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JNJ-Q2, a New Fluoroquinolone with Potent *In Vitro* Activity against *Staphylococcus aureus*, Including Methicillin- and Fluoroquinolone-Resistant Strains[▽]

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JNJ-Q2 is a broad-spectrum bactericidal fluoroquinolone with potent activity against Gram-positive and -negative pathogens. In this study, the *in vitro* activity of JNJ-Q2 was evaluated against 511 selected *Staphylococcus aureus* samples isolated in 2008-2009 from patients with acute bacterial skin and skin structure infections in the United States by using reference methodology. JNJ-Q2 was the most potent fluoroquinolone tested overall (MIC_{50} and MIC_{90}, 0.12 and 0.5 μg/ml, respectively) and against methicillin- and fluoroquinolone-resistant subgroups in direct comparisons to moxifloxacin, levofloxacin, and ciprofloxacin (each being ≥16-fold less potent than JNJ-Q2).

The quinolone class of antimicrobial agents has demonstrated high clinical utility in the treatment of a variety of human infections and has become one of the most widely applied classes. Resistance to fluoroquinolones usually occurs by alterations to target enzymes (DNA gyrase and topoisomerase IV) but also can occur by decreased uptake and/or drug efflux (2). For *Staphylococcus aureus*, recent (2009) surveillance data report an overall global fluoroquinolone resistance (FQR) rate of 37.9% (1). In 2008 in the United States, although fluoroquinolone resistance was at only 11% among methicillin-susceptible *S. aureus* (MSSA) isolates, it was at more than 70% in methicillin-resistant (MRSA) isolates, with the overall prevalence of MRSA being >55% (6). Clearly, resistance to agents in this class has limited their utility as empirical and targeted agents in clinical settings and in areas where MRSA is a prevalent pathogen.

JNJ-Q2 is a novel fluorinated 4-quinolone with potent activity against Gram-positive pathogens (including MRSA) and Gram-negative pathogens; it is in early clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). (7) JNJ-Q2 was shown to be very active against 345 MRSA isolates collected between 2004 and 2006, with MIC_{50} values of 16 and 0.12, MIC_{90} values of >32 and 0.25, and MIC ranges of 0.12 to >32 and 0.002 to 2 μg/ml for ciprofloxacin and JNJ-Q2, respectively (7). The aim of this study was to investigate the activity of JNJ-Q2 and fluoroquinolone comparators against more recent *S. aureus* isolates from patients with ABSSI in the United States.

The SENTRY Antimicrobial Surveillance Program has monitored a worldwide collection of pathogens since 1997, and the 2008-2009 samples were examined to select representative strains of JNJ-Q2-targeted pathogens from the United States and from patients with ABSSSI. Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, IA).

All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical and Laboratory Standards Institute (CLSI) recommendations (3). Susceptibility testing was performed for JNJ-Q2 and the fluoroquinolone comparators (ciprofloxacin, levofloxacin, and moxifloxacin) by using fresh-frozen broth microdilution panels manufactured by JMI Laboratories and for all other comparator antimicrobials by using validated broth microdilution panels manufactured by Trek Diagnostics Systems (Cleveland, OH). Quality assurance of the MIC values was performed by concurrent testing of CLSI-recommended quality control strains, including *S. aureus* ATCC 29213. Categorical interpretation of comparator MIC values was performed according to CLSI and EUCAST criteria, when available (4, 5).

Against all *S. aureus* isolates tested (511 isolates), JNJ-Q2 was the most active agent, with a MIC_{50} of 0.12 μg/ml, a MIC_{90} of 0.5 μg/ml, and a MIC range of ≤0.008 to 4 μg/ml (Table 1). In a comparison of MIC_{50} values, JNJ-Q2 demonstrated 16-, 64-, and 128-fold-greater activity than moxifloxacin, levofloxacin, and ciprofloxacin, respectively (Tables 1 and 2). In this selected population, antimicrobial resistance was elevated for levofloxacin and ciprofloxacin (both 80.0%), moxifloxacin (78.1%), and erythromycin (83.8%). Clindamycin showed a moderate rate of resistance (28.8% [29.2% by EUCAST criteria]). In contrast, resistance was very low for tetracycline (4.5% [6.5% by EUCAST criteria]) and trimethoprim-sulfamethoxazole (1.8%). All isolates were susceptible to vancomycin (MIC_{90}, 1 μg/ml), linezolid (MIC_{90}, 2 μg/ml), and daptomycin (MIC_{90}, 0.5 μg/ml) (Table 2).

In tests of the 308 FQR MRSA isolates, JNJ-Q2 was many-fold more active than the comparator fluoroquinolone antimicrobial agents (Tables 1 and 2). However, the MIC_{50} (0.25 μg/ml) and MIC_{90} (1 μg/ml) values were the highest in this subgroup compared to those of the other three subgroups and the overall collection. In addition, 13 of 14 isolates with JNJ-Q2 MIC values at >1 μg/ml (13 isolates at 2 μg/ml and 1 isolate at 4 μg/ml) were

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TABLE 1. Cumulative percent inhibited MIC distribution of JNJ-Q2 and comparison with other fluoroquinolones tested against *S. aureus* subgroups

Subgroup (no. of isolates tested) and antimicrobial agent[a]	No. (cumulative %) of isolates inhibited at indicated antimicrobial MIC (μg/ml)													MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16		
All isolates (511)															
JNJ-Q2	90 (17.6)	12 (20.0)	0 (20.0)	0 (20.0)	170 (53.2)	161 (84.7)	30 (90.6)	34 (97.3)	13 (99.8)	1 (100.0)				0.12	0.5
Moxifloxacin			27 (5.3)	70 (19.0)	5 (20.0)	0 (20.0)	0 (20.0)	10 (21.9)	179 (57.0)	62 (69.1)	94 (87.5)	10 (89.4)	54 (100.0)	2	>16
Levofloxacin					12 (2.3)	86 (19.2)	4 (20.0)	0 (20.0)	0 (20.0)	120 (43.4)	75 (58.1)	53 (68.5)	161 (100.0)	8	>16
Ciprofloxacin					1 (0.2)	22 (4.5)	75 (19.2)	4 (20.0)	0 (20.0)	0 (20.0)	94 (38.4)	88 (55.6)	227 (100.0)	16	>16
FQR MRSA (308)															
JNJ-Q2					127 (41.2)	116 (78.9)	24 (86.7)	28 (95.8)	12 (99.7)	1 (100.0)				0.25	1
Moxifloxacin								7 (2.3)	131 (44.8)	46 (59.7)	69 (82.1)	9 (85.1)	46 (100.0)	4	>16
Levofloxacin										92 (29.9)	51 (46.4)	36 (58.1)	129 (100.0)	16	>16
Ciprofloxacin											74 (24.0)	62 (44.2)	172 (100.0)	>16	>16
FQR MSSA (101)															
JNJ-Q2					43 (42.6)	45 (87.1)	6 (93.1)	6 (99.0)	1 (100.0)					0.25	0.5
Moxifloxacin								3 (3.0)	48 (50.5)	16 (66.3)	25 (91.1)	1 (92.1)	8 (100.0)	2	8
Levofloxacin										28 (27.7)	24 (51.5)	17 (68.3)	32 (100.0)	8	>16
Ciprofloxacin											20 (19.8)	26 (45.5)	55 (100.0)	>16	>16
FQS MRSA (50)															
JNJ-Q2	49 (98.0)	1 (100.0)												≤0.008	≤0.008
Moxifloxacin			13 (26.0)	36 (98.0)	1 (100.0)									0.06	0.06
Levofloxacin					2 (4.0)	46 (96.0)	2 (100.0)							0.25	0.25
Ciprofloxacin						7 (14.0)	41 (96.0)	2 (100.0)						0.5	0.5
FQS MSSA (52)															
JNJ-Q2	41 (78.9)	11 (100.0)												≤0.008	0.015
Moxifloxacin			14 (26.9)	34 (92.3)	4 (100.0)									0.06	0.06
Levofloxacin					10 (19.2)	40 (96.2)	2 (100.0)							0.25	0.25
Ciprofloxacin					1 (1.9)	15 (30.8)	34 (96.2)	2 (100.0)						0.5	0.5

[a] FQR, fluoroquinolone resistant; FQS, fluoroquinolone susceptible; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

TABLE 2. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials against 511 *S. aureus* isolates by fluoroquinolone and methicillin resistance status

Organism (no. of isolates tested) and antimicrobial agent[a]	MIC (μg/ml)			%S/%R[b]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
All isolates (511)					
JNJ-Q2	0.12	0.5	≤0.008–4	—/—	—/—
Moxifloxacin	2	>16	0.03–>16	20.0/78.1	20.0/78.1
Levofloxacin	8	>16	0.12–>16	20.0/80.0	20.0/80.0
Ciprofloxacin	16	>16	0.12–>16	20.0/80.0	20.0/80.0
Oxacillin	>2	>2	≤0.25–>2	29.9/70.1	29.9/70.1
Penicillin	32	>32	≤0.015–>32	10.0/90.0	10.0/90.0
Erythromycin	>2	>2	≤0.25–>2	16.0/83.8	16.0/83.8
Clindamycin	≤0.25	>2	≤0.25–>2	70.8/28.8	70.6/29.2
Linezolid	2	2	0.5–4	100.0/0.0	100.0/0.0
Tetracycline	≤2	≤2	≤2–>8	94.9/4.5	93.5/6.5
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	98.2/1.8	98.2/1.8
Daptomycin	0.5	0.5	0.12–1	100.0/—	100.0/0.0
Vancomycin	1	1	0.5–2	100.0/0.0	100.0/0.0
FQR MRSA (308)					
JNJ-Q2	0.25	1	0.12–4	—/—	—/—
Moxifloxacin	4	>16	1–>16	0.0/97.7	0.0/97.7
Levofloxacin	16	>16	4–>16	0.0/100.0	0.0/100.0
Ciprofloxacin	>16	>16	8–>16	0.0/100.0	0.0/100.0
Erythromycin	>2	>2	≤0.25–>2	6.5/93.5	6.5/93.5
Clindamycin	≤0.25	>2	≤0.25–>2	61.7/38.0	61.4/38.3
Linezolid	2	2	0.5–4	100.0/0.0	100.0/0.0
Tetracycline	≤2	≤2	≤2–>8	95.8/3.6	93.5/6.5
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	98.1/1.9	98.1/1.9
Daptomycin	0.5	0.5	0.12–1	100.0/—	100.0/0.0
Vancomycin	1	1	0.5–2	100.0/0.0	100.0/0.0
FQR MSSA (101)					
JNJ-Q2	0.25	0.5	0.12–2	—/—	—/—
Moxifloxacin	2	8	1–>16	0.0/97.0	0.0/97.0
Levofloxacin	8	>16	4–>16	0.0/100.0	0.0/100.0
Ciprofloxacin	>16	>16	8–>16	0.0/100.0	0.0/100.0
Erythromycin	>2	>2	≤0.25–>2	15.8/84.2	15.8/84.2
Clindamycin	≤0.25	>2	≤0.25–>2	71.3/28.7	71.3/28.7
Linezolid	2	2	1–2	100.0/0.0	100.0/0.0
Tetracycline	≤2	≤2	≤2–>8	96.0/4.0	96.0/4.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>2	97.0/3.0	97.0/3.0
Daptomycin	0.25	0.5	0.12–1	100.0/—	100.0/0.0
Vancomycin	1	1	0.5–2	100.0/0.0	100.0/0.0
FQS MRSA (50)					
JNJ-Q2	≤0.008	≤0.008	≤0.008–0.015	—/—	—/—
Moxifloxacin	0.06	0.06	0.03–0.12	100.0/0.0	100.0/0.0
Levofloxacin	0.25	0.25	0.12–0.5	100.0/0.0	100.0/0.0
Ciprofloxacin	0.5	0.5	0.25–1	100.0/0.0	100.0/0.0
Erythromycin	>2	>2	≤0.25–>2	6.0/92.0	6.0/92.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	98.0/2.0	98.0/2.0
Linezolid	2	2	1–2	100.0/0.0	100.0/0.0
Tetracycline	≤2	≤2	≤2–>8	92.0/6.0	92.0/8.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0/0.0	100.0/0.0
Daptomycin	0.5	0.5	0.25–0.5	100.0/—	100.0/0.0
Vancomycin	1	1	0.5–1	100.0/0.0	100.0/0.0
FQS MSSA (52)					
JNJ-Q2	≤0.008	0.015	≤0.008–0.015	—/—	—/—
Moxifloxacin	0.06	0.06	0.03–0.12	100.0/0.0	100.0/0.0
Levofloxacin	0.25	0.25	0.12–0.5	100.0/0.0	100.0/0.0
Ciprofloxacin	0.5	0.5	0.12–1	100.0/0.0	100.0/0.0
Erythromycin	≤0.25	>2	≤0.25–>2	82.7/17.3	82.7/17.3
Clindamycin	≤0.25	≤0.25	≤0.25–1	98.1/0.0	98.1/1.9
Linezolid	2	2	1–2	100.0/0.0	100.0/0.0
Tetracycline	≤2	≤2	≤2–>8	90.4/9.6	90.4/9.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–2	100.0/0.0	100.0/0.0
Daptomycin	0.5	0.5	0.12–1	100.0/—	100.0/0.0
Vancomycin	1	1	0.5–2	100.0/0.0	100.0/0.0

[a] FQR, fluoroquinolone resistant; FQS, fluoroquinolone susceptible; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.
[b] S, susceptible; R, resistant. Criteria are as published by the CLSI (4) and EUCAST (5). —, no breakpoint has been established.

in the FQR MRSA subgroup, with the remaining isolate (in the FQR MSSA subgroup) also being fluoroquinolone resistant. Against the FQR MSSA subgroup (Tables 1 and 2), JNJ-Q2, moxifloxacin, levofloxacin, and ciprofloxacin all had similar activity or only 2-fold-lower activity than that observed for the FQR MRSA subgroup. JNJ-Q2 was most active against fluoroquinolone-susceptible (FQS) isolates, regardless of MRSA or MSSA status. MIC_{50} and MIC_{90} results were ≤0.008 μg/ml and ≤0.008 μg/ml, respectively, for FQS MRSA and ≤0.008 and 0.015 μg/ml for FQS MSSA (Tables 1 and 2).

In summary, JNJ-Q2 MIC was very potent (MIC_{90}, ≤0.008 to 0.015 μg/ml) against all FQS *S. aureus* tested, an activity independent of methicillin susceptibility patterns. JNJ-Q2 was also very active (MIC_{90}, 0.5 to 1 μg/ml) against most FQR *S. aureus* isolates tested, independent of methicillin resistance status, but the potency was lower than that observed among the FQS population (≥32-fold at the MIC_{50} level). JNJ-Q2 was the most potent fluoroquinolone class agent tested overall and against all *S. aureus* subgroups compared directly to moxifloxacin, levofloxacin, and ciprofloxacin. These contemporary data support the use of JNJ-Q2 in clinical trials investigating the treatment of ABSSSI.

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REFERENCES

1. **Biedenbach, D. J., D. J. Farrell, R. E. Mendes, J. E. Ross, and R. N. Jones.** 2010. Stability of linezolid activity in an era of mobile oxazolidinone resistance determinants: results from the 2009 Zyvox Annual Appraisal of Potency and Spectrum program. Diagn. Microbiol. Infect. Dis. **68:**459–467.
2. **Bolon, M. K.** 2009. The newer fluoroquinolones. Infect. Dis. Clin. North Am. **23:**1027–1051.
3. **CLSI.** 2009. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: 8th ed. M07-A8. Clinical and Laboratory Standards Institute, Wayne, PA.
4. **CLSI.** 2011. Performance standards for antimicrobial susceptibility testing; 21st informational supplement. M100-S21. Clinical and Laboratory Standards Institute, Wayne, PA.
5. **EUCAST.** 2011. Clinical MIC breakpoints. EUCAST, Växjö, Sweden. http://www.eucast.org/clinical_breakpoints/.
6. **Farrell, D. J., R. E. Mendes, J. E. Ross, and R. N. Jones.** 2009. Linezolid surveillance program results for 2008 (LEADER Program for 2008). Diagn. Microbiol. Infect. Dis. **65:**392–403.
7. **Morrow, B. J., et al.** 2010. In vitro antibacterial activities of JNJ-Q2, a new broad-spectrum fluoroquinolone. Antimicrob. Agents Chemother. **54:**1955–1964.