Ceftobiprole Activity Tested against Bacterial Isolates from Hospitalized Patients with Pneumonia in European Hospitals and Israel (2013)

eP188

RK FLAMM, DJ FARRELL, JM STREIT, HS SADER, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

ECCMID 2014
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
robert-flamm@jmilabs.com

ABSTRACT

Objective: To evaluate the activity of ceftobiprole and comparator agents against pathogens isolated during 2013 from patients hospitalized with pneumonia in Europe and Israel. Ceftobiprole medocaril is a parenteral broad-spectrum, anti-MRSA cephalosporin with activity against Gram-positive and -negative pathogens including *Pseudomonas aeruginosa.* It is the first anti-MRSA cephalosporin approved for both the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults in 12 European Union countries.

Methods: Non-duplicate consecutive isolates from patients hospitalized with pneumonia were collected during 2013 from 26 medical centres in 13 European countries and Israel. Ceftobiprole, the active form of the prodrug ceftobiprole medocaril and comparator agents were susceptibility tested according to Clinical and Laboratory Standards Institute (CLSI) guidelines using validated dry-form broth microdilution panels. Quality control organisms were tested concurrently with the clinical isolates and results were within published limits. EUCAST interpretive criteria were applied according to current guidelines.

Results: The ceftobiprole $MIC_{50/90}$ values for 336 *S. aureus* were 0.5/2 mg/L, respectively. For methicillin-resistant *S. aureus* (MRSA, 28.3% of all *S. aureus*) $MIC_{50/90}$ values were 2/2 mg/L, respectively. The highest MIC value for methicillin-susceptible *S. aureus* (MSSA) was 0.5 mg/L and for MRSA it was 2 mg/L. Ceftobiprole was highly potent against all 47 *S. pneumoniae* isolates (100.0% susceptibility) with 48.9% of isolates with a ceftobiprole MIC value of ≤0.008 mg/L (highest ceftobiprole MIC, 0.5 mg/L). These included three penicillin-resistant isolates (6.4%), all with a penicillin MIC of 4 mg/L and a ceftobiprole MIC at 0.5 mg/L. These three isolates were also ceftriaxone-non-susceptible (ceftriaxone MIC, 1-2 mg/L). Ceftobiprole susceptibility for all Enterobacteriaceae was 74.6%. A total of 74.6, 76.2, and 77.8% of all Enterobacteriaceae were at a ceftobiprole MIC value of ≤0.25, 0.5, and 1 mg/L, respectively. Ceftobiprole was highly active against non-ESBL phenotype *E. coli* with $MIC_{50/90}$ values at 0.03/0.06 mg/L (99.4% susceptible). For non-ESBL-phenotype *Klebsiella* spp. the $MIC_{50/90}$ for ceftobiprole was 0.03/0.25 mg/L (96.5% susceptible). Against ESBL-positive phenotype strains of Enterobacteriaceae ceftobiprole showed higher MIC values. The activity of ceftobiprole against *P. aeruginosa* was similar to that of ceftazidime and cefepime with $MIC_{50/90}$ values of 2/>8 mg/L for ceftobiprole. The $MIC_{50/90}$ values for *P. aeruginosa* were 4/>16 mg/L for ceftazidime and cefepime (75.4 and 75.2% susceptible, respectively).

Conclusions: Ceftobiprole demonstrated potent broad-spectrum *in vitro* activity against pathogens from European and Israelian patients hospitalized with pneumonia including MRSA, penicillin-resistant/ceftriaxone-non-susceptible *S. pneumoniae*, Enterobacteriaceae and *P. aeruginosa.*

INTRODUCTION

Ceftobiprole medocaril was recently approved in Europe (Fall 2013) through the decentralized process (Basilea press release, October 23, 2013). It is indicated for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community acquired pneumonia in adults. Ceftobiprole medocaril is a prodrug that is rapidly hydrolyzed *in vivo* to the active form, ceftobiprole, which is a novel cephalosporin with broad-spectrum *in vitro* activity against pathogens causing respiratory tract infections.

The emergence of multidrug-resistant (MDR) bacteria causing respiratory tract infections is limiting the ability to use currently available therapies. This occurs for both Gram-positive and –negative organisms including multidrug-resistant *Streptococcus pneumoniae* (MDRSP), methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL and carbapenemase-producing bacteria. Ceftobiprole has potent *in vitro* activity against MDRSP and *S. aureus,* including MRSA, and also has potent activity against Enterobacteriaceae and *Pseudomonas aeruginosa* although it is not active against ESBL and carbapenemase producing Gram-negative bacteria.

We evaluated ceftobiprole and comparator antimicrobial agents in this study against isolates from bacterial species obtained from patients at medical centres in Europe and Israel during 2013.

METHODS

Isolates were consecutively collected (one isolate per infection episode) from patients with lower respiratory tract infections with an emphasis on obtaining isolates from invasive sampling (transtracheal aspirates, bronchoalveolar lavage, protected brush samples, etc.) at 26 medical centres in 13 European countries and Israel during 2013. Broth microdilution testing was performed according to Clinical and Laboratory Standards Institute (CLSI) methods in validated minimum inhibitory concentration (MIC) panels manufactured by ThermoFisher Inc., formerly TREK Diagnostics (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-A9, 2012). *Moraxella catarrhalis* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB; M45-A2). β-lactamase production was characterized by the nitrocefin disk test (Remel; Lenexa, Kansas, USA).

Quality control (QC) testing was performed using the following QC strains: *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. QC results were within published CLSI guidelines (M100-S24, M45-A2). Interpretive criteria were those of (CLSI [M100-S24] and EUCAST, 2014) except for ceftobiprole (MHRA, SmPC). Isolates with an ESBL phenotype were defined as a MIC ≥2 mg/L for one of ceftriaxone, or ceftazidime, or aztreonam [CLSI, 2014].

RESULTS

- The $MIC_{50/90}$ for ceftobiprole against all *S. aureus* was 0.5/2 mg/L; **Tables 1** and **2**). All *S. aureus* MIC values were ≤2 mg/L (100.0% susceptible. A total of 28.3% of *S. aureus* were MRSA. The $MIC_{50/90}$ for MRSA and methicillin-susceptible *S. aureus* (MSSA) were 2/2 and 0.25/0.5 mg/L, respectively (**Tables 1** and **2**).The highest MIC for MSSA was 0.5 mg/L.
- For *S. pneumoniae*, the ceftobiprole MIC range was ≤0.008-0.5 mg/L (**Tables 1** and **2**). All isolates of *S. pneumoniae* were susceptible to ceftobiprole ($MIC_{50/90}$ was 0.015/0.5 mg/L; **Tables 1** and **2**). Erythromycin resistance was 29.8% and penicillin resistance (Pen-R; MIC ≥2 mg/L)17.0%. Ceftobiprole was two-fold more active than ceftriaxone ($MIC_{50/90}$, ≤0.06/1 mg/L; **Table 2**) and cefepime ($MIC_{50/90}$, ≤0.5/1 mg/L; **Table 2**). MIC values for ceftobiprole ranged from 0.25-0.5 mg/L against penicillin-resistant (Pen-R; MIC ≥2 mg/L) isolates (**Table 2**). A total of 25.0% of penicillin-resistant and 4.3% of all *S. pneumoniae* strains were non-susceptible to ceftriaxone (CRO-non-S; CLSI interpretive criteria). All penicillin-resistant *S. pneumoniae* and 23.4% of all *S. pneumoniae* were CRO-non-S by EUCAST criteria (**Table 2**). The $MIC_{50/90}$ for ceftobiprole against CRO-non-S *S. pneumoniae* isolates (MIC ≥1 mg/L; EUCAST interpretive criteria) was 0.25 and 0.5 mg/L, respectively (**Table 2**).
- A total of 16.7% of *H. influenzae* were β-lactamase positive. Ceftobiprole was active against both β-lactamase-positive and –negative *H. influenzae* strains with an overall ceftobiprole $MIC_{50/90}$ of 0.06/0.25 mg/L (**Table 1**). Trimethoprim/sulfamethoxazole, ampicillin, and clarithromycin susceptibilities were all less than 90% (**Table 3**).
- A total of 74.7% of Enterobacteriaceae were susceptible to ceftobiprole (ceftobiprole $MIC_{50/90}$, 0.06/>8 mg/L (**Tables 1** and **3**). Ceftobiprole was highly active against non-ESBL phenotype strains of *E. coli* and *Klebsiella* spp. with $MIC_{50/90}$ 0.03/0.06 and 0.03/0.025 mg/L, respectively (**Tables 1** and **3**). A total of 99.4% of non-ESBL phenotype *E. coli* and 96.5% of non-ESBL-phenotype *Klebsiella* spp. were susceptible to ceftobiprole. Ceftobiprole was not active against ESBL-phenotype *E. coli* and ESBL-phenotype *Klebsiella* spp. (ceftobiprole $MIC_{50/90}$ against both was >8/>8 mg/L, respectively; **Table 1**). Susceptibility to levofloxacin for all *E. coli* was at 63.8/62.9% (CLSI/EUCAST criteria, respectively; **Table 3**). For all *Klebsiella* spp., levofloxacin susceptibility was 74.9/72.2% (**Table 3**).
- Ceftobiprole ($MIC_{50/90}$, 2/>8 mg/L; 66.1% at ≤4 mg/L [non-species specific breakpoint] activity against *P. aeruginosa* was similar to cefepime ($MIC_{50/90}$, 4/>16 mg/L; 75.2% susceptible) and ceftazidime ($MIC_{50/90}$, 4/>32 mg/L; 75.4% susceptible; **Tables 1** and **3**). Amikacin was the most active agent tested (90.2/86.1% susceptible; CLSI/EUCAST interpretive criteria, respectively; **Table 3**). Levofloxacin and meropenem susceptibility (CLSI/EUCAST criteria) for *P. aeruginosa* were at 66.4/58.3% and 64.6/64.6%; respectively (**Table 3**).

CONCLUSIONS

Ceftobiprole exhibited potent *in vitro* activity against a broad range of Gram-positive and -negative pathogens isolated from European and Israeli patients hospitalized with pneumonia during 2013. All *S. pneumoniae* (including isolates that were not susceptible to ceftriaxone nor penicillin) and *S. aureus* (including MRSA) were susceptible to ceftobiprole. Ceftobiprole also exhibited potent activity against Gram-negative bacteria including *H. influenzae*, non-ESBL-phenotype *E. coli* and *K. pneumoniae*. Additionally against *P. aeruginosa,* ceftobiprole showed similar activity to cefepime and ceftazidime. The spectrum of activity of ceftobiprole supports the role in the treatment of pulmonary infections caused by these organisms.

REFERENCES

1. Bush K, Heep M, Macielag MJ, Noel GJ (2007). Anti-MRSA β-lactams in development, with a focus on ceftobiprole: The first anti-MRSA β-lactam to demonstrate clinical efficacy. *Expert Opin Invest Drugs* 16: 419-429.
2. 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.
3. Clinical and Laboratory Standards Institute (2014). *M100-S24. Performance standards for antimicrobial susceptibility testing: 24th informational supplement*. Wayne, PA: CLSI.
4. European Committee on Antimicrobial Susceptibility Testing (2014). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, January 2014. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2014.
5. Hebeisen P, Heinze-Krauss I, Angehrn P, Hohl P, Page MG, Then RL (2001). In vitro and in vivo properties of Ro 63-9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. *Antimicrob Agents Chemother* 45: 825-836.
6. Jones RN (2010). Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis* 51 Suppl 1: S81-S87.
7. Rossolini GM, Dryden MS, Kozlov RS, Quintana A, Flamm RK, Lauffer JM, Lee E, Morrissey I, Group CS (2011). Comparative activity of ceftobiprole against Gram-positive and Gram-negative isolates from Europe and the Middle East: the CLASS study. *J Antimicrob Chemother* 66: 151-159.
8. Zevtera®. 2013. Summary of Product Characteristics. Available at http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1388122812881.pdf.

ACKNOWLEDGMENT

This study was supported by Basilea Pharmaceutica International Ltd.

Table 1. Summary of ceftobiprole activity tested against pathogens from patients hospitalized with bacterial pneumonia in Europe and Israel (2013).

Organism (no. tested)	No. of organisms (cumulative %) inhibited at ceftobiprole MIC (mg/L) of:												
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	≥8	MIC_{50}	MIC_{90}
Staphylococcus aureus (336)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	123 (36.9)	127 (74.7)	37 (85.7)	48 (100.0)	--	--	0.5	2
MSSA (241)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	123 (51.5)	117 (100.0)	--	--	--	--	0.25	0.5
MRSA (95)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (10.5)	37 (49.5)	48 (100.0)	--	--	2	2
Streptococcus pneumoniae (47)	23 (48.9)	10 (70.2)	1 (72.3)	0 (72.3)	0 (72.3)	8 (89.4)	5 (100.0)	--	--	--	--	0.015	0.5
Pen[a]-S (MIC, ≤0.06 mg/L; 32)	23 (71.9)	8 (96.9)	1 (100.0)	--	--	--	--	--	--	--	--	0.008	0.015
Pen[a]-I (MIC, 0.12 – 1 mg/L; 7)	0 (0.0)	2 (28.6)	0 (28.6)	0 (28.6)	0 (28.6)	5 (100.0)	--	--	--	--	--	0.25	--
Pen[a]-R (MIC,≥2 mg/L; 8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	5 (100.0)	--	--	--	--	0.5	--
CRO[b]-non-S (MIC, ≥1 mg/L; 11)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (54.5)	5 (100.0)	--	--	--	--	0.25	0.5
CRO[a]-non-S (MIC, ≥2 mg/L; 2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	--	--	--	--	0.5	--
Haemophilus influenzae (54)	0 (0.0)	0 (0.0)	21 (38.9)	18 (72.2)	8 (87.0)	6 (98.1)	1 (100.0)	--	--	--	--	0.06	0.25
β-lactamase-positive (9)	0 (0.0)	0 (0.0)	6 (66.7)	2 (88.9)	1 (100.0)	--	--	--	--	--	--	0.03	--
β-lactamase-negative (45)	0 (0.0)	0 (0.0)	15 (33.3)	16 (68.9)	7 (84.4)	6 (97.8)	1 (100.0)	--	--	--	--	0.06	0.25
Enterobacteriaceae (743)	1 (0.1)	72 (9.8)	265 (45.5)	148 (65.4)	42 (71.1)	27 (74.7)	12 (76.3)	12 (77.9)	8 (79.0)	10 (80.3)	146 (100.0)	0.06	>8
Escherichia coli (221)	0 (0.0)	21 (9.5)	102 (55.7)	40 (73.8)	10 (78.3)	5 (80.5)	2 (81.4)	0 (81.4)	1 (81.9)	1 (82.4)	39 (100.0)	0.03	>8
ESBL-phenotype[c] (46)	0 (0.0)	0 (0.0)	1 (2.2)	0 (2.2)	2 (6.5)	1 (8.7)	1 (10.9)	0 (10.9)	1 (13.0)	1 (15.2)	39 (100.0)	>8	>8
non-ESBL-phenotype (175)	0 (0.0)	21 (12.0)	101 (69.7)	40 (92.6)	8 (97.1)	4 (99.4)	1 (100.0)	--	--	--	--	0.03	0.06
Klebsiella spp. (224)	0 (0.0)	24 (10.7)	72 (42.9)	20 (51.8)	8 (55.4)	14 (61.6)	3 (62.9)	7 (66.1)	3 (67.4)	1 (67.9)	72 (100.0)	0.06	>8
ESBL-phenotype[c] (83)	0 (0.0)	0 (0.0)	1 (1.2)	1 (2.4)	0 (2.4)	0 (2.4)	0 (2.4)	6 (9.6)	3 (13.3)	1 (14.5)	71 (100.0)	>8	>8
non-ESBL-phenotype (141)	0 (0.0)	24 (17.0)	71 (67.4)	19 (80.9)	8 (86.5)	14 (96.5)	3 (98.6)	1 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)	0.03	0.25
Klebsiella pneumoniae (172)	0 (0.0)	23 (13.4)	62 (49.4)	10 (55.2)	3 (57.0)	5 (59.9)	0 (59.9)	5 (62.8)	3 (64.5)	1 (65.1)	60 (100.0)	0.06	>8
ESBL-phenotype[c] (71)	0 (0.0)	0 (0.0)	1 (1.4)	1 (2.8)	0 (2.8)	0 (2.8)	0 (2.8)	5 (9.9)	3 (14.1)	1 (15.5)	60 (100.0)	>8	>8
non-ESBL-phenotype (101)	0 (0.0)	23 (22.8)	61 (83.2)	9 (92.1)	3 (95.0)	5 (100.0)	--	--	--	--	--	0.03	0.06
Enterobacter spp. (151)	0 (0.0)	15 (9.9)	54 (45.7)	35 (68.9)	10 (75.5)	1 (76.2)	3 (78.1)	1 (78.8)	4 (81.5)	7 (86.1)	21 (100.0)	0.06	>8
Citrobacter spp. (23)	0 (0.0)	0 (0.0)	11 (47.8)	5 (69.6)	0 (69.6)	1 (73.9)	3 (87.0)	1 (91.3)	0 (91.3)	0 (91.3)	2 (100.0)	0.06	1
Proteus mirabilis (24)	0 (0.0)	9 (37.5)	12 (87.5)	3 (100.0)	--	--	--	--	--	--	--	0.03	0.06
Pseudomonas aeruginosa (419)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	12 (3.1)	116 (30.8)	89 (52.0)	59 (66.1)	142 (100.0)	2	>8

a. Penicillin.
b. Ceftriaxone.
c. ESBL phenotype defined as a MIC ≥2 mg/L for ceftriaxone or ceftazidime or aztreonam [CLSI, 2014].

Table 2. Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-positive pathogens from patients hospitalized with pneumonia in Europe and Israel (2013).

Organism group (no. tested)/ antimicrobial agent	MIC (mg/L)			%Susc. / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Staphylococcus aureus (336)					
Ceftobiprole	0.5	2	0.12 – 2	-/-	100.0 / 0.0
Oxacillin	0.5	>2	≤0.25 – >2	71.7 / 28.3	71.7 / 28.3
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	0.25	>4	≤0.12 – >4	71.1 / 28.6	71.1 / 28.6
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.12	0.25	0.06 – >32	94.0 / 5.1	93.8 / 6.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (241)					
Ceftobiprole	0.25	0.5	0.12 – 0.5	- / -	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.12	0.25	≤0.12 – >4	97.5 / 2.5	97.5 / 2.5
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.12	0.25	0.06 – >32	94.6 / 4.6	94.6 / 5.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (95)					
Ceftobiprole	2	2	0.5 – 2	- / -	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	>4	>4	≤0.12 – >4	4.2 / 94.7	4.2 / 94.7
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.25	1	0.06 – >32	92.6 / 6.3	91.6 / 8.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Vancomycin	0.5	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Streptococcus pneumoniae (47)					
Ceftobiprole	0.015	0.5	0.008 – 0.5	- / -	100.0 / 0.0
Cefepime	≤0.5	1	≤0.5 – 2	93.6 / 0.0	93.6 / 0.0
Ceftriaxone	≤0.06	1	≤0.06 – 2	95.7 / 0.0	76.6 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	83.0 / 17.0	83.0 / 17.0
Erythromycin	≤0.12	>16	≤0.12 – >16	70.2 / 29.8	70.2 / 29.8
Imipenem	≤0.12	0.25	≤0.12 – 0.5	87.2 / 0.0	100.0 / 0.0
Levofloxacin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	0.25 – 1	100.0 / -	100.0 / 0.0
Penicillin[b]	≤0.06	2	≤0.06 – 4	93.6 / 0.0	- / -
Penicillin[c]	≤0.06	2	≤0.06 – 4	68.1 / 17.0	68.1 / 6.4
Tetracycline	0.25	32	0.12 – >32	78.7 / 21.3	78.7 / 21.3
Trimethoprim/sulfamethoxazole	≤0.5	4	≤0.5 – >4	76.6 / 10.6	87.2 / 10.6
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-resistant (MIC ≥2 mg/L, 8)					
Ceftobiprole	0.5	-	0.25 – 0.5	- / -	100.0 / 0.0
Cefepime	1	-	≤0.5 – 2	75.0 / 0.0	75.0 / 0.0
Ceftriaxone	1	-	1 – 2	75.0 / 0.0	0.0 / 0.0
Clindamycin	≤0.25	-	≤0.25 – >2	50.0 / 50.0	50.0 / 50.0
Erythromycin	>16	-	≤0.12 – >16	25.0 / 75.0	25.0 / 75.0
Imipenem	0.25	-	≤0.12 – 0.5	37.5 / 0.0	100.0 / 0.0
Levofloxacin	1	-	0.5 – 1	100.0 / 0.0	100.0 / 0.0
Linezolid	1	-	0.5 – 1	100.0 / -	100.0 / 0.0
Penicillin[b]	2	-	2 – 4	62.5 / 0.0	- / -
Penicillin[c]	2	-	2 – 4	0.0 / 100.0	0.0 / 37.5
Tetracycline	32	-	0.25 – >32	25.0 / 75.0	25.0 / 75.0
Trimethoprim/sulfamethoxazole	1	-	≤0.5 – >4	25.0 / 25.0	62.5 / 25.0
Vancomycin	0.25	-	0.25 – 0.5	100.0 / -	100.0 / 0.0
Ceftriaxone-non-susceptible (MIC ≥1 mg/L, 11)					
Ceftobiprole	0.25	0.5	0.25 – 0.5	- / -	100.0 / 0.0
Cefepime	1	2	≤0.5 – 2	72.7 / 0.0	72.7 / 0.0
Ceftriaxone	1	2	1 – 2	81.8 / 0.0	0.0 / 0.0
Clindamycin	2	>2	≤0.25 – >2	45.5 / 54.5	45.5 / 54.5
Erythromycin	>16	>16	≤0.12 – >16	18.2 / 81.8	18.2 / 81.8
Imipenem	0.25	0.5	≤0.12 – 0.5	45.5 / 0.0	100.0 / 0.0
Levofloxacin	1	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Penicillin[b]	2	4	0.5 – 4	72.7 / 0.0	- / -
Penicillin[c]	2	4	0.5 – 4	0.0 / 72.7	0.0 / 27.3
Tetracycline	32	>32	0.25 – >32	27.3 / 72.7	27.3 / 72.7
Trimethoprim/sulfamethoxazole	1	>4	≤0.5 – >4	36.4 / 18.2	72.7 / 18.2
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2014] and EUCAST [2014].
b. Criteria as published by the CLSI [2014] for 'Penicillin parenteral (non-meningitis)'.
c. Criteria as published by the CLSI [2014] for 'Penicillin (oral penicillin V)'.

Table 3. Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-negative pathogens from patients hospitalized with pneumonia in Europe and Israel (2013).

Organism group (no. tested)/antimicrobial agent	MIC (mg/L)			%Susc. / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Haemophilus influenzae (54)					
Ceftobiprole	0.06	0.25	0.03 – 0.5	- / -	- / -
Amoxicillin/clavulanate	≤1	2	≤1 – 4	100.0 / 0.0	98.1 / 1.9
Ampicillin	0.5	>8	≤0.25 – >8	79.6 / 16.7	79.6 / 20.4
Azithromycin	1	2	0.25 – >4	98.1 / -	0.0 / 1.9
Cefepime	≤0.5	≤0.5	≤0.5	100.0 / -	0.0 / 100.0
Ceftriaxone	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Clarithromycin	8	16	2 – >16	87.0 / 1.9	0.0 / 1.9
Imipenem	0.5	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5	100.0 / 0.0	- / -
Tetracycline	0.5	0.5	0.25 – 8	98.1 / 1.9	98.1 / 1.9
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	63.0 / 27.8	63.0 / 35.2
Enterobacteriaceae[b] (743)					
Ceftobiprole	0.06	>8	0.008 – >8	- / -	74.7 / 25.3
Ampicillin/sulbactam	32	>32	≤0.25 – >32	34.5 / 51.8	34.5 / 65.5
Cefepime	≤0.5	>16	≤0.5 – >16	87.3 / 11.3	80.9 / 15.1
Ceftazidime	0.25	>32	0.03 – >32	78.1 / 20.1	74.3 / 21.9
Ceftriaxone	0.12	>8	≤0.06 – >8	73.5 / 24.8	73.5 / 24.8
Imipenem	≤0.12	1	≤0.12 – >8	91.7 / 5.0	95.0 / 2.6
Levofloxacin	≤0.12	>4	≤0.12 – >4	78.8 / 18.3	76.8 / 21.2
Meropenem	≤0.06	≤0.06	≤0.06 – >8	96.1 / 3.9	96.1 / 2.3
Piperacillin/tazobactam	4	>64	≤0.5 – >64	78.0 / 14.1	73.5 / 22.0
Tetracycline	2	>32	0.25 – >32	65.6 / 29.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	75.6 / 24.4	75.6 / 24.0
E. coli (221)					
Ceftobiprole	0.03	>8	0.015 – >8	- / -	80.5 / 19.5
Ampicillin/sulbactam	32	>32	1 – >32	29.9 / 52.5	29.9 / 70.1
Cefepime	≤0.5	>16	≤0.5 – >16	87.8 / 10.9	81.9 / 14.5
Ceftazidime	0.25	16	0.06 – >32	84.2 / 13.6	80.1 / 15.8
Ceftriaxone	≤0.06	>8	≤0.06 – >8	79.6 / 19.9	79.6 / 19.9
Imipenem	≤0.12	≤0.12	≤0.12 – 2	99.5 / 0.0	100.0 / 0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	63.8 / 33.5	62.9 / 36.2
Meropenem	≤0.06	≤0.06	≤0.06 – 1	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	64	≤0.5 – >64	86.4 / 9.5	80.0 / 13.6
Tetracycline	2	>32	0.5 – >32	63.6 / 36.4	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	64.7 / 35.3	64.7 / 34.8
Non-ESBL *E. coli*[c] (175)					
Ceftobiprole	0.03	0.06	0.015 – 0.5	- / -	99.4 /0.6
Ampicillin/sulbactam	16	>32	1 – >32	36.6 / 43.4	36.6 / 63.4
Cefepime	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	98.9 / 0.0
Ceftazidime	0.12	0.5	0.06 – 1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	77.1 / 20.0	76.0 / 22.9
Meropenem	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	≤0.5 – >64	91.4 / 6.3	87.9 / 8.6
Tetracycline	2	>32	0.5 – >32	70.3 / 29.7	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	69.1 / 30.9	69.1 / 30.3
Klebsiella spp. (224)					
Ceftobiprole	0.06	>8	0.015 – >8	- / -	61.6 /38.4
Ampicillin/sulbactam	16	>32	≤0.25 – >32	49.8 / 43.0	49.8 / 50.2
Cefepime	≤0.5	>16	≤0.5 – >16	75.4 / 22.8	69.6 / 26.8
Ceftazidime	0.25	>32	0.03 – >32	69.6 / 27.2	67.0 / 30.4
Ceftriaxone	0.12	>8	≤0.06 – >8	67.4 / 31.3	67.4 / 31.3
Imipenem	≤0.12	4	≤0.12 – >8	86.0 / 11.3	88.7 / 7.7
Levofloxacin	≤0.12	>4	≤0.12 – >4	74.9 / 21.1	72.2 / 25.1
Meropenem	≤0.06	4	≤0.06 – >8	88.2 / 11.8	88.2 / 6.8
Piperacillin/tazobactam	4	>64	≤0.5 – >64	65.8 / 26.6	62.6 / 34.2
Tetracycline	2	>32	0.25 – >32	73.1 / 22.4	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	68.0 / 32.0	68.0 / 32.0
Non-ESBL *Klebsiella* spp.[c] (141)					
Ceftobiprole	0.03	0.25	0.015 – >8	- / -	96.5 /3.5
Ampicillin	>8	>8	2 – >8	4.3 / 95.7	4.30 / 95.7
Ampicillin/sulbactam	4	32	1 – >32	78.6 / 11.4	78.60 / 21.4
Cefepime	≤0.5	≤0.5	≤0.5 – 8	100.0 / 0.0	99.3 / 0.7
Ceftazidime	0.12	0.25	0.03 – 1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Imipenem	≤0.12	0.25	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.12	0.25	≤0.12 – >4	94.3 / 3.6	94.3 / 5.7
Meropenem	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	4	8	≤0.5 – >64	94.2 / 2.9	92.1 / 5.8
Tetracycline	1	8	0.25 – >32	88.6 / 10.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 – >4	90.6 / 9.4	90.6 / 9.4
Enterobacter spp. (151)					
Ceftobiprole	0.06	>8	0.015 – >8	- / -	76.2 / 23.8
Ampicillin/sulbactam	32	>32	4 – >32	20.8 / 60.4	20.8 / 79.2
Cefepime	≤0.5	4	≤0.5 – >16	95.4 / 3.3	82.1 / 9.3
Ceftazidime	0.25	>32	0.03 – >32	66.9 / 31.8	64.2 / 33.1
Ceftriaxone	0.25	>8	≤0.06 – >8	63.3 / 36.7	63.3 / 36.7
Imipenem	0.25	1	≤0.12 – >8	97.3 / 2.0	98.0 / 0.7
Levofloxacin	≤0.12	1	≤0.12 – >4	93.4 / 3.3	90.1 / 6.6
Meropenem	≤0.06	≤0.06	≤0.06 – >8	98.7 / 1.3	98.7 / 0.7
Piperacillin/tazobactam	4	>64	≤0.5 – >64	71.3 / 12.0	66.7 / 28.7
Tetracycline	2	8	0.5 – >32	88.7 / 7.3	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	86.8 / 13.2	86.8 / 13.2
Citrobacter spp. (23)					
Ceftobiprole	0.06	1	0.03 – >8	- / -	73.9 / 26.1
Ampicillin/sulbactam	2	>32	2 – >32	63.6 / 31.8	63.6 / 36.4
Cefepime	≤0.5	1	≤0.5 – >16	91.3 / 8.7	91.3 / 8.7
Ceftazidime	0.25	>32	0.06 – >32	73.9 / 26.1	69.6 / 26.1
Ceftriaxone	0.25	>8	≤0.06 – >8	73.9 / 26.1	73.9 / 26.1
Imipenem	0.25	1	≤0.12 – >8	95.7 / 4.3	95.7 / 4.3
Levofloxacin	≤0.12	0.25	≤0.12 – >4	91.3 / 8.7	91.3 / 8.7
Meropenem	≤0.06	≤0.06	≤0.06 – >8	95.7 / 4.3	95.7 / 4.3
Piperacillin/tazobactam	2	64	2 – >64	77.3 / 9.1	72.7 / 22.7
Tetracycline	1	>32	1 – >32	82.6 / 13.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	95.0 / 4.3	95.7 / 4.3
Proteus mirabilis (24)					
Ceftobiprole	0.03	0.06	0.015 – 0.06	- / -	100.0 /0.0
Ampicillin/sulbactam	1	>32	0.5 – >32	66.7 / 29.2	66.7 / 33.3
Cefepime	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Ceftazidime	0.06	0.06	0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Imipenem	2	4	≤0.12 – 8	41.7 / 20.8	79.2 / 0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	87.5 / 12.5	79.2 / 12.5
Meropenem	≤0.06	0.12	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	1	≤0.5 – 8	100.00 / 0.0	100.0 / 0.0
Tetracycline	32	>32	32 – >32	0.0 / 100.0	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	70.8 / 29.2	70.8 / 20.8
Pseudomonas aeruginosa (419)					
Ceftobiprole	2	>8	0.25 – >8	- / -	- / -
Amikacin	2	16	≤0.25 – >32	90.2 / 6.7	86.1 / 9.8
Aztreonam	8	>16	≤0.12 – >16	62.3 / 22.7	2.9 / 22.7
Cefepime	4	>16	≤0.5 – >16	75.2 / 11.9	75.2 / 24.8
Ceftazidime	4	>32	0.12 – >32	75.4 / 20.3	75.4 / 24.6
Imipenem	1	>8	≤0.12 – >8	63.2 / 32.9	67.1 / 17.9
Levofloxacin	0.5	>4	≤0.12 – >4	66.4 / 28.3	58.3 / 33.6
Meropenem	0.5	>8	≤0.06 – >8	64.6 / 25.4	64.6 / 12.4
Piperacillin/tazobactam	8	>64	≤0.5 – >64	66.3 / 21.0	66.3 / 33.7
Tobramycin	0.5	>16	≤0.12 – >16	84.9 / 13.9	84.9 / 15.1

a. Criteria as published by the CLSI [2014] and EUCAST [2014].
b. Includes: *Citrobacter braakii* (1 strain), *Citrobacter freundii* (7 strains), *Citrobacter freundii* species complex (3 strains), *Citrobacter koseri* (12 strains), *Enterobacter aerogenes* (43 strains), *Enterobacter amnigenus* (2 strains), *Enterobacter asburiae* (3 strains), *Enterobacter cloacae* (81 strains), *Enterobacter cloacae* species complex (20 strains), *Enterobacter gergoviae* (1 strain), *Enterobacter kobei* (1 strain), *Escherichia coli* (221 strains), *Hafnia alvei* (8 strains), *Klebsiella oxytoca* (50 strains), *Klebsiella pneumoniae subsp. ozaenae* (1 strain), *Klebsiella pneumoniae* (172 strains), *Klebsiella variicola* (1 strain), *Morganella morganii* (7 strains), *Pantoea agglomerans* (2 strains), *Proteus mirabilis* (24 strains), *Proteus vulgaris* (6 strains), *Providencia stuartii* (4 strains), *Raoultella planticola* (2 strains), *Serratia liquefaciens* (3 strains), *Serratia marcescens* (67 strains), and unspeciated *Raoultella* (1 strain).
c. ESBL phenotype defined as a MIC ≥2 mg/L for ceftriaxone or ceftazidime or aztreonam [CLSI, 2014].