MICROBE 2016

Sunday-457

Boston, MA

June 16 - 20

In vitro Activity of Delafloxacin When Tested Against Contemporary Bacterial Pathogens from the USA (2014)

RK FLAMM, DJ FARRELL, HS SADER, PR RHOMBERG, RN JONES

JMI Laboratories, North Liberty, Iowa, USA

Robert K. Flamm, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Email: robert-flamm@jmilabs.com

Abstract

Background: DLX is an anionic fluoroquinolone in clinical development (oral and intravenous routes) for the treatment of acute bacterial skin and skin structure infections and community acquired bacterial pneumonia. In this study, DLX was tested against clinical isolates collected in USA medical centers as part of the 2014 SENTRY Antimicrobial Surveillance Program.

Methods: A total of 4,410 USA clinical isolates were tested for susceptibility (S) to DLX and comparators by reference broth microdilution.

Results: DLX was the most potent ($MIC_{50/90}$, ≤0.004/0.03 µg/mL) agent tested against methicillin-susceptible *Staphylococcus aureus* (MSSA) and based on MIC_{90} was eight- and 128-fold more potent than ceftaroline (CPT) and levofloxacin (LEV). Tigecycline ($MIC_{50/90}$, 0.06/0.06 µg/mL), DLX ($MIC_{50/90}$, 0.06/0.5 µg/mL), trimethoprim-sulfamethoxazole (SXT, $MIC_{50/90}$, ≤0.5/≤0.5 µg/mL), and daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) were the most potent agents tested against MRSA. MRSA exhibited high levels of resistance (R) against LEV (68.4%) and erythromycin (82.9%). DLX ($MIC_{50/90}$, 0.06/1 µg/mL), linezolid ($MIC_{50/90}$, 1/1 µg/mL) and SXT ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL) were the most active agents against *Enterococcus faecalis.* Against *S. pneumoniae* ($MIC_{50/90}$, 0.008/0.015 µg/mL), DLX was eight-fold more active than CPT ($MIC_{50/90}$, ≤0.015/0.12 µg/mL; 99.7% S), 16-fold more active than moxifloxacin ($MIC_{50/90}$, ≤0.12/0.25 µg/mL; 98.3% S), and 64-fold more active than LEV ($MIC_{50/90}$, 1/1 µg/mL; 98.3% S). All DLX MIC values for *S. pyogenes* were ≤0.015 µg/mL and for *S. dysgalactiae* ≤0.03 µg/mL. For *S. agalactiae*, 98.0% of isolates were ≤0.03 µg/mL; the highest MIC was only 0.5 µg/mL. Against Enterobacteriaceae, the DLX $MIC_{50/90}$ was 0.06/2 µg/mL with 82.3% of isolates at ≤1 µg/mL. Ciprofloxacin (CIP) and LEV S were 82.8 and 84.3%, respectively. DLX inhibited 75.0% of *P. aeruginosa* at ≤1 µg/mL; CIP and LEV exhibited S at 76.0 and 75.0%, respectively. DLX inhibited 59.0% of *Acinetobacter* spp. at ≤1 µg/mL. CIP S and LEV S were poor (48.0 and 50.0%, respectively).

Conclusions: DLX offers advantages in potency and spectrum *in vitro* when compared to currently marketed fluoroquinolone agents, especially with its enhanced activity against *S. aureus* including methicillin-resistant strains, and improved potency against *S. pneumoniae* and β-hemolytic streptococci.

Introduction

Delafloxacin, an anionic investigational fluoroquinolone antimicrobial agent is currently in phase III development for the treatment of acute bacterial skin and skin structure infections (ABSSSI). It is active against a broad range of Gram-positive and -negative bacteria including anaerobes and atypical bacteria (Chlamydia and Mycoplasma). The *in vitro* spectrum of activity for delafloxacin includes pathogens which are found in ABSSSI including fluoroquinolone-resistant staphylococci (methicillin-resistant *S. aureus* [MRSA] and methicillin-resistant coagulase-negative staphylococci [MR-CoNS]), β-hemolytic streptococci, Enterobacteriacae, and *Pseudomonas aeruginosa*. Delafloxacin is also active against bacteria associated with respiratory tract infections (hospital and community-acquired respiratory infections) including activity against fluoroquinolone-resistant *Streptococcus pneumoniae* and *Haemophilus influenzae*.

In this study, the activity of delafloxacin was examined against 4,410 contemporary clinical isolates collected from United States (USA) medical centers during surveillance year 2014.

Methods

Susceptibility testing: Reference broth microdilution MIC testing was performed using validated broth microdilution trays (CLSI M07-A10, 2015). Panels were produced by ThermoFisher Scientific (Cleveland, Ohio, USA). Categorical interpretation criteria were those of CLSI M100-S26 (2016) and EUCAST (2016). All *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates for which ceftriaxone or ceftazidime or aztreonam MICs were ≥2 µg/mL were considered to be screen-positive for ESBL production [CLSI, 2015]. Quality control (QC) strains per the CLSI M07-A10 standard were tested concurrently and included 1). *E. coli* ATCC 25922 and 35218, 2). *Staphylococcus aureus* ATCC 29213, 3). *Enterococcus faecalis* ATCC 29212, 4). *S. pneumoniae* ATCC 49619.

Isolates: Bacterial isolates (non-duplicate; 4,410 isolates) were collected from 69 medical centers located in the USA for the year 2014. Isolates were collected from patients with bloodstream (BSI), community-acquired and hospital respiratory tract, ABSSSI, and other infections. The largest numbers of isolates were from ABSSSI (1,681), respiratory (hospital; 805) and BSI (748) representing 73.3% of all isolates.

Results

- Delafloxacin was very active against tested *S. aureus* (≤0.004/0.25 µg/mL)) and CoNS (MIC_{90}, 0.5 µg/mL; **Table 1)**.
- The most potent antimicrobial tested against MSSA was delafloxacin ($MIC_{50/90}$, ≤0.004/0.03 µg/mL). Based on MIC_{90}, delafloxacin was eight-fold more potent than ceftaroline and 128-fold more potent than levofloxacin (**Table 1**; data not shown).
- Against MRSA isolates, tigecycline ($MIC_{50/90}$, 0.06/0.06 µg/mL), delafloxacin ($MIC_{50/90}$, 0.06/0.5 µg/mL), trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL) and daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) were the most potent antimicrobials (**Table 2**). Delafloxacin was 64-fold more potent than levofloxacin (by MIC_{50}) and at least sixteen-fold more potent by MIC_{90} criteria (**Table 2**).
- MRSA exhibited high levels of resistance against levofloxacin (68.4% resistant) and erythromycin (82.9/86.2% [CLSI/EUCAST]; **Table 2**). The greatest coverage of all *S. aureus* (MSSA and MRSA) was provided by daptomycin (99.7% susceptible), linezolid (100.0%) , tigecycline (100.0%), and vancomycin (100.0%; **Table 2**). Trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL) provided 98.4% coverage and ceftaroline ($MIC_{50/90}$, 0.25/1 µg/mL) 98.4% coverage (**Table 2**). All *S. aureus* isolates were inhibited by delafloxacin at ≤2 µg/mL (98.7% at ≤1 µg/mL; **Table 1**).
- The majority of *E. faecalis* isolates exhibited relatively low delafloxacin MIC results ($MIC_{50/90}$, 0.06/1 µg/mL) contrasting with *E. faecium* MIC values ($MIC_{50/90}$, >4/>4 µg/mL) (**Table 1**). There were eight vancomycin-resistant *E. faecalis* (2.7%), the highest delafloxacin MIC was 1 µg/mL. There were 143 vancomycin-resistant *E. faecium* (73.3%), delafloxacin MIC values ranged from 0.5->4 µg/mL.
- Delafloxacin was the most active agent tested against *S. pneumoniae* ($MIC_{50/90}$, 0.008/0.015 µg/mL; **Table 1**). All isolates were inhibited at a delafloxacin MIC of ≤0.25 µg/mL (**Table 1**). Delafloxacin was eight-fold more active than ceftaroline ($MIC_{50/90}$, ≤0.015/0.12 µg/mL; 99.7% susceptible), 16-fold more active than moxifloxacin ($MIC_{50/90}$, ≤0.12/0.25 µg/mL; 98.3% susceptible), and 64-fold more active than levofloxacin (1/1 µg/mL; 98.3% susceptible; **Table 2**).There were two isolates with penicillin MIC values of 8 µg/mL (high level penicillin-resistance; resistant to parenteral penicillin), both of which had delafloxacin MIC results of 0.008 µg/mL.
- Delafloxacin ($MIC_{50/90}$, 0.015/0.03 µg/mL) was the most active agent tested against viridans group streptococci and was very potent against *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae.* All delafloxacin MIC values for *S. pyogenes* and *S. dysgalactiae* were ≤0.03 µg/mL. For *S. agalactiae*, 98.0% of isolates were inhibited at a delafloxacin MIC of ≤0.03 µg/mL and the highest MIC was only 0.5 µg/mL (**Table 1**).
- Delafloxacin was active against the majority of Enterobacteriaceae, exhibiting $MIC_{50/90}$ values of 0.06/2 µg/mL with 82.3% of isolates inhibited at a delafloxacin concentration of ≤1 µg/mL (**Table 1**).
- Fluoroquinolone susceptibility as measured by ciprofloxacin and levofloxacin for Enterobacteriaceae ranged from 80.4-84.3% (**Table 3**).
- Against ESBL-producing enteric bacilli, fluoroquinolone activity was reduced. Against ESBL-phenotype *E. coli*, 26.9% of isolates were inhibited at ≤1 µg/mL of delafloxacin and against ESBL-phenotype *K. pneumoniae*, *22.9*% were inhibited at ≤1 µg/mL (**Table 1**).
- Delafloxacin was active against species with high rates of ceftazidime resistance due to AmpC production, including *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp*.* isolates. Delafloxacin inhibited 92.8% of *Enterobacter* spp. isolates at ≤1 µg/mL. Against *Citrobacter* spp., a total of 87.3% of isolate MIC values were at ≤1 µg/mL and for *Serratia* spp, 78.0% were inhibited at ≤1 µg/mL (data not shown).
- Against *P. aeruginosa*, ciprofloxacin ($MIC_{50/90}$, 0.12/>4 µg/mL) was two-fold more active than delafloxacin ($MIC_{50/90}$, 0.25/>4 µg/mL) which was two-fold more active than levofloxacin ($MIC_{50/90}$, 0.5/>4 µg/mL). Delafloxacin inhibited 75.0% of *P. aeruginosa* at ≤1 µg/mL. Ciprofloxacin and levofloxacin susceptibilities were 76.0/74.0% (CLSI/EUCAST) and 75.0/63.0 (CLSI/EUCAST), respectively (**Table 3**).
- *A. baumannii* isolates were resistant to many agents. Delafloxacin inhibited 59.0% of isolates at ≤1 µg/mL. Ciprofloxacin and levofloxacin susceptibility ranged from 48-50%. Only colistin ($MIC_{50/90}$, 1/2 µg/mL; 94% susceptible) and amikacin ($MIC_{50/90}$, 4/>32 µg/mL; 78.0% susceptible) exhibited susceptibility >65% (**Table 3**).

Table 1. MIC (µg/mL) distributions and cumulative frequency (%) for delafloxacin for all infection types (USA).

Organism	Count	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>4	MIC50	MIC90
Staphylococcus aureus	1,100	666 (60.5)	8 (61.3)	8 (62.0)	38 (65.5)	183 (82.1)	62 (87.7)	63 (93.5)	24 (95.6)	34 (98.7)	14 (100.0)	--	--	≤0.004	0.25
MSSA	591	515 (87.1)	7 (88.3)	4 (89.0)	10 (90.7)	27 (95.3)	11 (97.1)	8 (98.5)	6 (99.5)	2 (99.8)	1 (100.0)	--	--	≤0.004	0.03
MRSA	509	151 (29.7)	1 (29.9)	4 (30.6)	28 (36.1)	156 (66.8)	51 (76.8)	55 (87.6)	18 (91.2)	32 (97.4)	13 (100.0)	--	--	0.06	0.5
Coagulase-negative staphylococci	100	51 (51.0)	7 (58.0)	3 (61.0)	1 (62.0)	6 (68.0)	14 (82.0)	4 (86.0)	4 (90.0)	9 (99.0)	1 (100.0)	--	--	≤0.004	0.5
MSCoNS	42	28 (66.7)	4 (76.2)	2 (81.0)	1 (83.3)	1 (85.7)	4 (95.2)	1 (97.6)	0 (97.6)	1 (100.0)	--	--	--	≤0.004	0.12
MRCoNS	58	23 (39.7)	3 (44.8)	1 (46.6)	0 (46.6)	5 (55.2)	10 (72.4)	3 (77.6)	4 (84.5)	8 (98.3)	1 (100.0)	--	--	0.06	1
Enterococcus faecalis	300	--	2 (0.7)	0 (0.7)	28 (10.0)	150 (60.0)	39 (73.0)	9 (76.0)	27 (85.0)	37 (97.3)	8 (100.0)	--	--	0.06	1
vancomycin-susceptible	292	--	2 (0.7)	0 (0.7)	28 (10.3)	150 (61.6)	39 (75.0)	8 (77.7)	22 (85.3)	35 (97.3)	8 (100.0)	--	--	0.06	1
vancomycin-resistant	8	--	--	--	--	--	--	1 (12.5)	5 (75.0)	2 (100.0)	--	--	--	--	--
Enterococcus faecium	195	--	--	1 (0.5)	0 (0.5)	8 (4.6)	0 (4.6)	1 (5.1)	6 (8.2)	8 (12.3)	3 (13.8)	16 (22.1)	152 (100.0)	>4	>4
vancomycin-susceptible	52	--	--	1 (1.9)	0 (1.9)	8 (17.3)	0 (17.3)	1 (19.2)	5 (28.8)	8 (44.2)	3 (50.0)	1 (51.9)	25 (100.0)	2	>4
vancomycin-resistant	143	--	--	--	--	--	--	--	1 (0.7)	0 (0.7)	0 (0.7)	15 (11.2)	127 (100.0)	>4	>4
Streptococcus pneumoniae	300	34 (11.3)	169 (67.7)	84 (95.7)	7 (98.0)	3 (99.0)	2 (99.7)	1 (100.0)	--	--	--	--	--	0.008	0.015
penicillin-susceptible	283	34 (12.0)	159 (68.2)	78 (95.8)	7 (98.2)	2 (98.9)	2 (99.6)	1 (100.0)	--	--	--	--	--	0.008	0.015
penicillin-intermediate	15	--	8 (53.3)	6 (93.3)	0 (93.3)	1 (100.0)	--	--	--	--	--	--	--	0.008	0.015
penicillin-resistant	2	--	2 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--
Viridans group streptococci	200	34 (17.0)	43 (38.5)	73 (75.0)	34 (92.0)	7 (95.5)	4 (97.5)	2 (98.5)	1 (99.0)	1 (99.5)	1 (100.0)	--	--	0.015	0.03
Streptococcus pyogenes	283	67 (23.7)	170 (83.7)	46 (100.0)	--	--	--	--	--	--	--	--	--	0.008	0.015
Streptococcus agalactiae	150	18 (12.0)	70 (58.7)	56 (96.0)	3 (98.0)	0 (98.0)	1 (98.7)	1 (99.3)	1 (100.0)	--	--	--	--	0.008	0.015
Streptococcus dysgalactiae	82	19 (23.2)	51 (85.4)	11 (98.8)	1 (100.0)	--	--	--	--	--	--	--	--	0.008	0.015
Enterobacteriaceae	1500	3 (0.2)	16 (1.3)	132 (10.1)	261 (27.5)	389 (53.4)	163 (64.3)	74 (69.2)	94 (75.5)	102 (82.3)	116 (90.0)	70 (94.7)	80 (100.0)	0.06	2
Escherichia coli	300	2 (0.7)	11 (4.3)	77 (30.0)	71 (53.7)	14 (58.3)	13 (62.7)	7 (65.0)	3 (66.0)	11 (69.7)	34 (81.0)	34 (92.3)	23 (100.0)	0.03	4
non-ESBL-phenotype	248	2 (0.8)	10 (4.8)	75 (35.1)	69 (62.9)	12 (67.7)	12 (72.6)	6 (75.0)	2 (75.8)	7 (78.6)	17 (85.5)	20 (93.5)	16 (100.0)	0.03	4
ESBL-phenotype	52	--	1 (1.9)	2 (5.8)	2 (9.6)	2 (13.5)	1 (15.4)	1 (17.3)	1 (19.2)	4 (26.9)	17 (59.6)	14 (86.5)	7 (100.0)	2	>4
Klebsiella pneumoniae	225	--	--	2 (0.9)	30 (14.2)	108 (62.2)	25 (73.3)	11 (78.2)	11 (83.1)	6 (85.8)	4 (87.6)	11 (92.4)	17 (100.0)	0.06	4
non-ESBL-phenotype	190	--	--	2 (1.1)	30 (16.8)	107 (73.2)	24 (85.8)	11 (91.6)	9 (96.3)	2 (97.4)	2 (98.4)	2 (99.5)	1 (100.0)	0.06	0.25
ESBL-phenotype	35	--	--	--	--	1 (2.9)	1 (5.7)	0 (5.7)	2 (11.4)	4 (22.9)	2 (28.6)	9 (54.3)	16 (100.0)	4	>4
Klebsiella oxytoca	75	--	--	--	3 (4.0)	44 (62.7)	23 (93.3)	3 (97.3)	2 (100.0)	--	--	--	--	0.06	0.12
non-ESBL-phenotype	62	--	--	--	3 (4.8)	35 (61.3)	19 (91.9)	3 (96.8)	2 (100.0)	--	--	--	--	0.06	0.12
ESBL-phenotype	13	--	--	--	--	9 (69.2)	4 (100.0)	--	--	--	--	--	--	0.06	0.12
Proteus mirabilis	154	--	--	5 (3.2)	60 (42.2)	33 (63.6)	1 (64.3)	3 (66.2)	9 (72.1)	9 (77.9)	25 (94.2)	6 (98.1)	3 (100.0)	0.06	2
non-ESBL-phenotype	146	--	--	5 (3.4)	60 (44.5)	32 (66.4)	1 (67.1)	3 (69.2)	8 (74.7)	8 (80.1)	22 (95.2)	4 (97.9)	3 (100.0)	0.06	2
ESBL-phenotype	8	--	--	--	--	1 (12.5)	0 (12.5)	0 (12.5)	1 (25.0)	1 (37.5)	3 (75.0)	2 (100.0)	--	--	--
Enterobacter spp.	290	1 (0.3)	1 (0.7)	7 (3.1)	42 (17.6)	134 (63.8)	57 (83.4)	16 (89.0)	6 (91.0)	5 (92.8)	7 (95.2)	7 (97.6)	7 (100.0)	0.06	0.5
Enterobacter cloacae	224	1 (0.4)	1 (0.9)	5 (3.1)	38 (20.1)	112 (70.1)	32 (84.4)	8 (87.9)	3 (89.3)	5 (91.5)	7 (94.6)	6 (97.3)	6 (100.0)	0.06	1
Enterobacter aerogenes	63	--	--	2 (3.2)	4 (9.5)	21 (42.9)	23 (79.4)	8 (92.1)	3 (96.8)	0 (96.8)	0 (96.8)	1 (98.4)	1 (100.0)	0.12	0.25
Citrobacter spp.	118	--	4 (3.4)	29 (28.0)	25 (49.2)	18 (64.4)	6 (69.5)	7 (75.4)	4 (78.8)	10 (87.3)	7 (93.2)	0 (93.2)	8 (100.0)	0.06	2
Citrobacter koseri	43	--	4 (9.3)	29 (76.7)	7 (93.0)	1 (95.3)	1 (97.7)	0 (97.7)	0 (97.7)	1 (100.0)	--	--	--	0.015	0.03
Citrobacter freundii	71	--	--	--	18 (25.4)	16 (47.9)	3 (52.1)	7 (62.0)	4 (67.6)	9 (80.3)	7 (90.1)	0 (90.1)	7 (100.0)	0.12	2
Indole-positive Proteeae	183	--	--	9 (4.9)	27 (19.7)	26 (33.9)	31 (50.8)	11 (56.8)	20 (67.8)	17 (77.0)	19 (87.4)	8 (91.8)	15 (100.0)	0.12	4
Morganella morganii	69	--	--	--	4 (5.8)	10 (20.3)	20 (49.3)	4 (55.1)	8 (66.7)	9 (79.7)	5 (87.0)	5 (94.2)	4 (100.0)	0.25	4
Proteus vulgaris	46	--	--	2 (4.3)	15 (37.0)	9 (56.5)	9 (76.1)	4 (84.8)	2 (89.1)	2 (93.5)	2 (97.8)	1 (100.0)	--	0.06	1
Providencia spp.	68	--	--	7 (10.3)	8 (22.1)	7 (32.4)	2 (35.3)	3 (39.7)	10 (54.4)	6 (63.2)	12 (80.9)	2 (83.8)	11 (100.0)	0.5	>4
Serratia spp.	132	--	--	--	1 (0.8)	0 (0.8)	5 (4.5)	15 (15.9)	38 (44.7)	44 (78.0)	20 (93.2)	3 (95.5)	6 (100.0)	1	2
other (Enterobacteriaceae)	23	--	--	3 (13.0)	2 (21.7)	12 (73.9)	2 (82.6)	1 (87.0)	1 (91.3)	0 (91.3)	0 (91.3)	1 (95.7)	1 (100.0)	0.06	0.5
Pseudomonas aeruginosa	100	--	--	1 (1.0)	1 (2.0)	7 (9.0)	26 (35.0)	22 (57.0)	8 (65.0)	10 (75.0)	7 (82.0)	6 (88.0)	12 (100.0)	0.25	>4
ceftazidime-susceptible (≤8 µg/mL)	83	--	--	1 (1.2)	1 (2.4)	7 (10.8)	25 (41.0)	18 (62.7)	7 (71.1)	9 (81.9)	7 (90.4)	2 (92.8)	6 (100.0)	0.25	2
ceftazidime-resistant (>16 µg/mL)	15	--	--	--	--	--	--	4 (26.7)	1 (33.3)	1 (40.0)	0 (40.0)	3 (60.0)	6 (100.0)	4	>4
Acinetobacter baumannii	100	--	--	1 (1.0)	10 (11.0)	21 (32.0)	11 (43.0)	4 (47.0)	7 (54.0)	5 (59.0)	8 (67.0)	8 (75.0)	25 (100.0)	0.5	>4

Table 2. Activity of delafloxacin and comparator antimicrobial agents against Gram-positive bacteria (USA, 2014).

Organism (Number) / Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
***Staphylococcus aureus* (1,100)**									
Delafloxacin	≤0.004	0.25	≤0.004 — 2	-	-	-	-	-	-
Levofloxacin	0.25	>4	≤0.12 — >4	61.5	0.9	37.6	61.5	0.9	37.6
Ceftaroline	0.25	1	0.03 — 2	98.4	1.6	0.0	98.4	-	1.6
Clindamycin	≤0.25	>2	≤0.25 — >2	85.5	0.2	14.3	85.5	0.0	14.5
Daptomycin	0.25	0.5	≤0.06 — 2	99.7	-	-	99.7	-	0.3
Erythromycin	8	>16	≤0.12 — >16	39.7	6.9	53.4	40.1	2.6	57.2
Linezolid	1	1	0.25 — 2	100.0	-	0.0	100.0	-	0.0
Oxacillin	0.5	>2	≤0.25 — >2	53.7	-	46.3	53.7	-	46.3
Tetracycline	≤0.5	≤0.5	≤0.5 — >8	95.3	0.9	3.8	93.1	1.0	5.9
Tigecycline	0.06	0.06	≤0.015 — 0.5	100.0	-	-[b]	100.0	-	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	98.4	-	1.6	98.4	0.2	1.5
Vancomycin	1	1	0.25 — 2	100.0	0.0	0.0	100.0	-	0.0
MRSA (509)									
Delafloxacin	0.06	0.5	≤0.004 — 2	-	-	-	-	-	-
Levofloxacin	4	>4	≤0.12 — >4	30.5	1.2	68.4	30.5	1.2	68.4
Ceftaroline	1	1	0.25 — 2	96.5	3.5	0.0	96.5	-	3.5
Clindamycin	≤0.25	>2	≤0.25 — >2	77.0	0.2	22.8	77.0	0.0	23.0
Daptomycin	0.25	0.5	0.12 — 2	99.4	-	-	99.4	-	0.6
Erythromycin	>16	>16	≤0.12 — >16	11.0	6.1	82.9	11.6	2.2	86.2
Linezolid	1	1	0.25 — 2	100.0	-	0.0	100.0	-	0.0
Tetracycline	≤0.5	1	≤0.5 — >8	93.7	1.0	5.3	91.6	1.8	6.7
Tigecycline	0.06	0.06	≤0.015 — 0.5	100.0	-	-[b]	100.0	-	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	97.6	-	2.4	97.6	0.2	2.2
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
***Streptococcus pyogenes* (283)**									
Delafloxacin	0.008	0.015	≤0.004 — 0.015	-	-	-	-	-	-
Levofloxacin	0.5	1	0.25 — >4	99.6	0.0	0.4	96.8	2.8	0.4
Moxifloxacin	≤0.12	0.25	≤0.12 — 0.5	-	-	-	100.0	0.0	0.0
Amox-clav	≤1	≤1	≤1 — ≤1	-	-	-	100.0	-	0.0
Ceftaroline	≤0.015	≤0.015	≤0.015 — 0.03	100.0	-	-	100.0	-	0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 — 0.5	100.0	-	-	100.0	-	0.0
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	91.9	0.4	7.8	92.2	-	7.8
Erythromycin	≤0.12	>16	≤0.12 — >16	84.5	0.7	14.8	84.5	0.7	14.8
Meropenem	≤0.015	≤0.015	≤0.015 — 0.12	100.0	-	-	100.0	-	0.0
Penicillin	≤0.06	≤0.06	≤0.06 — 0.12	100.0	-	-	100.0	-	0.0
Tetracycline	≤0.5	>8	≤0.5 — >8	81.9	0.7	17.4	80.9	1.1	18.1
Vancomycin	0.25	0.5	0.25 — 0.5	100.0	-	-	100.0	-	0.0
***Streptococcus pneumoniae* (300)**									
Delafloxacin	0.008	0.015	≤0.004 — 0.25	-	-	-	-	-	-
Levofloxacin	1	1	0.5 — >4	98.3	0.0	1.7	98.3	-	1.7
Moxifloxacin	≤0.12	0.25	≤0.12 — 2	98.3	1.7	0.0	98.0	-	2.0
Amox-clav	≤1	2	≤1 — >8	90.7	3.3	6.0[c]	-	-	-
Ceftaroline	≤0.015	0.12	≤0.015 — 1	99.7	-	-[c]	99.7	-	0.3
Ceftriaxone	≤0.06	1	≤0.06 — 8	83.3 94.3	11.0 4.0	5.7[d] 1.7[c]	83.3 -	15.0 -	1.7 -
Clindamycin	≤0.25	>2	≤0.25 — >2	84.7	0.3	15.0	85.0	-	15.0
Erythromycin	≤0.12	>16	≤0.12 — >16	52.0	1.7	46.3	52.0	1.7	46.3
Meropenem	≤0.015	0.5	≤0.015 — 1	83.0 -	11.7 -	5.3 -	83.0 100.0	17.0 -	0.0[c] 0.0[c]
Penicillin	≤0.06	2	≤0.06 — 8	59.7 59.7 94.3	28.3 - 5.0	12.0[e] 40.3[f] 0.7[g]	59.7 59.7 -	- 34.7 -	40.3[c] 5.7[c] -
Tetracycline	≤0.5	>8	≤0.5 — >8	77.7	0.0	22.3	77.7	0.0	22.3
TMP-SMX	≤0.5	>4	≤0.5 — >4	69.3	12.3	18.3	76.0	5.7	18.3
***Enterococcus faecalis* (300)**									
Delafloxacin	0.06	1	0.008 — 2	-	-	-	-	-	-
Levofloxacin	1	>4	0.5 — >4	71.7	0.7	27.7	-	-	-
Ampicillin	1	2	0.5 — 8	100.0	-	0.0	99.7	0.3	0.0
Daptomycin	1	2	0.12 — 4	100.0	-	-	-	-	-
Erythromycin	>16	>16	≤0.12 — >16	4.0	38.0	58.0	-	-	-
Linezolid	1	1	≤0.12 — 4	99.7	0.3	0.0	100.0	-	0.0
Teicoplanin	≤2	≤2	≤2 — >16	97.7	0.0	2.3	97.3	-	2.7
Tetracycline	>8	>8	≤0.5 — >8	23.0	1.0	76.0	-	-	-
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	-	-	-	0.0	50.0	50.0
Vancomycin	1	2	0.5 — >16	97.3	0.0	2.7	97.3	-	2.7

a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Breakpoints from FDA Package Insert revised 12/2014.
c. Using Non Meningitis breakpoints.
d. Using Meningitis breakpoints.
e. Using Oral breakpoints.
f. Using Parenteral, Meningitis breakpoints.
g. Using Parenteral, Non Meningitis breakpoints.

Abbreviations: Amox-clav = Amoxicillin-clavulanate; TMP-SMX = Trimethoprim-sulfamethoxazole.

Table 3. Activity of delafloxacin and comparator antimicrobial agents against Gram-negative bacteria (USA, 2014).

Organism (Number) / Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
Enterobacteriaceae (1,500)									
Delafloxacin	0.06	2	≤0.004 — >4	-	-	-	-	-	-
Ciprofloxacin	≤0.03	>4	≤0.03 — >4	82.8	1.9	15.3	80.4	2.4	17.2
Levofloxacin	≤0.12	>4	≤0.12 — >4	84.3	1.8	13.9	82.3	1.9	15.7
Ampicillin-sulbactam	16	>32	0.5 — >32	49.7	17.9	32.4	49.7	-	50.3
Aztreonam	≤0.12	16	≤0.12 — >16	89.0	1.0	10.0	86.4	2.6	11.0
Cefepime	≤0.5	1	≤0.5 — >16	93.3	2.3	4.4[b]	90.3	4.4	5.3
Ceftazidime	0.25	16	0.03 — >32	88.8	1.1	10.1	85.6	3.2	11.2
Ceftriaxone	0.12	>8	≤0.06 — >8	82.9	2.0	15.1	82.9	2.0	15.1
Gentamicin	≤1	2	≤1 — >8	91.9	1.4	6.7	90.3	1.6	8.1
Meropenem	0.03	0.06	≤0.015 — >32	98.5	0.3	1.3	98.7	0.3	0.9
Piperacillin-tazobactam	2	16	≤0.5 — >64	91.3	3.8	4.9	88.1	3.3	8.7
Tigecycline	0.25	1	0.03 — 4	98.9	1.1	0.0[b]	94.8	4.1	1.1
***P. aeruginosa* (100)**									
Delafloxacin	0.25	>4	0.015 — >4	-	-	-	-	-	-
Ciprofloxacin	0.12	>4	≤0.03 — >4	76.0	5.0	19.0	74.0	2.0	24.0
Levofloxacin	0.5	>4	≤0.12 — >4	75.0	8.0	17.0	63.0	12.0	25.0
Amikacin	2	8	0.5 — >32	96.0	1.0	3.0	95.0	1.0	4.0
Aztreonam	8	>16	0.25 — >16	58.0	16.0	26.0	6.0	68.0	26.0
Cefepime	2	16	≤0.5 — >16	86.0	8.0	6.0	86.0	-	14.0
Ceftazidime	2	32	0.25 — >32	83.0	2.0	15.0	83.0	-	17.0
Colistin	2	2	≤0.5 — 4	98.0	2.0	0.0	100.0	-	0.0
Gentamicin	≤1	4	≤1 — >8	90.0	3.0	7.0	90.0	-	10.0
Meropenem	0.5	8	≤0.015 — 32	78.8	8.1	13.1	78.8	16.2	5.1
Piperacillin-tazobactam	4	64	≤0.5 — >64	82.0	9.0	9.0	82.0	-	18.0
***Acinetobacter baumannii* (100)**									
Delafloxacin	0.5	>4	0.015 — >4	-	-	-	-	-	-
Ciprofloxacin	>4	>4	0.06 — >4	48.0	1.0	51.0	48.0	-	52.0
Levofloxacin	2	>4	≤0.12 — >4	50.0	4.0	46.0	49.0	1.0	50.0
Amikacin	4	>32	1 — >32	78.0	2.0	20.0	75.0	3.0	22.0
Ampicillin-sulbactam	8	>32	0.5 — >32	55.6	21.2	23.2	-	-	-
Cefepime	8	>16	≤0.5 — >16	51.0	9.0	40.0	-	-	-
Ceftazidime	8	>32	0.5 — >32	59.0	3.0	38.0	-	-	-
Colistin	1	2	≤0.5 — >8	94.0	-	6.0	94.0	-	6.0
Gentamicin	4	>8	≤1 — >8	63.0	9.0	28.0	63.0	-	37.0
Meropenem	1	>32	0.06 — >32	52.0	2.0	46.0	52.0	6.0	42.0
Piperacillin-tazobactam	16	>64	≤0.5 — >64	52.0	5.0	43.0	-	-	-

a. Criteria as published by CLSI [2016] and EUCAST [2016]
b. Breakpoints from FDA Package Insert revised 12/2014

Conclusions

- Delafloxacin was shown to possess a broad-spectrum *in vitro* activity against contemporary Gram-positive and -negative bacteria from the USA. The $MIC_{50/90}$ against *S. aureus* was ≤0.004/0.25 µg/mL and against Enterobacteriaceae was 0.06/2 µg/mL.
- Delafloxacin is more potent *in vitro* against *S. aureus* and CoNS, including methicillin-resistant strains, and against *S. pneumoniae* and β-hemolytic streptococci than the currently marketed fluoroquinolones.
- Delafloxacin was shown to be active *in vitro* against organisms which may be found in community-acquired pneumonia and ABSSSI.

Acknowledgements

This study and abstract presentation were funded by a research grant from Melinta Therapeutics, Inc. (New Haven, CT)

References

1. Almer LS, Hoffrage JB, Keller EL, Flamm RK, Shortridge VD (2004). In vitro and bactericidal activities of ABT-492, a novel fluoroquinolone, against Gram-positive and Gram-negative organisms. *Antimicrob Agents Chemother* 48: 2771-2777.
2. Clinical and Laboratory Standards Institute (2016). *M100-S26. Performance standards for antimicrobial susceptibility testing: 26th informational supplement.* Wayne, PA: CLSI.
3. EUCAST (2016). Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, January 2016. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2016.
4. Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez HT (2003). In vitro activities of ABT-492, a new fluoroquinolone, against 155 aerobic and 171 anaerobic pathogens isolated from antral sinus puncture specimens from patients with sinusitis. *Antimicrob Agents Chemother* 47: 3008-3011.
5. Hammerschlag MR, Roblin PM (2004). The in vitro activity of a new fluoroquinolone, ABT-492, against recent clinical isolates of *Chlamydia pneumoniae*. *J Antimicrob Chemother* 54: 281-282.
6. Lemaire S, Tulkens PM, Van Bambeke F (2011). Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-gram-positive fluoroquinolones moxifloxacin and delafloxacin against *Staphylococcus aureus*. *Antimicrob Agents Chemother* 55: 649-658.
7. Nilius AM, Shen LL, Hensey-Rudloff D, Almer LS, Beyer JM, Balli DJ, Cai Y, Flamm RK (2003). In vitro antibacterial potency and spectrum of ABT-492, a new fluoroquinolone. *Antimicrob Agents Chemother* 47: 3260-3269.
8. Waites KB, Crabb DM, Duffy LB (2003). Comparative in vitro susceptibilities and bactericidal activities of investigational fluoroquinolone ABT-492 and other antimicrobial agents against human mycoplasmas and ureaplasmas. *Antimicrob Agents Chemother* 47: 3973-3975.
9. Zhanel GG, Palatnick L, Nichol KA, Low DE, Hoban DJ (2003). Antimicrobial resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* respiratory tract isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrob Agents Chemother* 47: 1875-1881.
10. Zhanel GG, Adam HJ, Low DE, Blondeau J, Decorby M, Karlowsky JA, Weshnoweski B, Vashisht R, Wierzbowski A, Hoban DJ (2011). Antimicrobial susceptibility of 15,644 pathogens from Canadian hospitals: results of the CANWARD 2007-2009 study. *Diagn Microbiol Infect Dis* 69: 291-306.