

ABSTRACT

Background: AAI101 is a novel extended-spectrum β -lactamase inhibitor (BLI) active against ESBLs and a broad array of other β -lactamases. AAI101 combined with cefepime has completed Phase 2 clinical development. Cefepime/AAI101 was granted Qualified Infectious Disease Product and Fast Track designations by the United States Food and Drug Administration. Emergence of new extended-spectrum β -lactamases (ESBLs) amongst Enterobacteriaceae has compromised the clinical efficacy of β -lactam/ β -lactamase inhibitor combinations such as piperacillin-tazobactam (PIP/TAZ). This study assessed the in vitro activity of cefepime/AAI101 against Enterobacteriaceae isolated from patients in the USA and Europe during 2014/2015.

Materials/methods: *E. coli*, *K. pneumoniae*, and *Enterobacter* isolates (n = 1,696) were collected during 2014/2015 from the USA (50%) and France, Germany, Italy, Spain and the UK (10% each). ESBLs were identified by genotyping. MICs were determined by broth microdilution following CLSI methodology.

Results: MIC₉₀ data for cefepime/AAI101 and β -lactam comparators are shown in the Table. Against *K. pneumoniae* cefepime/AAI101 activity was far superior to ceftolozane-tazobactam (TOL/TAZ) or PIP/TAZ, and similar to ceftazidime-avibactam (CAZ/AVI). Against *E. coli* cefepime/AAI101 activity was superior to PIP/TAZ, particularly ESBL-producing isolates, and similar to CAZ/AVI or TOL/TAZ. Cefepime/AAI101 activity vs. *Enterobacter* isolates was much greater than that of PIP/TAZ or TOL/TAZ, and was similar to CAZ/AVI.

Pathogen (n)	MIC ₉₀ (mg/L)					
	cefepime	cefepime/AAI101 [4*]	cefepime/AAI101 [8*]	CAZ/AVI [4*]	TOL/TAZ [4*]	PIP/TAZ [4*]
<i>K. pneumoniae</i> (799)	>64	0.5	0.5	0.5	8	>128
- ESBL <i>K. pneumoniae</i> (87)	>64	0.5	0.5	0.5	16	>128
<i>E. coli</i> (697)	16	0.12	0.12	0.25	0.5	8
- ESBL <i>E. coli</i> (103)	>64	0.25	0.12	0.25	1	64
<i>E. aerogenes</i> (100)	0.5	0.25	0.25	0.5	4	64
<i>E. cloacae</i> (100)	16	2	1	0.5	16	128

CAZ, ceftazidime, AVI, avibactam, TOL, ceftolozane; TAZ, tazobactam; PIP, piperacillin; *BLI at fixed conc. in mg/L

Conclusions: Addition of AAI101, a potent β -lactamase inhibitor, to cefepime renders this cephalosporin active against ESBL-producing *K. pneumoniae* and *E. coli*, and other Enterobacteriaceae. Improved susceptibility of ESBL-producing Enterobacteriaceae to cefepime/AAI101 compared to PIP/TAZ suggests that cefepime/AAI101 may be useful in hospitals where resistance to PIP/TAZ is significant.

INTRODUCTION

AAI101 is a new extended-spectrum β -lactamase inhibitor belonging to the penicillanic acid sulfone class (Figure 1), whose mechanism of action towards β -lactamases is distinguishable from that of tazobactam [1].

In this study, the activity of cefepime/AAI101 against *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* spp. was evaluated, with isolates coming from US medical centres across the country and from medical centres representing the five principal West European healthcare markets.

MATERIALS & METHODS

- A collection of 1,696 isolates of Enterobacteriaceae collected during 2014/2015 from USA (50%) and France, Germany, Spain Italy and the UK (10% each) were tested.
- MICs for cefepime/AAI101 [at fixed AAI101 concentrations of 4 or 8 mg/L] and comparator antibiotics were determined by broth microdilution using CLSI methodology [2]. AAI101, avibactam and ceftolozane were provided by Allegra Therapeutics SAS, and other antibacterials were purchased from commercial sources.
- Susceptibility was determined according to CLSI breakpoints [3] except for ceftazidime/avibactam, for which FDA breakpoints were used.
- For comparative purposes, susceptibility of AAI101 combinations with cefepime was determined using CLSI breakpoints for cefepime alone [3].

Figure 1. Chemical structure of AAI101

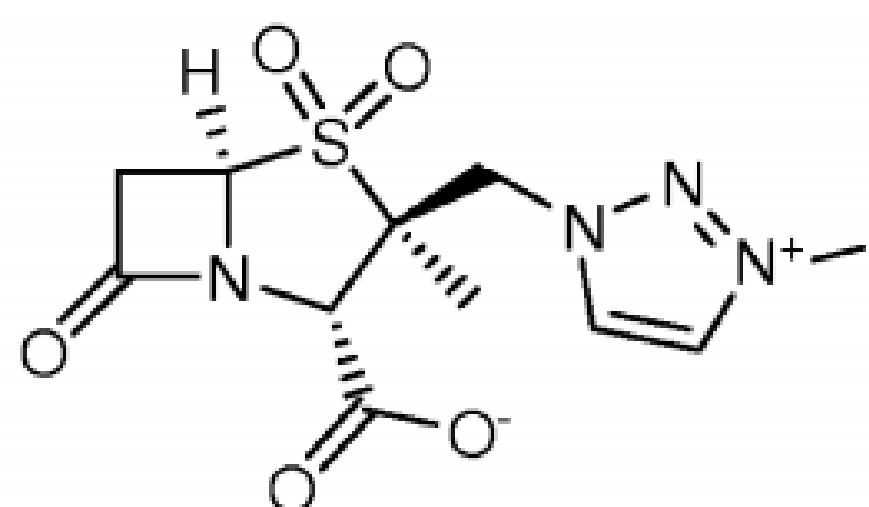


Table 1. Overview MIC₉₀ [mg/L] (% susceptibility) by pathogen

Pathogen	cefepime	cefepime/AAI101 (4)	cefepime/AAI101 (8)	ceftazidime	ceftazidime/avibactam	ceftolozane/tazobactam	meropenem	piperacillin/tazobactam
<i>E. coli</i> n=697	16 (85.8%)	0.12 (99.9%)	0.12 (99.9%)	16 (86.7%)	0.25 (100%)	0.5 (98.1%)	0.03 (99.6%)	8 (92.4%)
<i>K. pneumoniae</i> n=799	>64 (80.9%)	0.5 (92.9%)	0.5 (93.7%)	>64 (80.4%)	0.5 (99.6%)	8 (87.5%)	0.12 (92.7%)	>128 (83.1%)
<i>E. aerogenes</i> n=100	0.5 (97.0%)	0.25 (100%)	0.25 (100%)	64 (73.0%)	0.5 (100%)	4 (84.0%)	0.12 (100%)	64 (77.0%)
<i>E. cloacae</i> n=100	16 (79.0%)	2 (94.0%)	1 (96.0%)	>64 (58.8%)	0.5 (98.0%)	16 (71.0%)	0.12 (97.0%)	128 (68.0%)

Key: susceptible; intermediate or susceptible dose-dependent; resistant

Table 2. Summary MIC and susceptibility data for all Enterobacteriaceae (n=1996)

Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	83.7	3.2	13.0	0.06	32	0.015	> 64
Cefepime/AAI101 [4]	96.2	1.4	2.4	0.06	0.25	0.015	> 64
Cefepime/AAI101 [8]	96.8	1.3	1.9	0.06	0.25	0.015	> 64
Ceftazidime	81.2	1.9	16.9	0.25	64	0.03	> 64
Ceftazidime/Avibactam [4]	99.7	-	-	0.12	0.5	≤ 0.015	> 64
Ceftolozane/Tazobactam [4]	90.7	2.0	7.3	0.25	2	0.06	> 32
Ciprofloxacin	76.5	1.4	22.1	0.03	> 16	0.004	> 16
Gentamicin	89.0	0.5	10.5	0.5	16	0.12	> 32
Meropenem	96.2	0.2	3.6	0.03	0.06	0.008	> 8
Piperacillin/Tazobactam [4]	85.7	4.7	9.6	2	64	0.12	> 128

Table 3. Summary MIC and susceptibility for all ESBL-only producing Enterobacteriaceae (n=191)

Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	9.4	18.8	71.7	32	> 64	0.12	> 64
Cefepime/AAI101 [4]	98.4	1.1	0.5	0.06	0.25	0.015	16
Cefepime/AAI101 [8]	99.5	0.5	0.0	0.06	0.25	0.015	4
Ceftazidime	17.3	35.6	47.1	16	> 64	0.25	> 64
Ceftazidime/Avibactam [4]	100	-	-	0.12	0.25	≤ 0.015	2
Ceftolozane/Tazobactam [4]	79.6	7.8	12.6	0.5	8	0.12	> 32
Ciprofloxacin	13.6	5.2	81.2	> 16	> 16	0.008	> 16
Gentamicin	52.9	0.5	46.6	1	> 32	0.12	> 32
Meropenem	99.5	0.5	0.0	0.03	0.06	0.008	4
Piperacillin/Tazobactam [4]	69.6	11.0	19.4	8	> 128	0.5	> 128

RESULTS

Table 4. Summary MIC and susceptibility data for all *E. coli* (n=697)

Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	85.8	4.0	10.2	0.06	16	0.015	> 64
Cefepime/AAI101 [4]	99.9	0.0	0.1	0.06	0.12	0.015	> 64
Cefepime/AAI101 [8]	99.9	0.0	0.1	0.06	0.12	0.015	32
Ceftazidime	86.7	2.7	10.6	0.25	16	0.06	> 64
Ceftazidime/Avibactam [4]	100.0	-	-	0.12	0.25	≤ 0.015	2
Ceftolozane/Tazobactam [4]	98.1	0.6	1.3	0.25	0.5	0.06	> 32
Ciprofloxacin	68.0	0.7	31.3	0.015	> 16	0.004	> 16
Gentamicin	86.2	0.3	13.5	0.5	32	0.12	> 32
Meropenem	99.6	0.1	0.3	0.015	0.03	0.008	8
Piperacillin/Tazobactam [4]	92.4	3.3	4.3	2	8	≤ 0.12	> 128

Table 5. Summary MIC and susceptibility data for all *K. pneumoniae* (n=799)

Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	80.9	1.9	17.3	0.06	> 64	0.015	> 64
Cefepime/AAI101 [4]	92.9	2.8	4.4	0.06	0.5	0.015	> 64
Cefepime/AAI101 [8]	93.7	2.6	3.6	0.06	0.5	0.015	> 64
Ceftazidime	80.4	1.3	18.4	0.25	> 64	0.03	> 64
Ceftazidime/Avibactam [4]	99.6	-	-	0.12	0.5	≤ 0.015	> 64
Ceftolozane/Tazobactam [4]	87.5	1.8	10.8	0.25	8	0.06	> 32
Ciprofloxacin	80.0	2.1	17.9	0.03	> 16	0.004	> 16
Gentamicin	90.0	0.6	9.4	0.25	8	0.12	> 32
Meropenem	92.7	0.1	7.1	0.03	0.12	0.008	> 8
Piperacillin/Tazobactam [4]	83.1	2.9	14.0	4	> 128	0.25	> 128

Table 6. Summary MIC and susceptibility data for ESBL-only producing *K. pneumoniae* (n=87)

Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	5.7	12.6	81.6	64	> 64	0.03	> 64
Cefepime/AAI101 [4]	96.6	2.3	1.1	0.12	0.5	0.03	16
Cefepime/AAI101 [8]	98.9	1.1	0.0	0.12	0.5	0.03	4
Ceftazidime	5.7	8.0	86.2	64	> 64	0.25	> 64
Ceftazidime/Avibactam [4]	100.0	-	-	0.25	0.5	≤ 0.015	2
Ceftolozane/Tazobactam [4]	60.9	13.8	25.3	1	16	0.12	> 32
Ciprofloxacin	16.1	10.3	73.6	> 16	> 16	0.008	> 16
Gentamicin	44.8	1.1	54.0	32	> 32	0.25	> 32
Meropenem	98.9	0.0	1.1	0.03	0.12	0.015	4
Piperacillin/Tazobactam [4]	50.6	14.9	34.5	16	> 128	1	> 128

Table 7. Summary MIC and susceptibility data for KPC-only producing *K. pneumoniae* (n=29)

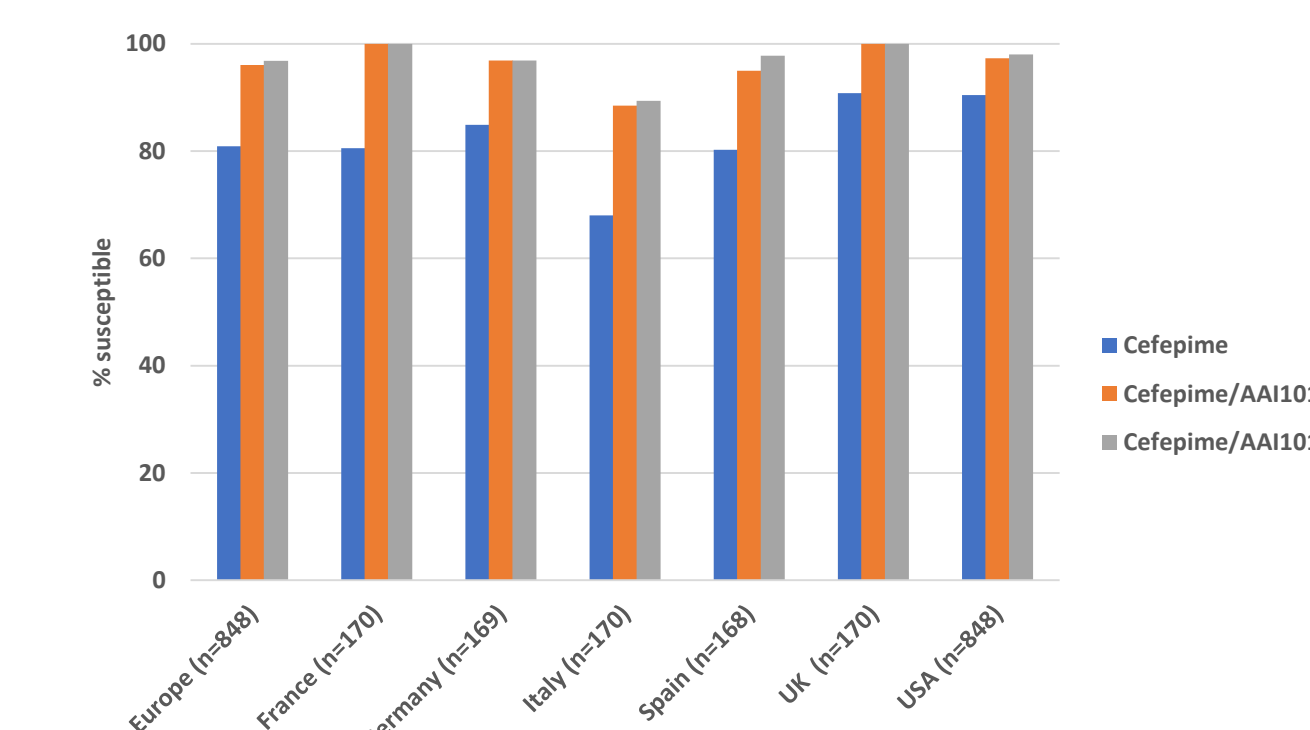
Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	0.0	0.0	100	> 64	> 64	16	> 64
Cefepime/AAI101 [4]	0.0	13.8	86.2	32	> 64	4	> 64
Cefepime/AAI101 [8]	6.9	13.8	79.3	32	> 64	2	> 64
Ceftazidime	0.0	0.0	100	> 64	> 64	32	> 64
Ceftazidime/Avibactam [4]	96.6	-	-	1	8	0.06	16
Ceftolozane/Tazobactam [4]	0.0	0.0	100	> 32	> 32	32	> 32
Ciprofloxacin	3.4	0.0	96.6	> 16	> 16	0.5	> 16
Gentamicin	79.3	10.3	10.3	2	> 32	0.25	> 32
Meropenem	0.0	0.0	100	> 8	> 8	4	> 8
Piperacillin/Tazobactam [4]	3.4	0	96.6	> 128	> 128	1	> 128

Table 8. Summary MIC and susceptibility data for all *E. cloacae* (n=100)

Drug	Percentage			MIC (mg/L)			
	Susceptible	Intermediate	Resistant	MIC ₅₀	MIC ₉₀	Min	Max
Cefepime	79.0	9.0	12.0	0.12	16	0.03	> 64
Cefepime/AAI101 [4]	94.0	2.0	4.0	0.12	2	0.03	> 64
Cefepime/AAI101 [8]	96.0	1.0	3.0	0.12	1	0.03	> 64
Ceftazidime	58.0	1.0	41.0	0.5	> 64	0.12	> 64
Ceftazidime/Avibactam [4]	98.0	-	-	0.25	0.5	0.03	> 64
Ceftolozane/Tazobactam [4]	71.0	9.0	20.0	0.5	16	0.25	> 32
Ciprofloxacin	89.0	1.0	10.0	0.03	2	0.008	> 16
Gentamicin	92.0	2.0	7.0	0.25	0.5	0.12	> 32
Meropenem	97.0	1.0	2.0	0.03	0.12	0.008	> 8
Piperacillin/Tazobactam [4]	68.0	14.0	18.0	4	128	1	> 128

Tables 2 – 8: the "Intermediate" category corresponds to "Susceptible Dose-Dependent" for cefepime and cefepime/AAI101. Some ESBL-only producing isolates coproduced original-spectrum β -lactamases (OSBLs).

Figure 2. Percentage susceptibility for cefepime and AAI101 combinations against Enterobacteriaceae (n=1696) by country/region



RESULTS

- Addition of 4 mg/L or 8 mg/L of AAI101 to cefepime restored the MIC₉₀ to the susceptible category for the combined panel of Enterobacteriaceae. The susceptibility rate of cefepime/AAI101 was comparable to that of meropenem. Cefepime/AAI101 was more active than ceftolozane/tazobactam and piperacillin/tazobactam (Table 2).

- Against a subset of genotyped, ESBL-only producing Enterobacteriaceae showing > 70% cefepime resistance, addition of AAI101 shifted almost all isolates to the susceptible category (Table 3).

- Cefepime/AAI101 susceptibility rates for *E. coli* were comparable to those of ceftolozane/tazobactam, meropenem and ceftazidime/avibactam, and were higher than that of piperacillin/tazobactam (Table 4).

- Cefepime/AAI101 susceptibility rates for *K. pneumoniae* were comparable to those of meropenem, and higher than those of piperacillin/tazobactam and ceftolozane/tazobactam. Ceftazidime/avibactam was the most potent drug tested (Table 5).

- Against a subset of genotyped, ESBL-only producing *K. pneumoniae* isolates with > 80% cefepime resistance, addition