA	CTX-M-15; OXA-1
E. coli	Israel	cIAI	NA	CTX-M-15; OXA-1
E. coli	Israel	cUTI	NA	CTX-M-15; OXA-1
K. pneumoniae	Romania	cUTI	NA	CTX-M-15; OXA-1; SHV-1
E. coli	Russia	cIAI	NA	CTX-M-15; OXA-1
K. pneumoniae	Russia	cIAI	NA	OXA-2; SHV-18
E. coli	Spain	cUTI	NA	CTX-M-27
E. coli	Turkey	cUTI	NA	CTX-M-15; TEM-1
K. pneumoniae	Ukraine	cUTI	NA	CMY-4; CTX-M-15; SHV-1

[a]TOC, test of cure; CAZ-AVI, ceftazidime-avibactam; BAT, best available therapy; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; NA, not available. cAmpC represents overexpression of the intrinsic chromosomal *ampC* gene according to qRT-PCR experiments.

observed among patients enrolled in the BAT arm (63.0% and 91.1%, respectively) (Table 2). The favorable microbiological responses observed among patients enrolled in the CAZ-AVI arm (80.0 to 85.0%) were consistently higher that those noted for BAT (57.9 to 64.3%), except among patients infected with carbapenemase-producing *Enterobacteriaceae*, where favorable microbiological responses of 50.0% were documented in both arms (Table 2).

DISCUSSION

These study results confirm the high occurrence of $bla_{\text{CTX-M}}$ among clinical trial *Enterobacteriaceae* isolates causing cIAI or cUTI. The majority of $bla_{\text{CTX-M}}$ variants were $bla_{\text{CTX-M-15}}$, which corroborates other clinical trials (16–18) and surveillance studies (8, 19, 20) demonstrating the dominance of $bla_{\text{CTX-M-15}}$ among *Enterobacteriaceae* (21, 22). This ESBL gene has disseminated globally; however, group 9 variants (especially CTX-M-14) appear dominant in China, Southeast Asia, South Korea, Japan, and Spain (21). Carbapenemase genes remained infrequently isolated (4.6%) among ceftazidime-resistant *Enterobacteriaceae* causing cIAI or cUTI. The occurrence of such isolates was lower than that observed in a surveillance study among cUTI and cIAI *Enterobacteriaceae* isolates in Europe (11.0%) (23). The lower carbapenemase rate in ceftazidime-resistant isolates in this clinical trial may be attributed to the respective sites included in the study or to the inclusion/exclusion criteria used to enroll each patient.

This study demonstrated similar clinical cure rates for CAZ-AVI and BAT (90.8 to 91.2%) in cIAI or cUTI caused by ceftazidime-resistant *Enterobacteriaceae*. These efficacy results also extended to the subset of pathogens carrying $bla_{\text{CTX-M}}$ (92.5 to 92.9%). The analysis generated here showed clinical cure rates for CAZ-AVI lower than those for BAT on two occasions, when *Enterobacteriaceae* isolates overexpressing intrinsic AmpC or carrying pAmpC-encoding genes (80.0 versus 89.5% for BAT) were present or *P.*

TABLE 4 Patients with baseline isolates who presented an unfavorable microbiological response or had an indeterminate status at TOC[a]

Arm and pathogen	Country	Infection	CAZ-AVI MIC (μg/ml)	Molecular characterization
CAZ-AVI				
C. freundii	Bulgaria	cUTI	0.5	CTX-M-15; OXA-1; TEM-1
E. cloacae	Bulgaria	cUTI	2	cAmpC; OXA-1; SHV-12; TEM-1
E. cloacae	Romania	cUTI	>256	CTX-M-15; NDM-1; OXA-1; TEM-1
E. cloacae/K. pneumoniae	Russia	cIAI	1/0.25	cAmpC/CTX-M-15; OXA-1; SHV-1; TEM-1
E. coli	Croatia	cUTI	0.12	CTX-M-15
E. coli	Israel	cUTI	0.5	CTX-M-15; OXA-1
E. coli	Romania	cUTI	0.06	CTX-M-15; OXA-1
E. coli	Russia	cUTI	0.25	CTX-M-15; OXA-1
E. coli	Romania	cUTI	0.12	CTX-M-15; TEM-1
E. coli	Russia	cIAI	0.12	CTX-M-15; TEM-1
E. coli	Russia	cUTI	≤0.008	CTX-M-15; TEM-1
E. coli	Ukraine	cUTI	0.06	CTX-M-15; TEM-1
K. pneumoniae	Bulgaria	cUTI	1	CTX-M-15; OXA-1; SHV-1; TEM-1
K. pneumoniae	Turkey	cUTI	0.25	CTX-M-15; OXA-1; SHV-1; TEM-1
K. pneumoniae	Turkey	cUTI	0.5	CTX-M-15; OXA-1; SHV-1; TEM-1
K. pneumoniae	Russia	cUTI	0.5	CTX-M-15; OXA-1; SHV-11; TEM-1
K. pneumoniae	Russia	cUTI	0.5	CTX-M-15; OXA-1; SHV-11; TEM-1
K. pneumoniae	Bulgaria	cUTI	0.12	CTX-M-15; OXA-1; SHV-38; TEM-1
K. pneumoniae	Bulgaria	cUTI	0.5	CTX-M-15; SHV-1
K. pneumoniae	Israel	cUTI	4	KPC-3; SHV-11
K. pneumoniae	Bulgaria	cUTI	>256	NDM-1; SHV-11
P. aeruginosa	Russia	cUTI	4	cAmpC
P. aeruginosa	Ukraine	cUTI	64	OXA-10; VEB-1
P. mirabilis	Romania	cUTI	0.5	ACC-4; TEM-1
P. mirabilis	Croatia	cUTI	0.06	CMY-16
P. mirabilis	Bulgaria	cUTI	0.5	CMY-16; SHV-12; TEM-1; VIM-1
BAT				
C. freundii	France	cUTI	NA	cAmpC; TEM-1
C. freundii	Bulgaria	cUTI	NA	CTX-M-15; CTX-M-3; cAmpC; OXA-1
E. cloacae	Bulgaria	cUTI	NA	CTX-M-15; CTX-M-3; cAmpC; OXA-1; TEM-1
E. cloacae	Israel	cIAI	NA	CTX-M-15; OXA-1
E. coli	Israel	cUTI	NA	CMY-2; TEM-1
E. coli	United States	cUTI	NA	CMY-2; TEM-1
E. coli	Russia	cUTI	NA	CMY-42; CTX-M-15; OXA-1
E. coli	Croatia	cUTI	NA	CTX-M-15
E. coli	Peru	cUTI	NA	CTX-M-15
E. coli	Bulgaria	cIAI	NA	CTX-M-15; OXA-1
E. coli	Bulgaria	cUTI	NA	CTX-M-15; OXA-1
E. coli	Israel	cIAI	NA	CTX-M-15; OXA-1
E. coli	Israel	cUTI	NA	CTX-M-15; OXA-1
E. coli	Mexico	cUTI	NA	CTX-M-15; OXA-1
E. coli	Romania	cUTI	NA	CTX-M-15; OXA-1
E. coli	Russia	cIAI	NA	CTX-M-15; OXA-1
E. coli	Turkey	cUTI	NA	CTX-M-15; OXA-1
E. coli	Bulgaria	cUTI	NA	CTX-M-15; OXA-1; TEM-1
E. coli	Romania	cUTI	NA	CTX-M-15; OXA-1; TEM-1
E. coli	Bulgaria	cUTI	NA	CTX-M-15; TEM-1
E. coli	Bulgaria	cUTI	NA	CTX-M-15; TEM-1
E. coli	Turkey	cUTI	NA	CTX-M-15; TEM-1
E. coli	Turkey	cUTI	NA	CTX-M-15; TEM-1
E. coli	Argentina	cUTI	NA	CTX-M-2
E. coli/E. coli	Turkey	cUTI	NA	CTX-M-15; CTX-M-3; TEM-1/CTX-M-15; TEM-1
K. oxytoca	Romania	cUTI	NA	CTX-M-15; OXA-1; TEM-1
K. oxytoca	Bulgaria	cUTI	NA	CTX-M-15; OXA-9; TEM-15
K. pneumoniae	Bulgaria	cUTI	NA	CMY-4; CTX-M-15; OXA-1; SHV-1
K. pneumoniae	Ukraine	cUTI	NA	CMY-4; CTX-M-15; SHV-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; CTX-M-3; SHV-1; TEM-1
K. pneumoniae	Romania	cUTI	NA	CTX-M-15; OXA-1; SHV-1
K. pneumoniae	Russia	cUTI	NA	CTX-M-15; OXA-1; SHV-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; OXA-1; SHV-1; SHV-11; TEM-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; OXA-1; SHV-1; TEM-1
K. pneumoniae	Peru	cUTI	NA	CTX-M-15; OXA-1; SHV-1; TEM-1
K. pneumoniae	Romania	cUTI	NA	CTX-M-15; OXA-1; SHV-1; TEM-1
K. pneumoniae	United States	cUTI	NA	CTX-M-15; OXA-1; SHV-1; TEM-1

(Continued on next page)

TABLE 4 (Continued)

Arm and pathogen	Country	Infection	CAZ-AVI MIC (μg/ml)	Molecular characterization
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; OXA-1; SHV-11
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; OXA-1; SHV-11; TEM-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; OXA-1; SHV-11; TEM-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; SHV-1
K. pneumoniae	Romania	cUTI	NA	CTX-M-15; SHV-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; SHV-1; TEM-1
K. pneumoniae	Romania	cUTI	NA	CTX-M-15; SHV-11; SHV-12; TEM-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-15; SHV-38; TEM-1
K. pneumoniae	Bulgaria	cUTI	NA	CTX-M-3; SHV-11
K. pneumoniae	Argentina	cUTI	NA	KPC-2; SHV-11; TEM-1
K. pneumoniae	Russia	cIAI	NA	OXA-2; SHV-18
K. pneumoniae	Bulgaria	cUTI	NA	SHV-11; TEM-1; VIM-4
P. aeruginosa	Turkey	cUTI	NA	cAmpC
P. aeruginosa	Turkey	cUTI	NA	OXA-2; PER-1
P. mirabilis	Argentina	cUTI	NA	CTX-M-3; OXA-9; SHV-5; TEM-1
P. rettgeri	Russia	cUTI	NA	CTX-M-3; NDM-1; TEM-1
S. marcescens	Bulgaria	cUTI	NA	CTX-M-15; CTX-M-3; OXA-1; TEM-1

[a]TOC, test of cure; CAZ-AVI, ceftazidime-avibactam; BAT, best available therapy; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; NA, not available. cAmpC represents overexpression of the intrinsic chromosomal *ampC* gene according to qRT-PCR experiments.

aeruginosa (84.6 versus 100.0% for BAT) was present. The reasons for these results are unclear, and the number of such isolates remained low, compromising data analysis. Clinical cure rates presented here against AmpC-producing isolates were similar to those (75.0 to 86.7%) obtained in a IAI phase 3 trial for CAZ-AVI and comparator agents (17). Also in agreement were the small number of patients infected with such isolates in this and the previous IAI phase 3 trial (17).

REPRISE (ClinicalTrials.gov identifier NCT01644643) was the first pathogen-directed study, and only 14 patients infected with carbapenemase-producing *Enterobacteriaceae* pathogens were enrolled. This number of patients was likely due to the high occurrence of ESBL-producing isolates, even when including participating medical centers with a history of elevated rates of isolates carrying a variety of carbapenemase genes (e.g., Europe and adjacent regions) (24). All patients in the CAZ-AVI arm infected by carbapenemase-producing pathogens (including a patient with *P. aeruginosa*) had favorable clinical cure rates, including those infected with MBL-producing isolates (2 NDM-1 [CAZ-AVI MIC, >256 μg/ml], 1 VIM-2 [CAZ-AVI MIC, 32 μg/ml], and 1 VIM-1 [CAZ-AVI MIC, 1 μg/ml]). However, patients infected with the NDM-1- and VIM-1-producing isolates in the CAZ-AVI arm had unfavorable microbiological responses at the TOC. Although clinical improvement was seen in some patients infected with MBL-producing pathogens, persistence of the causative pathogen may occur.

CAZ-AVI (80.0 to 85.0%) demonstrated favorable microbiological responses consistently higher than those with BAT (57.9 to 64.3%) among patients with non-carbapenemase-producing *Enterobacteriaceae*. Although the vast majority of patients included here had cUTI, similar microbiological responses were obtained at TOC for CAZ-AVI (62.7%) and doripenem (60.7%) against ceftazidime-resistant isolates during the CAZ-AVI phase 3 trials (RECAPTURE 1 and 2) for cUTI (13). Differences in trial designs limit direct comparisons, and the reasons for these discrepancies are unknown. Nonetheless, imipenem was the agent most utilized as a BAT in the REPRISE trial, and most unfavorable microbiological responses were associated with this drug (15). In addition, the overall clinical cure rates observed here for both arms (90.6 to 91.1%) were higher than the favorable microbiological responses (63.0 to 82.6%). Similar findings were observed in the RECAPTURE phase 3 trials for cUTI, where the clinical cure rates (90.8 to 90.5%) were higher than the microbiological responses (64.0 to 60.0%) at TOC when ceftazidime-resistant isolates were present (13).

The small number of patients infected with carbapenemase-producing isolates limits the interpretation of the clinical and microbiological outcome findings in this study. However, the study results presented here add valuable information related to the treatment of serious cUTI and cIAI caused by ceftazidime-resistant *Enterobacteriaceae*. Clinical cure rates for CAZ-AVI were similar to those obtained for the BAT arm against the overall ceftazidime-resistant *Enterobacteriaceae* population, whereas favorable microbiological responses for CAZ-AVI were consistently higher than those for BAT. These results expand on those reported previously (16, 17) by providing additional patients infected with ceftazidime-resistant pathogens, especially $bla_{\text{CTX-M}}$-carrying isolates. Moreover, the data analysis presented here indicates that CAZ-AVI may be used as an alternative agent to treat cUTI and cIAI.

MATERIALS AND METHODS

Patients, clinical isolates, study treatment, and endpoints. REPRISE (ClinicalTrials.gov identifier NCT01644643) was a prospective, international, randomized, open-label, phase 3 trial. Eligible patients were randomized in a 1:1 ratio to receive 5 to 21 days of treatment with either CAZ-AVI (2,000 mg CAZ–500 mg AVI), administered together as a 2-h intravenous (i.v.) infusion every 8 h, or BAT. Patients were stratified by entry diagnosis (cUTI and cIAI) and by region: (i) North America and Western Europe, (ii) Eastern Europe, and (iii) other regions. The investigator determined the BAT, which was based on the standard of care and local label recommendations, and BAT was documented before randomization. Patients with cUTI had 2 follow-up visits, at 21 to 25 days (FU1) and at 28 to 32 days (FU2) from randomization. Patients with cIAI had only 1 follow-up visit at 28 to 35 days from randomization (FU1). Carmeli et al. (15) provide additional information related to the clinical trial.

A total of 284 baseline *Enterobacteriaceae* and 18 *P. aeruginosa* isolates with elevated ceftazidime MIC results (≥8 μg/ml; referred to here as ceftazidime resistant) causing cIAI/cUTI in the microbiological modified intention-to-treat (mMITT) population were included. These baseline isolates were recovered during the first patient visit from 295 patients (aged 18 to 90 years) hospitalized in the Americas (Argentina, 8 subjects; Mexico, 7; Peru, 5; United States, 5), Europe (Bulgaria, 86; Croatia, 12; Czech Republic, 6; France, 3; Spain, 4; Ukraine, 28), Russia (66), Turkey (22), Israel (15), South Africa (2), and South Korea (2). When multiple isolates of the same species and demonstrating the same pulsed-field gel electrophoresis (PFGE) or multilocus sequence typing (MLST) profile were obtained from a patient, only 1 isolate was included. Six patients (3 from each arm) had 2 isolates of different species recovered at the baseline visit, and both isolates from each patient were included in the analysis. The primary endpoint was assessment of clinical response (cure, failure, or indeterminate) at the TOC visit 7 to 10 days after the last infusion of study therapy in the mMITT population, whereas a favorable microbiological response was defined by the eradication or presumed eradication of the causative pathogen (15).

Susceptibility testing, selection criteria, and screening of β-lactamases. All baseline clinical isolates were centrally tested for susceptibility by broth microdilution (Clinical and Laboratory Standards Institute [CLSI] document M07-A10, 2015) (25). *Enterobacteriaceae* were selected according to preestablished MIC criteria and subjected to screening for non-ESBL-, ESBL-, pAmpC-, and carbapenemase-encoding genes, and enzymes were assigned based on amino acid identity, as previously described (16, 17). The transcription levels of chromosomally encoded AmpC were determined in *Enterobacter* spp., *Citrobacter* spp., and *P. aeruginosa* by quantifying the target gene mRNA level using a normalized expression analysis method and relative comparison to susceptible control strains (16, 17). A given isolate was determined to overexpress the *ampC* gene when at least a 10-fold greater difference of *ampC* transcripts was detected than with a species-specific wild-type reference control strain.

Statistical analyses. Descriptive summaries are provided for clinical and microbiological responses at the TOC visit between groups. Analyses were performed between arms stratified by group of organisms/species, phenotype, and β-lactamase resistance mechanisms of baseline isolates.

Data availability. Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the United States and/or European Union or (ii) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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