Ceftobiprole Activity when Tested against Clinical Bacterial Pathogens from Europe, Turkey and Israel 2014

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AMENDED ABSTRACT

Objectives: To evaluate the antimicrobial activity of ceftobiprole (BPR) against prevalent Gram-positive and -negative pathogens isolated in Europe (EU) during 2014. Ceftobiprole medocaril is a broad-spectrum, anti-MRSA cephalosporin with activity against Gram-negative pathogens including *Pseudomonas aeruginosa* and has recently obtained regulatory approval in EU for the treatment of hospital-acquired pneumonia (HAP, excluding ventilator-associated pneumonia) and community-acquired pneumonia (CAP) in adults.

Methods: 12,037 consecutive, non-duplicate isolates from infections were collected from 38 medical centers located in Europe, Turkey, and Israel during 2014. Species identification was confirmed by the central monitoring laboratory and all isolates were susceptibility (S) tested using reference CLSI methods. EUCAST (2015) interpretive criteria were used to determine %S.

Results: BPR had potent activity against methicillin-susceptible (MS) *Staphylococcus aureus* (SA), MS-coagulase-negative staphylococci (CoNS), beta-haemolytic streptococci, and *S. pneumoniae* (**Table**). BPR was active against methicillin-resistant (MR) SA and MR-CoNS with MIC_{90} values of 2 µg/mL and 4 µg/mL, respectively. BPR was not active against the vast majority of *E. faecium* (MIC_{50}, >16 µg/mL), but was active against *E. faecalis*. BPR was very active against *H. influenzae*, active against the majority of Enterobacteriaceae, moderately active against *P. aeruginosa*, but had limited activity against *Acinetobacter* spp. (MIC_{50}, >16 µg/mL).

Conclusions: BPR exhibited a wide spectrum of antimicrobial activity against 12,037 contemporary EU pathogens and excellent potency against most Gram-positive pathogens including MRSA and MR-CoNS. BPR exhibited high potency against *H. influenzae* and the majority of Enterobacteriaceae, but was less active against many *P. aeruginosa* and most *Acinetobacter* spp.. This data shows the potent activity of BPR against a broad range of key HAP and CAP pathogens obtained from patients in Europe, Turkey and Israel during 2014.

	MIC (µg/mL)			
Organism (no. of strains)	MIC_{50}	MIC_{90}	MIC Range	%S
S. aureus (2,040)	0.5	1	0.03 - 4	99.8
MRSA (511)	1	2	0.12 - 4	99.2
MSSA (1,529)	0.25	0.5	0.03 - 2	100.0
CoNS (464)	0.5	2	0.015 - 8	-[a]
MR-CoNS (316)	1	4	0.12 - 8	-
MS-CoNS (148)	0.25	0.5	0.015 - 1	-
E. faecalis (499)	0.5	4	0.12 - >16	-
β-haemolytic strep. (253)	0.015	0.03	≤0.008 – 0.03	-
S. pneumoniae (804)	≤0.008	0.5	≤0.008 - 4	99.0
Enterobacteriaceae (5,154)	0.03	>16	≤0.008 - >16	74.5
P. aeruginosa (1,246)	2	>16	0.25 - >16	-
H. influenzae (568)	0.03	0.06	≤0.004 – 0.5	-

INTRODUCTION

Ceftobiprole is a novel parenteral cephalosporin active against Gram-positive and -negative bacteria. Its antimicrobial activity is due to the ability to inhibit penicillin binding proteins (PBPs). Ceftobiprole has shown potent inhibition of PBPs from Gram-positive bacteria including those with decreased affinity to other β-lactams such as PBP2a in methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2X in penicillin-resistant *Streptococcus pneumoniae*. Against *Escherichia coli,* ceftobiprole has its greatest activity for PBP3 (the primary target of cephalosporins and monobactams) and PBP2. For *Pseudomonas aeruginosa* it has a similar binding profile to ceftazidime and cefepime, but also exhibits increased binding to PBP2.

Ceftobiprole is administered as the prodrug ceftobiprole medocaril which is rapidly hydrolyzed in vivo to the active form, ceftobiprole. During clinical development, ceftobiprole medocaril has been studied in hospitalized community-acquired bacterial pneumonia, hospital-acquired bacterial pneumonia, and acute bacterial skin and skin structure infections. It was approved in 2013 through the decentralized regulatory process in 12 European countries for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults.

We evaluated ceftobiprole and comparator antimicrobial agents in this study against isolates from bacterial species obtained from patients in European (as well as in Turkey and Israel) medical centers during 2014.

MATERIALS AND METHODS

Bacterial isolates: Bacterial isolates (non-duplicate; 12,037 isolates) were collected prospectively during 2014 from patients at 38 medical centers located in Europe (35 centers), Turkey, and Israel. Isolates were collected from a variety of infection types to include bloodstream, respiratory, skin and soft tissue, urinary and others. Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight mass spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions.

Antimicrobial susceptibility testing: Broth microdilution testing was performed according to Clinical and Laboratory Standards Institute (CLSI) methods in validated minimum inhibitory concentration (MIC) panels manufactured by Thermo Fisher Inc. (Cleveland, Ohio, USA) to determine the antimicrobial susceptibility of ceftobiprole and comparator agents. *S. pneumoniae* strains were tested in CA-MHB supplemented with 2.5-5% lysed horse blood and *Haemophilus influenzae* were tested in *Haemophilus* test medium (M07-A10, 2015). β-lactamase production was characterized by the nitrocefin disk test (Remel; Lenexa, Kansas, USA). The ESBL phenotype was defined as a MIC of ≥2 µg/mL for ceftazidime or ceftriaxone or aztreonam.

Quality control (QC) testing was performed concurrently to assure proper test conditions and procedures. MIC QC strains included *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619. *E. coli* ATCC 25922 and ATCC 35218, *P. aeruginosa* ATCC 27853, and *H. influenzae* ATCC 49247 and 49766. All MIC QC results were within the published CLSI ranges. Susceptibility interpretive criteria were based on the CLSI guideline (M100-S25) and EUCAST (2015).

RESULTS

- The $MIC_{50/90}$ for ceftobiprole against *S. aureus* was 0.5/1 µg/mL (**Tables 1** and **2**). All *S. aureus* MIC values were ≤4 µg/mL (99.8% susceptible). Overall, 25.0% of *S. aureus* were methicillin-resistant *S. aureus* (MRSA). The $MIC_{50/90}$ for MRSA and methicillin-susceptible *S. aureus* (MSSA) were 1/2 and 0.25/0.5 µg/mL, respectively (**Tables 1** and **2**). Greatest coverage of *S. aureus* (MSSA and MRSA) was provided by vancomycin and linezolid (both 100.0% susceptible), daptomycin (>99.9%), ceftobiprole (99.8%), trimethoprim/sulfamethoxazole (98.4%), and ceftaroline (95.7%; **Table 2**). Only 83.0% of MRSA isolates were susceptible to ceftaroline (**Table 2**).
- The $MIC_{50/90}$ for ceftobiprole against 464 isolates of coagulase-negative staphylococci (CoNS) was 0.5/2 µg/mL and all MIC values were ≤8 µg/mL (**Tables 1** and **2**). The $MIC_{50/90}$ for MR-CoNS and MS-CoNS were 1/4 and 0.25/0.5 µg/mL, respectively (**Tables 1** and **2**). Ceftaroline ($MIC_{50/90}$, 0.25/1 µg/mL) and ceftobiprole ($MIC_{50/90}$, 0.5/2 µg/mL) were the most potent β-lactam agents tested against CoNS (**Table 2**).
- Ceftobiprole demonstrated good potency against 499 isolates of *Enterococcus faecalis* ($MIC_{50/90}$, 0.5/4 µg/mL), but not against 306 isolates of *E. faecium* (MIC_{50}, >16 µg/mL; **Table 1**).
- Against *S. pneumoniae* (804 isolates), ceftobiprole (99.9% susceptible by the EUCAST-approved breakpoint of ≤0.5 µg/mL), ceftaroline (99.8/99.1% susceptible by CLSI/EUCAST breakpoints, respectively) and imipenem were the most active β-lactam agents tested (**Table 2**). For other common-use antimicrobials, penicillin resistance (105 isolates with MIC at ≥2 µg/mL, CLSI oral breakpoint) was 13.1%, erythromycin resistance 28.0%, tetracycline resistance 25.5%, and trimethoprim/sulfamethoxazole resistance 21.1% (**Table 2**). All strains were susceptible to linezolid and vancomycin. Levofloxacin resistance was noted in 0.9/1.1% (CLSI/EUCAST) of the isolates (**Table 2**).
- Ceftobiprole exhibited high potency ($MIC_{90,}$ 0.03 µg/mL) against 253 isolates of β-haemolytic streptococci and no MIC exceeded 0.06 µg/mL (**Table 1**). All isolates were susceptible to penicillin, ceftaroline, ceftriaxone, cefepime, daptomycin, linezolid and vancomycin. Levofloxacin resistance was 1.2%. Resistance to erythromycin and clindamycin were 20.6 and 13.8%, respectively (**Table 2**).
- Ceftaroline and ceftobiprole were the most active β-lactam agents tested against 117 isolates of viridans group streptococci ($MIC_{50/90}$, 0.03/0.12 µg/mL for ceftaroline, $MIC_{50/90}$, 0.06/0.5 µg/mL for ceftobiprole; **Table 1**). Penicillin and levofloxacin resistance were 7.7% (14.5% intermediate by EUCAST criteria) and 5.1%, respectively. Resistance to clindamycin and erythromycin was 18.8 and 39.3%, respectively. Linezolid and vancomycin showed the broadest coverage for this organism group (100.0% susceptible; **Table 2**).
- Ceftobiprole inhibited all isolates of *H. influenzae* at ≤0.5 µg/mL (**Table 1**). The presence of a β-lactamase enzyme in 83 isolates (14.3%) had negligible effect on the activity of the carbapenems or cephalosporins (**Table 3**). All other agents tested exhibited excellent activity against *H. influenzae* with the exception being trimethoprim-sulfamethoxazole (25.7% to 29.9% resistance; **Table 3**).
- A total of 74.5% of Enterobacteriaceae were susceptible to ceftobiprole ($MIC_{50/90}$, 0.03/>16 µg/mL; **Tables 1** and **3**). Non-ESBL Enterobacteriaceae were mostly susceptible to ceftobiprole, 99.6% for *E. coli* and 98.5% for *K. pneumoniae* (**Table 1**). Ceftobiprole demonstrated a similar susceptibility profile to that of other expanded spectrum cephalosporins (most like cefepime) against the commonly occurring Enterobacteriaceae species (**Table 3**).
- Ceftobiprole inhibited 64.5% of *P. aeruginosa* at ≤4 µg/mL, while cefepime and ceftazidime inhibited 79.1 and 72.8% of the isolates at susceptibility breakpoints, respectively (**Table 3**).
- The activity of ceftobiprole against *Acinetobacter* spp. was limited and ceftobiprole was inactive against almost all *Stenotrophomonas maltophilia* isolates (**Table 1**).

Table 1. MIC and cumulative % frequency distributions for ceftobiprole.

	Number (cumulative %) of isolates inhibited at ceftobiprole MIC (µg/mL):														
Species or group (number tested)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	MIC_{50}	MIC_{90}
Staphylococcus aureus (2040)			2 (0.1)	1 (0.1)	5 (0.4)	792 (39.2)	780 (77.5)	337 (94.0)	119 (99.8)	4 (100.0)				0.5	1
MSSA (1529)			2 (0.1)	1 (0.2)	4 (0.5)	790 (52.1)	730 (99.9)	1 (99.9)	1 (100.0)					0.25	0.5
MRSA (511)					1 (0.2)	2 (0.6)	50 (10.4)	336 (76.1)	118 (99.2)	4 (100.0)				1	2
Coag.-negative staphylococci (464)		2 (0.4)	2 (0.9)	7 (2.4)	28 (8.4)	98 (29.5)	103 (51.7)	152 (84.5)	39 (92.9)	28 (98.9)	5 (100.0)			0.5	2
MSCoNS (148)		2 (1.4)	2 (2.7)	7 (7.4)	27 (25.7)	78 (78.4)	24 (94.6)	8 (100.0)						0.25	0.5
MRCoNS (316)					1 (0.3)	20 (6.6)	79 (31.6)	144 (77.2)	39 (89.6)	28 (98.4)	5 (100.0)			1	4
Enterococcus spp. (805)					16 (2.0)	127 (17.8)	200 (42.6)	48 (48.6)	46 (54.3)	40 (59.3)	28 (62.7)	10 (64.0)	290 (100.0)	2	>16
Enterococcus faecalis (499)					16 (3.2)	127 (28.7)	199 (68.5)	45 (77.6)	37 (85.0)	37 (92.4)	25 (97.4)	10 (99.4)	3 (100.0)	0.5	4
Enterococcus faecium (306)							1 (0.3)	3 (1.3)	9 (4.2)	3 (5.2)	3 (6.2)	0 (6.2)	287 (100.0)	>16	>16
Streptococcus pneumoniae (804)	407 (50.6)	152 (69.5)	48 (75.5)	22 (78.2)	23 (81.1)	65 (89.2)	79 (99.0)	6 (99.8)	1 (99.9)	1 (100.0)				≤0.008	0.5
Viridans group streptococci (117)	18 (15.4)	17 (29.9)	19 (46.2)	15 (59.0)	20 (76.1)	15 (88.9)	2 (90.6)	4 (94.0)	5 (98.3)	0 (98.3)	1 (99.1)	1 (100.0)		0.06	0.5
Beta-haemolytic streptococci (253)	118 (46.6)	50 (66.4)	85 (100.0)	0 (100.0)										0.015	0.03
Enterobacteriaceae (5154)	26 (0.5)	640 (12.9)	2182 (55.3)	653 (67.9)	199 (71.8)	138 (74.5)	62 (75.7)	58 (76.8)	40 (77.6)	37 (78.3)	12 (78.5)	22 (78.9)	1085 (100.0)	0.03	>16
Escherichia coli (2320)	1 (0.0)	347 (15.0)	1198 (66.6)	258 (77.8)	51 (80.0)	22 (80.9)	11 (81.4)	6 (81.6)	4 (81.8)	8 (82.2)	5 (82.4)	4 (82.5)	405 (100.0)	0.03	>16
ESBL-phenotype (477)		3 (0.6)	22 (5.2)	6 (6.5)	4 (7.3)	6 (8.6)	6 (9.9)	5 (10.9)	3 (11.5)	8 (13.2)	5 (14.3)	4 (15.1)	405 (100.0)	>16	>16
non-ESBL-phenotype (1843)	1 (0.1)	344 (18.7)	1176 (82.5)	252 (96.2)	47 (98.8)	16 (99.6)	5 (99.9)	1 (99.9)	1 (100.0)					0.03	0.06
Klebsiella pneumoniae (1030)		130 (12.6)	304 (42.1)	65 (48.4)	23 (50.7)	9 (51.6)	6 (52.1)	11 (53.2)	5 (53.7)	3 (54.0)	1 (54.1)	4 (54.5)	469 (100.0)	0.12	>16
ESBL-phenotype (505)		0 (0.0)	3 (0.6)	6 (1.8)	2 (2.2)	3 (2.8)	3 (3.4)	9 (5.1)	5 (6.1)	3 (6.7)	1 (6.9)	4 (7.7)	466 (100.0)	>16	>16
non-ESBL-phenotype (525)		130 (24.8)	301 (82.1)	59 (93.3)	21 (97.3)	6 (98.5)	3 (99.0)	2 (99.4)	0 (99.4)	0 (99.4)	0 (99.4)	0 (99.4)	3 (100.0)	0.03	0.06
Klebsiella oxytoca (221)		2 (0.9)	34 (16.3)	41 (34.8)	30 (48.4)	47 (69.7)	13 (75.6)	5 (77.8)	2 (78.7)	1 (79.2)	0 (79.2)	0 (79.2)	46 (100.0)	0.25	>16
ESBL-phenotype (47)								2 (4.3)	0 (4.3)	1 (6.4)	0 (6.4)	0 (6.4)	44 (100.0)	>16	>16
non-ESBL-phenotype (174)		2 (1.1)	34 (20.7)	41 (44.3)	30 (61.5)	47 (88.5)	13 (96.0)	3 (97.7)	2 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	2 (100.0)	0.12	0.5
Enterobacter spp. (572)		25 (4.4)	251 (48.3)	103 (66.3)	30 (71.5)	17 (74.5)	11 (76.4)	15 (79.0)	24 (83.2)	16 (86.0)	2 (86.4)	4 (87.1)	74 (100.0)	0.06	>16
Citrobacter spp. (173)		20 (11.6)	113 (76.9)	13 (84.4)	3 (86.1)	5 (89.0)	4 (91.3)	8 (96.0)	1 (96.5)	1 (97.1)	0 (97.1)	1 (97.7)	4 (100.0)	0.03	0.5
Proteus mirabilis (279)		62 (22.2)	146 (74.6)	21 (82.1)	7 (84.6)	13 (89.2)	6 (91.4)	10 (95.0)	2 (95.7)	2 (96.4)	0 (96.4)	2 (97.1)	8 (100.0)	0.03	0.5
Indole-positive proteus spp. (227)	25 (11.0)	48 (32.2)	88 (70.9)	5 (73.1)	2 (74.0)	1 (74.4)	1 (74.9)	2 (75.8)	0 (75.8)	0 (75.8)	0 (75.8)	4 (77.5)	51 (100.0)	0.03	>16
Serratia spp. (260)			28 (10.8)	137 (63.5)	42 (79.6)	18 (86.5)	6 (88.8)	1 (89.2)	0 (89.2)	4 (90.8)	2 (91.5)	1 (91.9)	21 (100.0)	0.06	4
Pseudomonas aeruginosa (1246)						12 (1.0)	36 (3.9)	297 (27.7)	305 (52.2)	154 (64.5)	161 (77.4)	99 (85.4)	182 (100.0)	2	>16
Acinetobacter spp. (429)	1 (0.2)	3 (0.9)	3 (1.6)	8 (3.5)	5 (4.7)	23 (10.0)	30 (17.0)	18 (21.2)	4 (22.1)	1 (22.4)	3 (23.1)	3 (23.8)	327 (100.0)	>16	>16
Stenotrophomonas maltophilia (154)							1 (0.6)	0 (0.6)	0 (0.6)	0 (0.6)	0 (0.6)	0 (0.6)	153 (100.0)	>16	>16
Haemophilus influenzae (568)	30 (5.8)	155 (32.6)	240 (74.8)	117 (95.4)	22 (99.3)	2 (99.6)	2 (100.0)							0.03	0.06
beta-lactamase-positive (83)	5 (6.0)	37 (50.6)	29 (85.5)	10 (97.6)	2 (100.0)									0.015	0.06
beta-lactamase-negative (485)	25 (5.8)	118 (29.5)	211 (73.0)	107 (95.1)	20 (99.2)	2 (99.6)	2 (100.0)							0.03	0.06
Haemophilus parainfluenzae (3)			1 (33.3)	1 (66.7)	0 (66.7)	0 (66.7)	0 (66.7)	1 (100.0)						0.06	-

Table 2. Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-positive pathogens from Europe, Turkey and Israel (2014).

Organism group (no. tested)/	MIC (µg/mL)			%Susc. / %Resistant	
antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Staphylococcus aureus (2,040)					
Ceftobiprole	0.5	1	0.03 – 4	-/-[b]	99.8 / 0.2
Ceftaroline	0.25	1	0.03 - 4	95.7 / 0.1	95.7 / 4.3
Oxacillin	0.5	>2	≤0.25 – >2	75.0 / 25.0	75.0 / 25.0
Daptomycin	0.25	0.5	≤0.06 - 2	>99.9 / -	>99.9 / <0.1
Levofloxacin	0.25	>4	≤0.12 – >4	75.5 / 24.3	75.4 / 24.3
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.5	≤0.5	≤0.5 – >8	92.9 / 6.4	92.7 / 7.2
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 - >4	99.3 / 0.7	99.3 / 0.4
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (1,529)					
Ceftobiprole	0.25	0.5	0.03 – 2	- / -	100.0 / 0.0
Ceftaroline	0.25	0.25	0.03 - 1	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 - 1	100.0 / -	100.0 / 0.0
Levofloxacin	0.25	0.25	≤0.12 – >4	95.5 / 4.4	95.5 / 4.4
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.5	≤0.5	≤0.5 – >8	94.9 / 4.6	94.8 / 5.2
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 - >4	99.5 / 0.5	99.5 / 0.3
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (511)					
Ceftobiprole	1	2	0.12 – 4	- / -	99.2 / 0.8
Ceftaroline	1	2	0.25 – 4	83.0 / 0.6	83.0 / 17.0
Daptomycin	0.25	0.5	≤0.06 - 2	99.8 / -	99.8 / 0.2
Levofloxacin	>4	>4	≤0.12 – >4	15.7 / 83.8	15.7 / 83.8
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.5	>8	≤0.5 – >8	87.1 / 11.7	86.7 / 13.1
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 - >4	98.4 / 1.6	98.4 / 1.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
CoNS (464)[d]					
Ceftobiprole	0.5	2	0.015 – 8	- / -	- / -
Ceftaroline	0.25	1	0.03 - 4	- / -	- / -
Oxacillin	2	>2	≤0.25 – >2	31.9 / 68.1	31.9 / 68.1
Daptomycin	0.25	0.5	≤0.06 - 1	100.0 / -	100.0 / 0.0
Levofloxacin	0.5	>4	≤0.12 – >4	50.4 / 45.0	50.4 / 45.0
Linezolid	0.5	0.5	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.5	>8	≤0.5 – >8	86.2 / 11.9	81.9 / 15.3
TMP/SMX[c]	≤0.5	>4	≤0.5 - >4	70.9 / 29.1	70.9 / 14.9
Vancomycin	1	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Enterococcus spp. (805)[e]					
Ceftobiprole	2	>16	0.12 – >16	- / -	- / -
Ampicillin	1	>8	≤0.25 – >8	64.1 / 35.9	63.6 / 35.9
Ceftaroline	4	>32	0.25 - >32	- / -	- / -
Daptomycin	1	2	≤0.06 - 4	100.0 / -	- / -
Linezolid	1	1	0.25 – 8	99.8 / 0.1	- / -
Vancomycin	1	>16	0.25 – >16	89.2 / 10.3	89.2 / 10.8

Organism group (no. tested)/	MIC (µg/mL)			%Susc. / %Resistant	
antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Streptococcus pneumoniae (804)					
Ceftobiprole	≤0.008	0.5	≤0.008 – 4	- / -	99.0 / 1.0
Ceftaroline	≤0.015	0.12	≤0.015 - 1	99.8 / -	99.1 / 0.9
Ceftriaxone[f]	≤0.06	1	≤0.06 – >8	93.0 / 1.0	- / -
Clindamycin	≤0.25	>2	≤0.25 – >2	79.5 / 19.5	80.5 / 19.5
Erythromycin	≤0.12	>16	≤0.12 – >16	71.6 / 28.0	71.6 / 28.0
Imipenem	≤0.12	0.25	≤0.12 – 2	85.3 / 1.5	100.0 / 0.0
Levofloxacin	1	1	0.25 – >4	98.9 / 0.9	98.9 / 1.1
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Penicillin[g]	≤0.06	2	≤0.06 – >8	95.3 / 0.6	- / -
Penicillin[h]	≤0.06	2	≤0.06 – >8	67.3 / 13.1	67.3 / 32.7
Tetracycline	≤0.5	>8	≤0.5 – >8	73.8 / 25.5	73.8 / 25.5
TMP/SMX	≤0.5	>4	≤0.5 – >4	69.9 / 21.1	75.4 / 21.1
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Beta-hemolytic streptococci (253)[i]					
Ceftobiprole	0.015	0.03	≤0.008 – 0.03	- / -	- / -
Ceftaroline	≤0.015	≤0.015	≤0.015 – 0.03	100.0 / -	100.0 / 0.0
Penicillin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	85.4 / 13.8	86.2 / 13.8
Erythromycin	≤0.12	>16	≤0.12 – >16	79.0 / 20.6	79.0 / 20.6
Levofloxacin	0.5	1	0.25 – >4	98.8 / 1.2	96.4 / 1.2
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Tetracycline	4	>8	≤0.5 – >8	49.8 / 47.4	48.2 / 50.2
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (117)[j]					
Ceftobiprole	0.06	0.5	≤0.008 – 16	- / -	- / -
Ceftaroline	0.03	0.12	≤0.015 – 4	- / -	- / -
Penicillin	≤0.06	2	≤0.06 – >8	74.4 / 7.7	77.8 / 7.7
Clindamycin	≤0.25	>2	≤0.25 – >2	81.2 / 18.8	81.2 / 18.8
Erythromycin	≤0.12	>16	≤0.12 – >16	58.1 / 39.3	- / -
Levofloxacin	1	2	≤0.12 – >4	94.0 / 5.1	- / -
Linezolid	0.5	1	0.25 – 1	100.0 / -	- / -
Tetracycline	≤0.5	>8	≤0.5 – >8	67.5 / 30.8	- / -
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2015] and EUCAST [2015].
b. "-" = no breakpoints available.
c. TMP/SMX = Trimethoprim/sulfamethoxazole.
d. Organisms include: *Staphylococcus capitis* (29), *S. schleiferi* (one), *S. cohnii* (one), *S. caprae* (two), *S. epidermidis* (252), *S. haemolyticus* (59), *S. hominis* (43), *S. intermedius* (one), *S. lugdunensis* (30), *S. pettenkoferi* (two), *S. pseudintermedius* (one), *S. saprophyticus* (17), *S. sciuri* (one), *S. simulans* (four), *S. warneri* (19), *S. xylosus* (two).
e. Organisms include: *Enterococcus faecalis* (499), *E. faecium* (306).
f. Criteria as published by the CLSI [2015] for 'non-meningitis'.
g. Criteria as published by the CLSI [2015] for 'Penicillin parenteral (non-meningitis)'.
h. Criteria as published by the CLSI [2015] for 'Penicillin (oral penicillin V)'.
i. Organisms include: *Streptococcus pyogenes* (103), *S. agalactiae* (104), *S. dysgalactiae* (46)
j. Organisms include: *Streptococcus australis* (one), *S. canis* (one), *S. constellatus* (14), *S. gallolyticus* (five), *S. gordonii* (three), *S. lutetiensis* (one), *S. anginosus* group (one), *S. mitis* group (six), *S. mitis/oralis* (20), *S. parasanguinis* (four), *S. salivarius* group (two), *S. salivarius* (eight), *S. suis* (one), *S. anginosus* (20), *S. infantis* (one), *S. mitis* (four), *S. oralis* (19), *S. sanguinis* (six).

Table 3. Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-negative pathogens from Europe, Turkey and Israel (2014).

Organism group (no. tested)/ antimicrobial agent	MIC (µg/mL)			%Susc. / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Haemophilus influenzae (568)					
Ceftobiprole	0.03	0.06	≤0.004– 0.5	- / -	- / -
Ceftaroline	0.008	0.015	≤0.001– 0.12	100.0 / -	99.3 / 0.7
Amoxicillin/clavulanate	≤1	≤1	≤1 – 4	100.0 / 0.0	99.3 / 0.7
Ampicillin	≤0.25	8	≤0.25 – >8	84.0 / 14.3	84.0 / 16.0
Azithromycin	0.5	1	≤0.03 – 4	100.0 / -	2.8 / 0.0
Cefepime	≤0.5	≤0.5	≤0.5 - 1	100.0 / -	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.12	≤0.12	≤0.12 - >4	99.8 / -	99.6 / 0.4
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5	100.0 / 0.0	99.3 / 0.7
Tetracycline	0.5	0.5	≤0.12 – 16	99.3 / 0.5	99.3 / 0.7
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	67.6 / 25.7	67.6 / 29.9
Enterobacteriaceae[b] (5,154)					
Ceftobiprole	0.03	>16	≤0.008 – >16	- / -	74.5 / 25.5
Ceftaroline	0.25	>32	≤0.015 – >32	65.4 / 29.3	65.4 / 34.6
Ampicillin/sulbactam	16	>32	≤0.25 – >32	40.7 / 42.6	40.7 / 59.3
Cefepime	≤0.5	>16	≤0.5 – >16	81.2 / 15.2	78.7 / 17.1
Ceftazidime	0.25	32	≤0.015 – >32	80.1 / 16.6	75.4 / 19.9
Ceftriaxone	0.12	>8	≤0.06 – >8	73.1 / 25.2	73.1 / 25.2
Imipenem	≤0.12	1	≤0.12 – >8	90.7 / 3.7	96.3 / 2.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	77.0 / 20.6	75.4 / 23.0
Piperacillin/tazobactam	2	64	≤0.5 – >64	84.8 / 9.7	80.3 / 15.2
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	68.7 / 31.3	68.7 / 30.6
Pseudomonas aeruginosa (1,246)					
Ceftobiprole	2	>16	0.25 – >16	- / -	- / -
Ceftaroline	32	>32	0.25 - >32	- / -	- / -
Amikacin	2	16	≤0.25 – >32	90.9 / 5.1	85.0 / 9.1
Gentamicin	2	>8	≤1 – >8	79.9 / 16.9	79.9 /20.1
Aztreonam	8	>16	≤0.12 – >16	54.3 / 28.8	3.2 / 28.8
Cefepime	4	16	≤0.5 – >16	79.1 / 8.5	79.1 / 20.9
Ceftazidime	4	>32	0.25 – >32	72.8 / 20.4	72.8 / 27.2
Imipenem	1	>8	≤0.12 – >8	66.9 / 27.2	72.8 / 14.0
Levofloxacin	0.5	>4	≤0.12 – >4	68.6 / 25.5	60.4 / 31.4
Piperacillin/tazobactam	4	>64	≤0.5 – >64	72.8 / 14.1	72.8 / 27.2

a. Criteria as published by the CLSI [2015] and EUCAST [2015].
b. Organisms include: *Citrobacter amalonaticus* (three), *C. braakii* (15), *C. freundii* (58), *C. freundii species complex* (18), *C. koseri* (78), *C. youngae* (one), *Enterobacter aerogenes* (140), *E. amnigenus* (three), *E. asburiae* (11), *Escherichia coli* (2,320), *E. cloacae* (337), *E. cloacae species complex* (77), *E. cancerogenus* (one), *E. kobei* (two), *Cronobacter sakazakii* (one), *Hafnia alvei* (32), *Klebsiella variicola* (four), *K. oxytoca* (221), *K. pneumoniae subsp. ozaenae* (one), *K. pneumoniae* (1,030), *Leclercia adecarboxylata* (one), *Morganella morganii* (138), *Pantoea agglomerans* (one), *Proteus mirabilis* (279), *P. penneri* (six), *P. vulgaris* (47), *Providencia rettgeri* (14), *P. stuartii* (28), *Unspeciated Raoultella* (13), *Raoultella ornithinolytica* (eight), *R. planticola* (five), *Serratia fonticola* (one), *S. liquefaciens* (21), *S. marcescens* (235), *S. rubidaea* (one), *S. odorifera* (one), *S. plymuthica* (one), *Yersinia pseudotuberculosis* (one).

CONCLUSIONS

- Ceftobiprole exhibited potent in vitro activity against a broad range of Gram-positive and -negative pathogens isolated from patients in European, Turkish and Israeli hospitals during 2014.
- These in vitro results from an extensive European surveillance study evaluating 12,037 organisms, confirm a large volume of earlier reports on the broad-spectrum of activity of ceftobiprole.

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