1138

Activity of JNJ-Q2, a New Fluoroquinolone, Tested Against Contemporary (2010) European Pathogens Isolated from Patients with Acute Bacterial Skin and Skin-Structure Infections

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AMENDED ABSTRACT

Objectives: To determine the activity of JNJ-Q2 tested against contemporary (2010) European isolates of the most common bacterial species isolated from patients with acute bacterial skin and skin-structure infections (ABSSSI). JNJ-Q2 is a broad-spectrum bactericidal fluoroquinolone (FQ) with potent activity against Gram-positive and -negative pathogens, including methicillin-resistant (MR) *Staphylococcus aureus* (SA), and is in clinical development for the treatment of ABSSSI and community-acquired bacterial pneumonia.

Methods: A total of 1,273 pathogens were collected from patients with ABSSSI in 32 medical centres in 15 European countries (including Turkey and Israel) in 2010. Species/organism group (number of isolates tested) were: SA (1,062) and beta-hemolytic streptococci (BHS, 211; 48.8% *S. pyogenes*). Isolates were tested for susceptibility by CLSI broth microdilution methods (M07-A8 and M100-S21). Susceptibility interpretations for comparator agents were determined using EUCAST (2011) and CLSI (2011) breakpoints.

Results: Table 1 shows the cumulative percentage MIC frequency against the species/groups tested. Against 1,062 SA, JNJ-Q2 ($MIC_{50/90}$, 0.015/0.5 mg/L) inhibited all isolates at a MIC ≤2 mg/L. Although activity was lower against MRSA (MIC_{50}, 0.25 mg/L) compared to methicillin-susceptible (MS) SA (MIC_{50}, 0.008 mg/L), 95.1% of MRSA were inhibited at a JNJ-Q2 MIC value of ≤0.5 mg/L. Against MRSA, JNJ-Q2 was four- to 16-fold more active than moxifloxacin (MOX; $MIC_{50/90}$, 4/8 mg/L) and at least 32-fold more active than levofloxacin (LEV; $MIC_{50/90}$, ≥8/≥8 mg/L) and ciprofloxacin (CIP; $MIC_{50/90}$, ≥8/≥8 mg/L). JNJ-Q2 demonstrated excellent activity ($MIC_{50/90}$, 0.008/0.015 mg/L) against BHS, inhibiting 100.0% of isolates at a MIC of ≤0.06 mg/L. JNJ-Q2 was 16-fold more active than MOX ($MIC_{50/90}$, 0.12/0.25 mg/L) and 64-fold more active than CIP ($MIC_{50/90}$, 0.5/1 mg/L) against BHS.

Conclusions: JNJ-Q2 demonstrated very potent activity against this collection of common bacterial pathogens isolated from patients with ABSSSI in European medical centers during 2010. JNJ-Q2 also exhibited four-fold or greater activity compared to CIP, LEV and MOX against these isolates. The JNJ-Q2 in vitro results were very promising and support further clinical development of this new FQ for treatment of ABSSSI, including cases caused by MRSA.

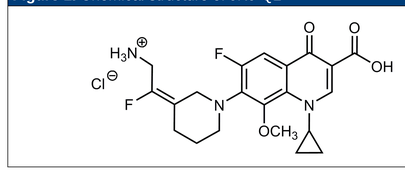
INTRODUCTION

The quinolone class of antimicrobial agents have demonstrated high clinical utility in a variety of human infections and has become one of the most widely prescribed classes. Resistance to fluoroquinolones (FQ) usually occurs by alterations to target enzymes (DNA gyrase and topoisomerase IV) but also by decreased uptake and/or efflux.

JNJ-Q2 (Figure 1) is a novel fluorinated 4-quinolone with potent activity against Gram-positive pathogens (including MRSA) and Gram-negative pathogens; and it is in clinical development for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP).

In this presentation, we summarize *in vitro* tested results for JNJ-Q2 and comparator antimicrobial agents against Gram-positive pathogens isolated in 2010 from patients with ABSSSI in Europe.

Figure 1. Chemical structure of JNJ-Q2



MATERIALS AND METHODS

Bacterial Strain Collection. The SENTRY Antimicrobial Surveillance Program has monitored a worldwide collection of pathogens since 1997, and the 2010 samples were examined to select JNJ-Q2 targeted pathogens from European patients with ABSSSI. A total of 1,273 pathogens were collected from patients with ABSSSI in 32 medical centres in 15 European countries (including Turkey and Israel). Species identifications were performed by the submitting laboratories with confirmation performed by the central reference laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical and Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009) using validated panels manufactured by TREK Diagnostic Systems (Cleveland, Ohio, USA). The quality assurance of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S21, 2011) control strains, including *S. aureus* ATCC 29213. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S21, 2011) and EUCAST (2011) criteria.

RESULTS

- Against all *S. aureus* (1,062 isolates) tested, JNJ-Q2 was very active with a MIC_{50}, MIC_{90}, and MIC range of 0.015, 0.5, and ≤0.004 to 2 mg/L, respectively (Table 1). Comparing MIC_{50} values, JNJ-Q2 demonstrated four-, 32-, and at least 32-fold greater activity than moxifloxacin, ciprofloxacin and levofloxacin, respectively (Table 2).
- By EUCAST criteria, antimicrobial resistance (R) in *S. aureus* was elevated for levofloxacin (LEV, 44.2%), ciprofloxacin (CIP, 44.7%), moxifloxacin (MOX, 42.7%), and erythromycin (38.0%). Clindamycin showed a moderate rate of R (15.3%). In contrast, R was very low for tetracycline (7.1%) and trimethoprim/sulfamethoxazole (1.5%). All isolates were susceptible (S) to vancomycin and linezolid and with 99.9% of isolates testing S to daptomycin (Table 2).
- When testing the 407 LEV-R-MRSA and 62 LEV-R-MSSA, JNJ-Q2 was still many-fold more potent than the comparator FQ antimicrobial agents (Tables 1 and 2). However, for both FQR-subgroups, the MIC_{50} (0.25 mg/L) and MIC_{90} (0.5 mg/L) values were the highest compared to the two LEV-S-subgroups and the overall collection.
- JNJ-Q2 was most active against LEV-S-isolates, regardless of MRSA or MSSA status. The MIC_{50} and MIC_{90} for LEV-S-MRSA and LEV-S-MSSA (Tables 1 and 2) were at 0.008 mg/L and 0.008-0.015 mg/L, respectively. The highest MIC observed in both groups of organisms was only 0.25 mg/L.
- Against 211 beta-hemolytic streptococci (including 103 *S. pyogenes*) JNJ-Q2 was the most potent (MIC_{90}, 0.015 mg/L) antimicrobial agent tested with all isolates being inhibited at an MIC of ≤0.06 mg/L. JNJ-Q2 demonstrated many-fold higher activity than LEV, MOX and CIP (Table 2).

Table 1. MIC (mg/L) and cumulative percent inhibited distributions of JNJ-Q2 tested against 1,273 ABSSSI pathogens isolated in Europe (2010)

Organism/group	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}
S. aureus (1062)	232 (21.9)	291 (49.3)	65 (55.4)	1 (55.5)	7 (56.1)	101 (65.6)	232 (87.5)	111 (97.9)	19 (99.7)	3 (100.0)	0.015	0.5
MSSA, lev-S[a] (545)	226 (41.5)	268 (90.6)	46 (99.1)	1 (99.3)	0 (99.3)	2 (99.6)	2 (100.0)				0.008	0.008
MSSA, lev-R[b] (62)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	22 (38.7)	28 (83.9)	8 (96.8)	2 (100.0)		0.25	0.5
MRSA, lev-S (45)	5 (11.1)	21 (57.8)	19 (100.0)								0.008	0.015
MRSA, lev-R (407)	0 (0.0)	1 (0.3)	0 (0.3)	0 (0.3)	4 (1.2)	77 (20.2)	202 (69.8)	103 (95.1)	19 (99.3)	3 (100.0)	0.25	0.5
BH[c] streptococci (211)	13 (6.2)	129 (67.3)	66 (98.6)	3 (100.0)							0.008	0.015
S. pyogenes (103)	2 (2.9)	58 (59.2)	40 (98.1)	2 (100.0)							0.008	0.015
S. agalactiae (55)	2 (3.6)	36 (69.1)	17 (100.0)								0.008	0.015
other BHS[d] (53)	8 (15.1)	35 (81.1)	9 (98.1)	0 (98.1)	1 (100.0)						0.008	0.015

a. Lev-S = levofloxacin-susceptible. b. Lev-R = levofloxacin-resistant. c. BH = beta-hemolytic. d. = Includes: *Streptococcus dysgalactiae* (seven isolates), *Streptococcus equisimilis* (one isolate), Group C *Streptococcus* (14 isolates), and Group G *Streptococcus* (31 isolates).

Table 2. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials tested against 1,273 ABSSSI pathogens isolated in Europe (2010)

Organism (no. tested)/ Antimicrobial agent[a]	MIC in mg/L			CLSI[b]	EUCAST[b]
	MIC_{50}	MIC_{90}	Range	%S / %R	%S / %R
All *S. aureus* (1.062)					
JNJ-Q2	0.015	0.5	≤0.004 – 2	-[c] / -	- / -
Levofloxacin	≤0.5	>4	≤0.5 – >4	55.6 / 44.2	55.6 / 44.2
Moxifloxacin	0.06	8	≤0.008 – >8	55.6 / 42.7	55.6 / 42.7
Ciprofloxacin	0.5	>4	≤0.03 – >4	55.3 / 44.4	55.3 / 44.7
Oxacillin	0.5	>2	≤0.25 – >2	57.4 / 42.6	57.4 / 42.6
Erythromycin	≤0.25	>4	≤0.25 – >4	61.4 / 37.4	61.4 / 38.0
Clindamycin	≤0.25	>2	≤0.25 – >2	84.7 / 15.3	84.1 / 15.3
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	93.2 / 6.1	92.5 / 7.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	98.4 / 1.6	98.4 / 1.5
Daptomycin	0.25	0.5	0.12 – 2	99.9 / -	99.9 / 0.1
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
LEV-R-MRSA (407)					
JNJ-Q2	0.25	0.5	0.008 – 2	- / -	- / -
Levofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Moxifloxacin	4	8	0.06 – >8	0.2 / 96.1	0.2 / 96.1
Ciprofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Erythromycin	>4	>4	≤0.25 – >4	24.6 / 74.2	24.6 / 74.9
Clindamycin	≤0.25	>2	≤0.25 – >2	64.9 / 35.1	64.6 / 35.1
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	93.6 / 6.1	92.4 / 6.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	96.8 / 3.2	96.8 / 3.2
Daptomycin	0.25	0.5	0.12 – 2	99.8 / -	99.8 / 0.2
Vancomycin	0.5	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
LEV-R-MSSA (62)					
JNJ-Q2	0.25	0.5	0.06 – 1	- / -	- / -
Levofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Moxifloxacin	4	8	1 – >8	0.0 / 95.2	0.0 / 95.2
Ciprofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Erythromycin	≤0.25	>4	≤0.25 – >4	56.5 / 41.9	56.5 / 43.5
Clindamycin	≤0.25	>2	≤0.25 – >2	80.6 / 19.4	79.0 / 19.4
Linezolid	1	1	1 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	91.9 / 6.5	91.9 / 8.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	0.5	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
LEV-S-MRSA (45)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.015	- / -	- / -
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	0.06	0.12	0.015 – 0.12	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	0.25	1	0.12 – 2	97.8 / 0.0	97.8 / 2.2
Erythromycin	≤0.25	>4	≤0.25 – >4	82.2 / 17.8	82.2 / 17.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	93.3 / 6.7	93.3 / 6.7
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	0.5	>8	≤0.25 – >8	57.8 / 37.8	57.8 / 42.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	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
LEV-S-MSSA (545)					
JNJ-Q2	0.008	0.008	≤0.004 – 0.25	- / -	- / -
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	0.06	0.06	≤0.008 – 8	99.4 / 0.6	99.4 / 0.6
Ciprofloxacin	0.25	0.5	≤0.03 – 4	99.3 / 0.4	99.3 / 0.7
Erythromycin	≤0.25	>4	≤0.25 – >4	87.5 / 11.2	87.5 / 11.7
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	99.1 / 0.9	98.3 / 0.9
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	96.0 / 3.5	95.4 / 4.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	99.3 / 0.7	99.3 / 0.6
Daptomycin	0.25	0.25	0.12 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
S. pyogenes (103)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.03	- / -	- / -
Levofloxacin	≤0.5	2	≤0.5 – 4	99.0 / 0.0	87.4 / 1.0
Moxifloxacin	0.12	0.25	0.06 – 0.5	- / -	100.0 / 0.0
Ciprofloxacin	0.5	2	0.25 – >4	- / -	- / -
Penicillin	≤0.03	≤0.03	≤0.03	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	- / -	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	≤0.25 – >4	93.2 / 6.8	93.2 / 6.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	99.0 / 1.0	99.0 / 1.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	- / -	97.1 / 2.9
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
S. agalactiae (55)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.015	- / -	- / -
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0	96.4 / 0.0
Moxifloxacin	0.12	0.25	0.06 – 0.25	- / -	100.0 / 0.0
Ciprofloxacin	0.5	1	0.25 – 1	- / -	- / -
Penicillin	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	- / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	74.5 / 23.6	74.5 / 23.6
Clindamycin	≤0.25	>2	≤0.25 – >2	83.6 / 16.4	83.6 / 16.4
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Other beta-haemolytic streptococci[d] (53)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.06	- / -	- / -
Levofloxacin	≤0.5	1	≤0.5 – >4	96.2 / 1.9	96.2 / 3.8
Moxifloxacin	0.12	0.25	0.06 – 2	- / -	98.1 / 1.9
Ciprofloxacin	0.5	1	0.25 – >4	- / -	- / -
Penicillin	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	- / -	100.0 / 0.0
Erythromycin	≤0.25	2	≤0.25 – >4	86.8 / 13.2	86.8 / 13.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	96.2 / 3.8	96.2 / 3.8
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >4	- / -	98.1 / 1.9
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0

a. LEV = levofloxacin, S = susceptible, R = resistant, MSSA = methicillin-susceptible *S. aureus*, MRSA = methicillin-resistant *S. aureus*
b. Criteria as published by the CLSI [2011] and EUCAST [2011].
c. - = No breakpoint has been established.
d. = Includes: *Streptococcus dysgalactiae* (seven isolates), *S. equisimilis* (one isolate), Group C *Streptococcus* (14 isolates), and Group G *Streptococcus* (31 isolates).

CONCLUSIONS

- JNJ-Q2 MIC was very active (MIC_{90}, 0.008-0.015 mg/L) against all LEV-S-SA tested, a potency independent of methicillin S patterns.
- JNJ-Q2 was very active (MIC_{90}, 0.5 mg/L) against most LEV-R-SA tested, independent of methicillin R status, but the potency was lower than that observed among the LEV-S population (32-fold at the MIC_{50} level).
- JNJ-Q2 was the most potent FQ class agent tested overall and against all SA subgroups when compared directly to LEV, MOX and CIP.
- JNJ-Q2 was the most potent antimicrobial agent tested (MIC_{90}, 0.015 mg/L) against beta-hemolytic streptococci demonstrating many-fold higher activity than LEV, MOX and CIP.

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REFERENCES

1. Clinical and Laboratory Standards Institute (2009). *M07-A8, Methods of dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-eighth edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2011). *M100-S21. Performance standards for antimicrobial susceptibility testing: 21st informational supplement*. Wayne, PA: CLSI.
3. EUCAST (2011). Breakpoint tables for interpretation of MICs and zone diameters.Version1.3, January 2011. Available at http://www.eucast.org/clinical_breakpoints/. Accessed March 18, 2011.
4. Hooper DC, Rubinstein E (eds.) (2003). Quinolone Antimicrobial Agents 3rd edition. ASM Press, Washington D.C.
5. Jones RN, Ross JE, Bell JM, Fumiaki I, Kobayashi I, Turnidge JD (2009). Zyvox annual appraisal of potency and spectrum program: linezolid resistance program results for 2008. *Diagn Microb Infect Dis* 65:404-413.
6. Morrow BJ, He W, Amsler KM, Foleno BD, Macielag MJ, Lynch AS, Bush K (2010). In vitro antibacterial activities of JNJ-Q2, a new broad-spectrum fluoroquinolone. *Antimicrob Agents Chemother* 54:1955-64.