Antimicrobial Activity of BAL30072, Alone and in Combination with Meropenem Tested Against Gram-Negative Bacteria Causing Serious Infections in Hospitals from China, India, Latin America and Southeast Asia-Pacific

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ABSTRACT

Background: BAL30072 (BAL, Basilea Pharmaceutica International Ltd.) is a novel monosulfactam with potent Gram-negative activity (GN) and potential to treat serious infections, including those caused by antimicrobial-resistant (R) GN pathogens.

Methods: BAL, MER, BAL+MER (1:1) and comparators were susceptibility (S) tested by CLSI broth microdilution methods against 1,836 GN strains collected from 57 medical centers located in (no. of isolates/centers) China (CH; 511/11), India (IN; 305/4), Latin America (LA, 508/15) and Southeast Asia-Pacific (APAC, 512/27) mostly from 2010 (83.4%) and 2009 (14.2%). The collection included: Enterobacteriaceae (ENT; 826), *P. aeruginosa* (PSA; 662) and *A. baumannii* (ACB; 348).

Results: BAL alone was active against ENT species ($MIC_{50/90}$, 0.06/4 µg/ml) and BAL+MER ($MIC_{50/90}$, ≤0.015/0.06 µg/ml) was slightly more active than MER alone ($MIC_{50/90}$, 0.03/0.06 µg/ml). BAL+MER and MER MIC results did not vary significantly by geographic region/nation, however BAL did show increased MIC_{90} results in ENT strains from IN and LA. BAL was active against PSA ($MIC_{50/90}$, 1/4 µg/ml) and BAL+MER ($MIC_{50/90}$, 0.25/1 µg/ml) had MIC results 2- to 16-fold lower than MER ($MIC_{50/90}$, 0.5/16 µg/ml).152/184 (82.6%) MER-NS PSA isolates had BAL+MER MIC results ≤2 µg/ml. BAL had equal activity to BAL+MER ($MIC_{50/90}$, 1/8 µg/ml) but better than MER ($MIC_{50/90}$, >32/>32 µg/ml) against ACB.

Conclusions: BAL was very active against GN pathogens, and when combined with MER was more active against ENT and PSA compared to either agent alone. For ACB BAL was much more active than MER alone. BAL, and the combination of BAL+MER. appears to offer a useful therapeutic alternative for treatment of serious GN infections.

Organism (no. tested)	Cumulative % inhibited at BAL (and BAL+MER) MIC (µg/mL) of:								
	≤0.06	0.12	0.25	0.5	1	2	4	8	16
ENT (826)	52.8 (94.2)	64.8 (97.1)	72.6 (97.7)	77.7 (98.1)	83.2 (98.5)	87.2 (98.8)	90.9 (98.9)	92.5 (99.3)	93.2 (99.5)
PSA (662)	3.8 (15.7)	9.2 (40.0)	22.1 (66.9)	48.3 (83.1)	72.7 (90.8)	86.9 (95.2)	93.1 (97.1)	96.1 (99.1)	99.1 (99.7)
ACB (348)	0.3 (2.0)	3.2 (12.6)	14.4 (27.3)	39.1 (48.6)	63.2 (70.4)	77.9 (82.5)	85.3 (87.6)	90.2 (92.5)	91.1 (94.3)

INTRODUCTION

BAL30072 ((3S)-3-[(2Z)-(2-amino(1,3-thiazol-4-yl))-3-[(1,5-dihydroxy-4-oxo(2-hydropyridyl))methoxy]-3-azaprop-2-enoylamino]-4,4-dimethyl-2-oxoazetidinyl hydroxysulfonate) is a novel siderophore monosulfactam currently in Phase I clinical testing. BAL30072 belongs to the sulfactam class of antimicrobials and, unlike earlier members of this class (e.g. tigemonam), shows potent activity against non-fermentative Gram-negative bacilli. Similar to aztreonam, BAL30072 is stable to class B metallo-β-lactamases and acts as an inhibitor of class C enzymes. BAL30072 appears to be stable to many class A and class D carbapenemases and has demonstrated potent activity against a broad range of Gram-negative pathogenic bacteria, including multidrug-resistant *Acinetobacter baumannii*.

Meropenem is a well-established carbapenem with broad spectrum of activity against Gram-negative organisms and high rates of clinical and bacteriological response among patients with complicated skin and skin-structure infections, complicated intra-abdominal infections, pediatric bacterial meningitis, and nosocomial pneumonia, and it is well tolerated. Meropenem is very stable to ESBL and Class C enzymes, but it is hydrolyzed by “carbapenemases”, such as KPC and metallo-β-lactamases. We evaluated the activity of BAL30072, meropenem, BAL30072 plus meropenem (1:1 ratio) and various comparator agents tested against pathogens isolated from medical centers located in selected geographic regions/countries.

MATERIALS AND METHODS

Medical Centers: A total of 57 medical centers were included: 11 sites in China; 4 sites in India; 15 sites in Latin America (Argentina [2], Brazil [6], Chile [2], Colombia [1] and Mexico [4]); and 27 sites in Southeast Asia and South Africa (Australia [7], Hong Kong [1], Korea [6], Malaysia [1], New Zealand [3], Singapore [1], South Africa [1], Taiwan [4] and Thailand [3]). Strains were sent for reference susceptibility testing (>30 agents) and identification confirmation as part of a surveillance program for monitoring by a GLP/CLIA-certified laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Organism collection: All organisms were collected between 2009 and 2010 which included: Enterobacteriaceae (826; including *Escherichia coli* [308], *Klebsiella* spp. [209], *Enterobacter* spp. [108], *Salmonella* spp. [60], *Serratia marcescens* [51], *Citrobacter* spp. [31], Indole-positive *Proteus* [30], *Proteus mirabilis* [29]), *Pseudomonas aeruginosa* (662), and *Acinetobacter baumannii* (348). These were collected from serious bloodstream (60.6%), respiratory tract (20.4%), skin and skin structure (12.1%) and other miscellaneous (6.9%) infections.

Antimicrobial susceptibility tests: The 1,836 Gram-negative pathogens were tested against BAL30072 alone and in combination with meropenem (1:1 ratio) and comparator agents by the broth microdilution method as described in the CLSI M07-A9 (2012) document in frozen-format reference panels produced by JMI Laboratories. The interpretations of results were taken from those published by the CLSI (M100-S22, 2012) and EUCAST (2012). Concurrent quality control (QC) testing used ATCC strains *E. coli* 25922 and *P. aeruginosa* 27853. All QC results were within CLSI M100-S22 (2012) published ranges.

RESULTS

- BAL30072 was very active when tested against *A. baumannii* ($MIC_{50/90}$, 1/8 µg/ml; **Table 2**); with 85% of strains inhibited at ≤4 µg/ml. BAL30072/meropenem had similar activity to BAL30072 ($MIC_{50/90}$, 1/8 µg/ml; **Table 2**); while meropenem showed more limited activity against this organism (MIC_{50} and MIC_{90}, >32 µg/ml; **Tables 1** and **2**). Ciprofloxacin and amikacin were less active with greater than half the strains resistant. Colistin was the only other drug active against these strains (**Table 2**).
- BAL30072 was very active against *P. aeruginosa*, with MIC_{50} and MIC_{90} values of 1 and 4 µg/ml, respectively. BAL30072/meropenem was highly active against *P. aeruginosa*, with MIC_{50} (0.25 µg/ml) and MIC_{90} (1 µg/ml) values two- to 16-fold lower than those of meropenem ($MIC_{50/90}$, 0.5/16 µg/ml) and BAL30072 ($MIC_{50/90}$, 1/4 µg/ml) tested alone (**Tables 1** and **2**). Furthermore, BAL30072 was eight-fold more active than aztreonam ($MIC_{50/90}$, 8/32 µg/ml; **Table 2**) against these strains.
- BAL30072 inhibited 93.1% of *P. aeruginosa* isolates at ≤4 µg/ml. Meropenem inhibited 72.2% of *P. aeruginosa* strains at ≤2 µg/ml, which is the meropenem susceptible breakpoint established by CLSI and EUCAST and BAL30072/meropenem inhibited 95.2% of *P. aeruginosa* strains at ≤2 µg/ml (**Table 1**). Remarkably, 152 of 184 (82.6%) of meropenem non-susceptible *P. aeruginosa* strains exhibited BAL30072/meropenem MIC ≤2 µg/ml (data not shown).
- The most active comparator agent tested against *P. aeruginosa* was colistin (98.6% susceptible by both CLSI and EUCAST criteria), followed by amikacin (84.0/81.0% susceptible [CLSI/EUCAST criteria]), cefepime (73.3/73.3%), meropenem (72.2/72.2%), ciprofloxacin (71.8/67.4%), piperacillin/tazobactam (65.1/65.1%) and aztreonam (59.4/2.7%; **Table 2**).
- BAL30072 was active against Enterobacteriaceae species with MIC_{50} and MIC_{90} values of 0.06 and 4 µg/ml, respectively. BAL30072/meropenem (1:1 ratio) was very active with MIC_{50} and MIC_{90} values of ≤0.015 and 0.06 µg/ml, respectively. The combination BAL30072/meropenem was slightly more active than meropenem ($MIC_{50/90}$, 0.03/0.06 µg/ml) tested alone, and at least four-fold more active than BAL30072 (**Tables 1** and **2**).
- BAL30072 was active against *E. coli* with MIC_{50} and MIC_{90} values of 0.06 and 2 µg/ml, respectively. BAL30072/meropenem was the most active compound tested against *E. coli* ($MIC_{50/90}$, ≤0.015/0.03 µg/ml and MIC range, ≤0.015-0.25 µg/ml). Meropenem was also very active against these organisms ($MIC_{50/90}$, ≤0.015/0.03 µg/ml and 99.7% susceptible; **Table 2**).
- BAL30072 was active against *Klebsiella spp.* with MIC_{50} and MIC_{90} values of 0.06 and 32 µg/ml, respectively. *Klebsiella* spp. strains were very susceptible to BAL30072/meropenem with 95.2% of strains being inhibited at ≤1 µg/ml (data not shown). BAL30072/meropenem combination ($MIC_{50/90}$ of ≤0.015/0.06 µg/ml) was slightly more active than meropenem ($MIC_{50/90}$, 0.03/0.12 µg/ml; 92.8% susceptible) when tested against these organisms (**Table 2**).
- BAL30072/meropenem ($MIC_{50/90}$, 0.03/0.12 µg/ml) and meropenem ($MIC_{50/90}$, 0.03/0.25 µg/ml) were very active against *Enterobacter* spp. Overall, 106 of 108 strains (98.1%) were inhibited at ≤1 µg/ml of BAL30072/meropenem and the remaining two strains had BAL30072/meropenem MIC values of 2 (India) and 16 µg/ml (Latin America; data not shown).
- BAL30072 alone and BAL30072/meropenem were also active against *Citrobacter* spp. (MIC_{90}, 2 and 0.06 µg/ml, respectively), *P. mirabilis* (MIC_{90}, 4 and 0.03 µg/ml, respectively), indole-positive *Proteae* (MIC_{90}, 8 and 0.12 µg/ml, respectively), *S. marcescens* (MIC_{90}, 1 and 0.06 µg/ml, respectively) and *Salmonella* spp. (MIC_{90}, ≤0.015 µg/ml for both compounds; **Table 2**).
- BAL30072/meropenem MIC results for Enterobacteriaceae did not vary significantly by geographic region/nation. When tested against *P. aeruginosa*, meropenem MIC values were slightly higher in India ($MIC_{50/90}$, 1/>32 µg/ml) and Latin America ($MIC_{50/90}$, 1/32 µg/ml) compared to China ($MIC_{50/90}$, 0.5/16 µg/ml) and Southeast Asia ($MIC_{50/90}$, 0.5/16 µg/ml). Likewise, BAL30072 did show slightly increased MIC_{90} results in Enterobacteriaceae strains from India and Latin America (**Table 3**).

Table 1. BAL30072, BAL30072/meropenem and meropenem MIC distributions of the major pathogen groups (All regions combined).

Organism/antimicrobial agent (no. tested)	No. of isolates (cumulative %) inhibited at each MIC (µg/ml)												
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
A. baumannii (348)													
BAL30072	0 (0.0)	1 (0.3)	0 (0.3)	10 (3.2)	39 (14.4)	86 (39.1)	84 (63.2)	51 (77.9)	26 (85.3)	17 (90.2)	3 (91.1)	3 (92.0)	28 (100.0)
BAL30072/meropenem	1 (0.3)	2 (0.9)	4 (2.0)	37 (12.6)	51 (27.3)	74 (48.6)	76 (70.4)	42 (82.5)	18 (87.6)	17 (92.5)	6 (94.3)	6 (96.0)	14 (100.0)
Meropenem	0 (0.0)	2 (0.6)	0 (0.6)	8 (2.9)	42 (14.9)	28 (23.0)	20 (28.7)	24 (35.6)	12 (39.1)	6 (40.8)	7 (42.8)	24 (49.7)	175 (100.0)
P. aeruginosa (662)													
BAL30072	8 (1.2)	5 (2.0)	12 (3.8)	36 (9.2)	85 (22.1)	174 (48.3)	161 (72.7)	94 (86.9)	41 (93.1)	20 (96.1)	20 (99.1)	5 (99.8)	1 (100.0)
BAL30072/meropenem	9 (1.4)	12 (3.2)	83 (15.7)	161 (40.0)	178 (66.9)	107 (83.1)	51 (90.8)	29 (95.2)	13 (97.1)	13 (99.1)	4 (99.7)	2 (100.0)	0 (100.0)
Meropenem	1 (0.2)	7 (1.2)	32 (6.0)	80 (18.1)	123 (36.7)	120 (54.8)	72 (65.7)	43 (72.2)	36 (77.6)	35 (82.9)	60 (92.0)	24 (95.6)	29 (100.0)
Enterobacteriaceae (826)													
BAL30072	204 (24.7)	121 (39.3)	111 (52.8)	99 (64.8)	65 (72.6)	42 (77.7)	45 (83.2)	33 (87.2)	31 (90.9)	13 (92.5)	6 (93.2)	23 (96.0)	33 (100.0)
BAL30072/meropenem	529 (64.0)	188 (86.8)	61 (94.2)	24 (97.1)	5 (97.7)	3 (98.1)	4 (98.5)	2 (98.8)	1 (98.9)	3 (99.3)	2 (99.5)	1 (99.6)	3 (100.0)
Meropenem	218 (26.4)	390 (73.6)	151 (91.9)	33 (95.9)	4 (96.4)	4 (96.9)	4 (97.3)	2 (97.6)	1 (97.7)	2 (97.9)	2 (98.2)	1 (98.3)	14 (100.0)

Table 2. Activity of BAL30072 alone and in combination with meropenem and comparator antimicrobial agents when tested against Gram-negative organisms.

Organism/antimicrobial agent (no. tested)	MIC (µg/ml)			%S / %R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
A. baumannii (348)					
BAL30072	1	8	0.03 – >32	- / -	- / -
BAL30072/meropenem	1	8	≤0.015 – >32	- / -	- / -
Meropenem	>32	>32	0.03 – >32	39.1 / 59.2	35.6 / 59.2
Aztreonam	>32	>32	0.06 – >32	4.6 / 83.0	- / -
Cefepime	>16	>16	≤0.12 – >16	26.4 / 69.5	- / -
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	27.0 / 73.0	- / -
Ciprofloxacin	>4	>4	≤0.5 – >4	26.4 / 73.6	26.4 / 73.6
Amikacin	>32	>32	1 – >32	37.4 / 58.9	35.6 / 62.6
Tigecycline[b]	0.5	2	≤0.03 – >4	- / -	- / -
Colistin	≤0.5	1	≤0.5 – >4	99.7 / 0.3	99.7 / 0.3
P. aeruginosa (662)					
BAL30072	1	4	≤0.015 – >32	- / -	- / -
BAL30072/meropenem	0.25	1	≤0.015 – 32	- / -	- / -
Meropenem	0.5	16	≤0.015 – >32	72.2 / 22.4	72.2 / 17.1
Aztreonam	8	32	0.25 – >32	59.4 / 23.0	2.7 / 23.0
Cefepime	4	>16	0.25 – >16	73.3 / 15.0	73.3 / 26.7
Piperacillin/tazobactam	8	>64	≤0.5 – >64	65.1 / 20.5	65.1 / 34.9
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	71.8 / 26.1	67.4 / 28.2
Amikacin	4	>32	≤0.25 – >32	84.0 / 13.0	81.0 / 16.0
Tigecycline[b]	4	>4	0.25 – >4	- / -	- / -
Colistin	1	2	≤0.5 – >4	98.6 / 0.2	98.6 / 1.4
E. coli (308)					
BAL30072	0.06	2	≤0.015 – >32	- / -	- / -
BAL30072/meropenem	≤0.015	0.03	≤0.015 – 0.25	- / -	- / -
Meropenem	≤0.015	0.03	≤0.015 – >32	99.7 / 0.3	99.7 / 0.3
Aztreonam	0.12	>32	≤0.03 – >32	63.6 / 32.1	59.1 / 32.1
Cefepime	≤0.12	>16	≤0.12 – >16	72.1 / 22.1	61.7 / 33.4
Piperacillin/tazobactam	2	16	≤0.5 – >64	92.5 / 2.3	86.0 / 7.5
Ciprofloxacin	>4	>4	≤0.5 – >4	46.8 / 52.6	45.1 / 53.2
Amikacin	2	8	0.5 – >32	97.7 / 1.6	97.1 / 2.3
Tigecycline[b]	0.12	0.25	≤0.03 – 1	100.0 / 0.0	100.0 / 0.0
Colistin	≤0.5	≤0.5	≤0.5 – >4	- / -	99.7 / 0.3
Klebsiella spp.[c] (209)					
BAL30072	0.06	32	≤0.015 – >32	- / -	- / -
BAL30072/meropenem	≤0.015	0.06	≤0.015 – >32	- / -	- / -
Meropenem	0.03	0.12	≤0.015 – >32	92.8 / 6.7	93.3 / 5.7
Aztreonam	0.12	>32	≤0.03 – >32	64.1 / 34.4	60.8 / 34.4
Cefepime	≤0.12	>16	≤0.12 – >16	75.6 / 21.5	64.1 / 28.7
Piperacillin/tazobactam	4	>64	≤0.5 – >64	81.3 / 14.4	76.1 / 18.7
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	68.4 / 26.3	63.6 / 31.6
Amikacin	≤4	16	≤4 – >32	92.8 / 6.2	87.6 / 7.2
Tigecycline[b]	0.25	0.5	0.06 – 4	99.0 / 0.0	98.1 / 1.0
Colistin	≤0.5	≤0.5	≤0.5 – >4	- / -	99.5 / 0.5
Enterobacter spp.[d] (108)					
BAL30072	0.25	>32	≤0.015 – >32	- / -	- / -
BAL30072/meropenem	0.03	0.12	≤0.015 – 16	- / -	- / -
Meropenem	0.03	0.25	≤0.015 – >32	95.4 / 3.7	96.3 / 2.8
Aztreonam	4	>32	≤0.03 – >32	52.8 / 39.8	49.1 / 39.8
Cefepime	≤0.12	>16	≤0.12 – >16	78.7 / 17.6	61.1 / 25.0
Piperacillin/tazobactam	4	>64	≤0.5 – >64	70.4 / 13.0	63.9 / 29.6
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	75.9 / 23.1	75.0 / 24.1
Amikacin	1	16	0.5 – >32	92.6 / 7.4	87.0 / 7.4
Tigecycline[b]	0.25	1	≤0.03 – >4	97.2 / 0.9	96.3 / 2.8
Colistin	≤0.5	>4	≤0.5 – >4	- / -	86.9 / 13.1
Citrobacter spp.[e] (31)					
BAL30072	0.25	2	≤0.015 – 32	- / -	- / -
BAL30072/meropenem	≤0.015	0.06	≤0.015 – 0.5	- / -	- / -
Meropenem	0.03	0.12	≤0.015 – 16	96.8 / 3.2	96.8 / 3.2
Aztreonam	0.12	>32	≤0.03 – >32	64.5 / 35.5	64.5 / 35.5
Cefepime	≤0.12	>16	≤0.12 – >16	80.6 / 16.1	74.2 / 25.8
Piperacillin/tazobactam	4	>64	1 – >64	71.0 / 12.9	71.0 / 29.0
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	74.2 / 22.6	74.2 / 25.8
Amikacin	1	32	0.5 – >32	83.9 / 9.7	83.9 / 16.1
Tigecycline[b]	0.25	0.5	0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Colistin	≤0.5	1	≤0.5 – 1	- / -	100.0 / 0.0

Organism/antimicrobial agent (no. tested)	MIC (µg/ml)			%S / %R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
P. mirabilis (29)					
BAL30072	0.06	4	≤0.015 – 4	- / -	- / -
BAL30072/meropenem	≤0.015	0.03	≤0.015 – 0.03	- / -	- / -
Meropenem	0.06	0.06	0.03 – 0.12	100.0 / 0.0	100.0 / 0.0
Aztreonam	≤0.03	16	≤0.03 – 32	89.7 / 10.3	79.3 / 10.3
Cefepime	≤0.12	>16	≤0.12 – >16	69.0 / 24.1	69.0 / 31.0
Piperacillin/tazobactam	≤0.5	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	0.5	>4	≤0.03 – >4	58.6 / 31.0	55.2 / 41.4
Amikacin	2	32	1 – >32	89.7 / 3.4	86.2 / 10.3
Tigecycline[b]	1	4	0.25 – 4	89.7 / 0.0	69.0 / 10.3
Colistin	>4	>4	>4	- / -	0.0 / 100.0
Proteus spp.[f] (27)					
BAL30072	0.5	8	≤0.015 – >32	- / -	- / -
BAL30072/meropenem	0.06	0.12	≤0.015 – 0.12	- / -	- / -
Meropenem	0.06	0.12	0.03 – 0.12	100.0 / 0.0	100.0 / 0.0
Aztreonam	≤0.03	8	≤0.03 – 32	88.9 / 7.4	85.2 / 7.4
Cefepime	≤0.12	8	≤0.12 – >16	92.6 / 3.7	81.5 / 11.1
Piperacillin/tazobactam	≤0.5	4	≤0.5 – 64	96.3 / 0.0	92.6 / 3.7
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	77.8 / 22.2	74.1 / 22.2
Amikacin	1	2	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.5	2	0.12 – 2	100.0 / 0.0	88.9 / 0.0
Colistin	>4	>4	>4	- / -	0.0 / 100.0
S. marcescens (51)					
BAL30072	0.06	1	0.03 – >32	- / -	- / -
BAL30072/meropenem	0.03	0.06	≤0.015 – 0.25	- / -	- / -
Meropenem	0.06	0.06	0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
Aztreonam	0.12	32	≤0.03 – >32	88.2 / 11.8	84.3 / 11.8
Cefepime	≤0.12	2	≤0.12 – >16	90.2 / 3.9	86.3 / 9.8
Piperacillin/tazobactam	1	8	≤0.5 – >64	96.1 / 2.0	94.1 / 3.9
Ciprofloxacin	≤0.5	1	≤0.5 – >4	90.2 / 3.9	88.2 / 9.8
Amikacin	2	4	0.5 – >32	94.1 / 3.9	94.1 / 5.9
Tigecycline[b]	0.5	1	0.25 – 2	100.0 / 0.0	92.2 / 0.0
Colistin	>4	>4	1 – >4	- / -	7.8 / 92.2
Salmonella spp.[g] (60)					
BAL30072	≤0.015	0.06	≤0.015 – 1	- / -	- / -
BAL30072/meropenem	≤0.015	≤0.015	≤0.015 – 0.03	- / -	- / -
Meropenem	≤0.015	0.03	≤0.015 – 0.06	100.0 / 0.0	100.0 / 0.0
Aztreonam	0.12	0.12	≤0.03 – 16	98.3 / 1.7	98.3 / 1.7
Cefepime	≤0.12	≤0.12	≤0.12 – 16	98.3 / 0.0	96.7 / 1.7
Piperacillin/tazobactam	2	4	1 – 64	98.3 / 0.0	98.3 / 1.7
Ciprofloxacin	0.25	0.5	≤0.03 – >4	93.3 / 5.0	91.7 / 6.7
Amikacin	1	2	≤0.25 – 4	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.12	0.25	0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Colistin	≤0.5	1	≤0.5 – >4	- / -	93.3 / 6.7
Enterobacteriaceae[h] (826)					
BAL30072	0.06	4	≤0.015 – >32	- / -	- / -
BAL30072/meropenem	≤0.015	0.06	≤0.015 – >32	- / -	- / -
Meropenem	0.03	0.06	≤0.015 – >32	97.3 / 2.4	97.6 / 2.1
Aztreonam	0.12	>32	≤0.03 – >32	68.3 / 28.7	64.5 / 28.7
Cefepime	≤0.12	>16	≤0.12 – >16	77.8 / 17.8	67.7 / 26.2
Piperacillin/tazobactam	2	64	≤0.5 – >64	87.0 / 6.8	82.2 / 13.0
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	64.5 / 32.7	62.1 / 35.5
Amikacin	≤4	8	≤4 – >32	95.0 / 3.9	92.6 / 5.0
Tigecycline[b]	0.25	1	≤0.03 – >4	99.0 / 0.1	97.0 / 1.0
Colistin	≤0.5	>4	≤0.5 – >4	- / -	84.7 / 15.3

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. US FDA breakpoints were applied [Typical Product Insert, 2011].
c. Includes: *K. oxytoca* (28 strains) and *K. pneumoniae* (181 strains).
d. Includes: *E. aerogenes* (27 strains) and *E. cloacae* (81 strains).
e. Includes: *C. amalonaticus* (1 strain), *C. braakii* (1 strain), *C. freundii* (19 strains), *C. koseri* (9 strains), and Unspecified *Citrobacter* (1 strain).
f. Includes: *M. morganii* (12 strains), *P. vulgaris* (6 strains), *P. rettgeri* (4 strains), and *P. stuartii* (5 strains).
g. Includes: *S. paratyphi* (14 strains), *S. typhi* (37 strains), Group B *Salmonella* (3 strains), Group C *Salmonella* (1 strain), and unspecified *Salmonella* (5 strains).
h. Includes: *C. amalonaticus* (1 strain), *C. braakii* (1 strain), *C. freundii* (19 strains), *C. koseri* (9 strains), *E. aerogenes* (27 strains), *E. cloacae* (81 strains), *E. coli* (308 strains), *K. oxytoca* (28 strains), *K. pneumoniae* (181 strains), *M. morganii* (12 strains), *P.mirabilis* (29 strains), *P. penneri* (3 strains), *P. vulgaris* (6 strains), *P. rettgeri* (4 strains), *P. stuartii* (5 strains), *S. paratyphi* (14 strains), *S. typhi* (37 strains), *S. marcescens* (51 strains), Group B *Salmonella* (3 strains), Group C *Salmonella* (1 strain), unspecified *Citrobacter* (1 strain), and unspecified *Salmonella* (5 strains).

Table 3. BAL30072, BAL30072/meropenem (1:1) and meropenem MIC_{50} and MIC_{90} values for the major pathogen groups by geographic region.

Organism/ antimicrobial agent	MIC_{50}/MIC_{90} (no. tested)				
	China	India	Latin America	Southeast Asia	All regions
A. baumannii	(103)	(41)	(103)	(101)	(348)
BAL30072	1/>32	1/4	2/>32	1/8	1/8
BAL30072/meropenem	0.5/8	1/4	1/16	0.5/8	1/8
Meropenem	4/>32	>32/>32	32/>32	>32/>32	>32/>32
P. aeruginosa	(202)	(63)	(199)	(198)	(662)
BAL30072	0.5/4	1/4	1/4	0.5/2	1/4
BAL30072/meropenem	0.25/1	0.25/2	0.25/1	0.25/1	0.25/1
Meropenem	0.5/16	1/>32	1/32	0.5/16	0.5/16
Enterobacteriaceae	(206)	(201)	(206)	(213)	(826)
BAL30072	0.06/4	0.12/8	0.06/8	0.06/1	0.06/4
BAL30072/meropenem	≤0.015/0.06	≤0.015/0.06	≤0.015/0.06	≤0.015/0.03	≤0.015/0.06
Meropenem	0.03/0.12	0.03/0.06	0.03/0.06	0.03/0.06	0.03/0.06

CONCLUSIONS

- BAL30072 was very active against Gram-negative pathogens, including *A. baumannnii,* and when combined with meropenem was more active against Enterobacteriaceae and *P. aeruginosa* compared to either agent tested alone.
- BAL30072 and the combination of BAL30072/meropenem appear to offer a useful therapeutic alternative for treatment of infections caused by serious Gram-negative organisms sampled from China, India, Latin America and Southeast Asia.

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REFERENCES

1. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement*. Wayne, PA: CLSI.
3. European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2012.
4. Higgins PG, Stefanik D, Page MG, Hackel M, Seifert H (2012). In vitro activity of the siderophore monosulfactam BAL30072 against meropenem-non-susceptible *Acinetobacter baumannii*. *J Antimicrob Chemother* 67: 1167-1169.
5. Mohr JF, 3rd (2008). Update on the efficacy and tolerability of meropenem in the treatment of serious bacterial infections. *Clin Infect Dis* 47 Suppl 1: S41-S51.
6. Mushtaq S, Warner M, Livermore D (2010). Activity of the siderophore monobactam BAL30072 against multiresistant non-fermenters. *J Antimicrob Chemother* 65: 266-27.
7. Page MG, Dantier C, Desarbre E (2010). In vitro properties of BAL30072, a novel siderophore sulfactam with activity against multiresistant gram-negative bacilli. *Antimicrob Agents Chemother* 54: 2291-2302.
8. Russo TA, Page MG, Beanan JM, Olson R, Hujer AM, Hujer KM, Jacobs M, Bajaksouzian S, Endimiani A, Bonomo RA (2011). In vivo and in vitro activity of the siderophore monosulfactam BAL30072 against *Acinetobacter baumannii*. *J Antimicrob Chemother* 66: 867-873.