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Activity of JNJ-Q2, a New Fluoroquinolone, Tested Against Contemporary Pathogens Relevant to Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

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AMENDED ABSTRACT

Background: JNJ-Q2 is a broad-spectrum bactericidal 4-fluoroquinolone (FQ) with potent activity against Gram-positive and -negative pathogens. JNJ-Q2 is in clinical development for the treatment of ABSSSI.

Methods: This study included 3,650 contemporary (2010) pathogens relevant to ABSSSI (96 centers in 26 countries). *S. aureus* (SA; 45.6% methicillin (oxacillin)-susceptible [MS-] SA; 54.4% methicillin (oxacillin)-resistant [MR-] SA) and beta-hemolytic streptococci (BHS; including 278 *S. pyogenes*) were susceptibility (S) tested by CLSI broth microdilution. S rates for comparator agents were determined using CLSI and EUCAST breakpoints.

Results: JNJ-Q2 demonstrated good activity overall ($MIC_{50/90}$, 0.015/0.5 µg/ml) against 3,081 SA with all isolates inhibited at a MIC of ≤2 µg/ml. JNJ-Q2 was 16-fold more potent than moxifloxacin (MOX; MIC_{90}, 8 µg/ml) and at least 16-fold more potent than levofloxacin (LEV; MIC_{90}, >4 µg/ml). Overall, LEV-resistance (R) was high at 45.8%. Excellent activity was observed for JNJ-Q2 against all LEV-S MSSA ($MIC_{50/90}$, 0.008/0.008 µg/ml) and MRSA ($MIC_{50/90}$, 0.008/0.015 µg/ml) from all geographic regions. Although JNJ-Q2 potency was lower against LEV-R compared to LEV-S populations, JNJ-Q2 still showed good activity against both LEV-R MSSA ($MIC_{50/90}$, 0.25/0.5 µg/ml) and LEV-R MRSA ($MIC_{50/90}$, 0.25/0.5 µg/ml). JNJ-Q2 demonstrated excellent activity (MIC_{90}, 0.015 µg/ml) against all BHS.

Conclusions: JNJ-Q2 demonstrated very potent activity against these contemporary bacterial pathogens isolated globally from patients with ABSSSI. JNJ-Q2 exhibited greater activity compared to LEV and MOX against these species, including strains R to currently utilized FQs.

INTRODUCTION

Acute bacterial skin and skin-structure infections (ABSSSIs) are one of the most commonly encountered infections in humans with *Staphylococcus aureus* causing the great majority of these infections. Recent clinical trials for ABSSSI have found *S. aureus* as the baseline pathogen in 75-82% of patients (with MRSA accounting for 43-63% of *S. aureus*), followed by *Streptococcus pyogenes* (4-12.5%) and *Streptococcus agalactiae* (3-6%).

JNJ-Q2 is a novel fluorinated 4-quinolone with potent activity against Gram-positive (including MRSA) and Gram-negative pathogens and has been demonstrated to have balanced potency against both DNA gyrase and topoisomerase IV. JNJ-Q2 is in clinical development for the treatment of ABSSSI and community-acquired bacterial pneumonia (CABP). Previously, JNJ-Q2 was shown to be active against 511 selected *S. aureus* isolates (including 308 fluoroquinolone-resistant MRSA) collected between 2008 to 2009, with levofloxacin/JNJ-Q2 MIC_{50} values, MIC_{90} values, and MIC ranges of 8/0.12, >16/0.5 and 0.12 - >16/≤0.008 - 4 µg/ml, respectively.

The aims of this study were to determine comparative in vitro activity of JNJ-Q2 tested against clinical isolates collected in 2010 relevant to ABSSSI, and to monitor the activity of JNJ-Q2 compared to numerous other broad-spectrum antimicrobial agents when tested against contemporary clinical isolates in North American, European, Asia-Pacific (includes the Republic of China Network) and Latin American medical centers for the year 2010.

MATERIALS AND METHODS

Susceptibility testing. For JNJ-Q2 and moxifloxacin, CLSI reference frozen-form broth microdilution method (CLSI, 2009) was used, applying cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood added for streptococcal species. For all other comparator agents, the validated dry-form reference broth microdilution method was applied using panels produced by TREK Diagnostics (Cleveland, Ohio, USA). Interpretive criteria for the comparator agents were as published by the CLSI (CLSI, 2011) and EUCAST (EUCAST, 2011). CLSI quality control (QC) MIC ranges were utilized to assure test performances (CLSI, 2011). QC was tested daily with *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 and all values were within specified limits.

Bacterial isolates. A total of 3,650 isolates obtained in the 2010 surveillance program are shown by geographical region and organism group in Table 1. Isolates were obtained from 96 medical centers in 26 countries. Of the 3,650 isolates, 1619 (44.4%) were confirmed to be isolated from specimens obtained from patients diagnosed with ABSSSI, 595 (16.3%) isolates were from blood cultures, 197 (5.4%) from specimens obtained from hospitalized patients diagnosed with respiratory tract infections, and 1239 (33.9%) from patients in which the submitting laboratory was asked to send Gram-positive pathogens from any infection type.

RESULTS

The spectrum of activity and potencies of JNJ-Q2 and comparator agents tested against 3,650 clinical isolates are presented in Tables 2 and 3.

Activity of JNJ-Q2 against *S. aureus*

- JNJ-Q2 demonstrated good activity ($MIC_{50/90}$, 0.015/0.5 µg/ml) against 3,081 *S. aureus* (SA) with >95% of the isolates inhibited at a MIC of ≤0.5 µg/ml and all isolates inhibited at a MIC of ≤2 µg/ml (Table 2).
- Against all 3,081 isolates, JNJ-Q2 (MIC_{90}, 0.5 µg/ml) was 16-fold more potent than moxifloxacin (MIC_{90}, 8 µg/ml) and at least 16-fold more potent than ciprofloxacin and levofloxacin (MIC_{90}, both >4 µg/ml; Table 3).
- Overall, fluoroquinolone resistance was high at 42.6% (moxifloxacin), 45.8% (levofloxacin), and 46.7% (ciprofloxacin) see Table 3. Fluoroquinolone (levofloxacin) resistance ranged from 40.2% in North America to 59.2% in Latin America, and methicillin-resistance ranged from 42.6% in Europe to 67.6% in Latin America (data not shown).
- Excellent activity was observed for JNJ-Q2 tested against levofloxacin-susceptible MSSA ($MIC_{50/90}$, 0.008/0.008 µg/ml) and MRSA ($MIC_{50/90}$, 0.008/0.015 µg/ml; Table 2). Although JNJ-Q2 potency was less against levofloxacin-resistant organisms than against levofloxacin-susceptible populations, JNJ-Q2 still showed good activity against both levofloxacin-resistant MSSA ($MIC_{50/90}$, 0.25/0.5 µg/ml; Table 2) and MRSA ($MIC_{50/90}$, 0.25/0.5 µg/ml; Table 2).

Activity of JNJ-Q2 against β-haemolytic streptococci (BHS)

- JNJ-Q2 demonstrated excellent in-vitro activity ($MIC_{50/90}$, 0.008/0.015 µg/ml) against *S. pyogenes* inhibiting all isolates at a MIC value of ≤0.06 µg/ml (Table 2). Erythromycin resistance was 11.5% overall (Table 3) ranging from 6.8% in Europe to 33.3% in the Asia Pacific region. Against *S. pyogenes*, JNJ-Q2 (MIC_{90}, 0.015 µg/ml) had a 16-fold greater potency than moxifloxacin (MIC_{90}, 0.25 µg/ml), 64-fold greater potency than levofloxacin (MIC_{90}, 1 µg/ml), and 128-fold greater potency than ciprofloxacin (MIC_{90}, 2 µg/ml; Table 3).
- JNJ-Q2 also exhibited excellent activity ($MIC_{50/90}$, 0.008/0.015 µg/ml) against *S. agalactiae* (Table 2). One strain (from China) had a JNJ-Q2 MIC of 0.25 µg/ml with the remaining 160 isolates inhibited by MICs at ≤0.03 µg/ml (Table 2).
- JNJ-Q2 also demonstrated excellent activity ($MIC_{50/90}$, 0.008/0.015 µg/ml) against 130 isolates of other BHS inhibiting all isolates at a MIC of ≤0.06 µg/ml (Table 2).

Table 1. Distribution of 3,650 isolates by species or organism group and geographic region.

Organism/group	Asia-W. Pacific	Europe	Latin America	North America	Total
S. aureus	431	1062	377	1211	3081
Levofloxacin-intermediate	3	3	4	19	29
MRSA, levofloxacin-resistant	204	407	211	419	1241
MRSA, levofloxacin-susceptible	65	45	43	264	417
MSSA, levofloxacin-resistant	27	62	12	68	169
MSSA, levofloxacin-susceptible	132	545	107	441	1225
Beta-hemolytic streptococci	58	211	63	237	569
Total	489	1,273	440	1,448	3650

Table 2. MIC frequency and cumulative percent inhibited distributions of JNJ-Q2 by species and/or organism group.

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 (3081)	633 (20.5)	844 (47.9)	150 (52.8)	15 (53.3)	29 (54.2)	434 (68.3)	600 (87.8)	273 (96.7)	72 (99.0)	31 (100.0)	0.015	0.5
MSSA, lev-S[a] (1225)	498 (40.7)	621 (91.3)	94 (99.0)	7 (99.6)	0 (99.6)	3 (99.8)	2 (100.0)				0.008	0.008
MSSA, lev-R[b] (169)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	60 (37.3)	73 (80.5)	21 (92.9)	10 (98.8)	2 (100.0)	0.25	0.5
MRSA, lev-S (417)	134 (32.1)	220 (84.9)	56 (98.3)	6 (99.8)	1 (100.0)						0.008	0.015
MRSA, lev-R (1241)	0 (0.0)	1 (0.1)	0 (0.1)	1 (0.2)	18 (1.6)	355 (30.2)	523 (72.4)	252 (92.7)	62 (97.7)	29 (100.0)	0.25	0.5
BH[c] streptococci (569)	35 (6.2)	371 (71.4)	156 (98.8)	4 (99.5)	2 (99.8)	0 (99.8)	1 (100.0)				0.008	0.015
S. pyogenes (278)	9 (3.2)	186 (70.1)	80 (98.9)	2 (99.6)	1 (100.0)						0.008	0.015
S. agalactiae (161)	6 (3.7)	96 (63.4)	56 (98.1)	2 (99.4)	0 (99.4)	0 (99.4)	1 (100.0)				0.008	0.015
other BHS[d] (130)	20 (15.4)	89 (83.8)	20 (99.2)	0 (99.2)	1 (100.0)						0.008	0.015

a. Lev-S = levofloxacin-susceptible; b. Lev-R = levofloxacin-resistant ; c. BH = beta-haemolytic ; d. BHS = beta-haemolytic streptococci

Table 3. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials against ABSSSI pathogens.

Organism (no. tested)/ Antimicrobial agent[a]	MIC in µg/ml: MIC_{50}	MIC_{90}	Range	CLSI[b] %S[c] / %R[d]	EUCAST[b] %S / %R
S. aureus–all isolates (3,081)					
JNJ-Q2	0.015	0.5	≤0.004 – 2	-[e] / -	- / -
Moxifloxacin	0.12	8	≤0.008 – >8	53.3 / 42.6	53.3 / 42.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	53.3 / 45.8	53.3 / 45.8
Ciprofloxacin	0.5	>4	≤0.03 – >4	52.3 / 46.7	52.3 / 47.7
Oxacillin	>2	>2	≤0.25 – >2	45.6 / 54.4	45.6 / 54.4
Ceftriaxone[f]	>8	>8	0.5 – >8	45.0 / 54.4	45.6 / 54.4
Erythromycin	>4	>4	≤0.25 – >4	43.3 / 55.1	43.3 / 55.9
Clindamycin	≤0.25	>2	≤0.25 – >2	74.7 / 25.2	74.4 / 25.3
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	88.1 / 11.0	86.8 / 12.2
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	96.2 / 3.8	96.2 / 3.6
Daptomycin	0.25	0.5	≤0.06 – 2	99.9 / -	99.9 / 0.1
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin-R[g]-MRSA (1,241)					
JNJ-Q2	0.25	0.5	0.008 – 2	- / -	- / -
Moxifloxacin	4	8	0.06 – >8	0.1 / 91.9	0.1 / 91.9
Levofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Ciprofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Erythromycin	>4	>4	≤0.25 – >4	13.1 / 85.4	13.1 / 86.2
Clindamycin	>2	>2	≤0.25 – >2	48.9 / 51.1	48.8 / 51.1
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	82.4 / 17.3	80.3 / 17.6
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	92.0 / 8.0	92.0 / 8.0
Daptomycin	0.25	0.5	0.12 – 2	99.8 / -	99.8 / 0.2
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin-R-MRSA (169)					
JNJ-Q2	0.25	0.5	0.06 – 2	- / -	- / -
Moxifloxacin	4	8	1 – >8	0.0 / 93.5	0.0 / 93.5
Levofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Ciprofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
Ceftriaxone	4	4	2 – 8	93.5 / 0.0	100.0 / 0.0
Erythromycin	>4	>4	≤0.25 – >4	33.7 / 63.9	33.7 / 64.5
Clindamycin	≤0.25	>2	≤0.25 – >2	72.2 / 27.8	71.6 / 27.8
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	87.0 / 11.8	85.8 / 13.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	96.4 / 3.6	96.4 / 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
Levofloxacin-S[f]-MRSA (417)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.06	- / -	- / -
Moxifloxacin	0.03	0.12	≤0.008 – 0.5	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	0.25	1	0.06 – 4	96.6 / 0.2	96.6 / 3.4
Erythromycin	>4	>4	≤0.25 – >4	35.7 / 64.0	35.7 / 64.3
Clindamycin	≤0.25	0.5	≤0.25 – >2	90.2 / 9.8	89.9 / 9.8
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	8	≤0.25 – >8	89.4 / 8.6	88.5 / 10.8
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	99.0 / 1.0	99.0 / 0.2
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
Levofloxacin-S-MSSA (1,225)					
JNJ-Q2	0.008	0.008	≤0.004 – 0.25	- / -	- / -
Moxifloxacin	0.06	0.06	≤0.008 – 8	99.7 / 0.3	99.7 / 0.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	0.25	0.5	≤0.03 – 4	98.4 / 0.2	98.4 / 1.6
Ceftriaxone	4	4	0.5 – >8	98.5 / 0.1	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	78.4 / 19.8	78.4 / 20.7
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.9 / 4.1	95.3 / 4.1
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	93.6 / 5.3	93.0 / 6.9
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	99.3 / 0.7	99.3 / 0.5
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin-I[h]-*S. aureus* (29)					
JNJ-Q2	0.12	0.12	≤0.004 – 0.25	- / -	- / -
Moxifloxacin	1	2	0.03 – 2	13.8 / 27.6	13.8 / 27.6
Levofloxacin	2	2	2	0.0 / 0.0	0.0 / 0.0
Ciprofloxacin	>4	>4	0.12 – >4	10.3 / 86.2	10.3 / 89.7
Erythromycin	>4	>4	≤0.25 – >4	24.1 / 72.4	24.1 / 72.4
Clindamycin	≤0.25	>2	≤0.25 – >2	79.3 / 17.2	75.9 / 20.7
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	86.2 / 13.8	86.2 / 13.8
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	96.6 / 3.4	96.6 / 3.4
Daptomycin	0.25	0.25	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
Streptococcus pyogenes (278)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.06	- / -	- / -
Moxifloxacin	0.12	0.25	0.06 – 4	- / -	99.3 / 0.4
Levofloxacin	≤0.5	1	≤0.5 – >4	98.9 / 0.4	91.4 / 1.1
Penicillin	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	2	≤0.25 – >4	88.5 / 11.5	88.5 / 11.5
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.4 / 7.6	92.4 / 7.6
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	- / -	97.1 / 2.5
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Streptococcus agalactiae (161)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.25	- / -	- / -
Moxifloxacin	0.12	0.25	0.06 – 8	- / -	99.4 / 0.6
Levofloxacin	≤0.5	1	≤0.5 – >4	99.4 / 0.6	97.5 / 0.6
Penicillin	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	60.2 / 39.1	60.2 / 39.1
Clindamycin	≤0.25	>2	≤0.25 – >2	75.8 / 24.2	75.8 / 24.2
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	- / -	99.4 / 0.6
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Other β-haemolytic streptococci[h] (130)					
JNJ-Q2	0.008	0.015	≤0.004 – 0.06	- / -	- / -
Moxifloxacin	0.12	0.25	≤0.004 – 2	- / -	99.2 / 0.8
Levofloxacin	≤0.5	1	≤0.5 – >4	98.5 / 0.8	97.7 / 1.5
Penicillin	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	76.2 / 23.8	76.2 / 23.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.5 / 8.5	91.5 / 8.5
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	- / -	95.4 / 4.6
Daptomycin	≤0.06	0.12	≤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. FQ = fluoroquinolone, S = susceptible, R = resistant, MSSA = methicillin-susceptible *S. aureus*, MRSA = methicillin-resistant *S. aureus*, TMP/SMX = Trimethoprim/sulfamethoxazole.
b. Criteria as published by the CLSI (CLSI, 2011) and EUCAST (EUCAST, 2011).
c. S = susceptible.
d. R = resistant.
e. No breakpoint has been established.
f. US-FDA breakpoints were applied [Rocephin Package Insert, 2010].
g. I = intermediate.
h. Includes: *Streptococcus dysgalactiae* (12 isolates), *Streptococcus equisimilis* (1 isolate), Group C *Streptococcus* (39 isolates), Group F *Streptococcus* (3 isolates), and Group G *Streptococcus* (75 isolates).

CONCLUSIONS

- In this 2010 surveillance study of contemporary and geographically diverse isolates, JNJ-Q2 exhibited good activity overall ($MIC_{50/90}$, 0.015/0.5 µg/ml) against 3,081 *S. aureus* with >95% of the isolates inhibited at a MIC of ≤0.5 µg/ml.
- The potency of JNJ-Q2 was observed to be less in levofloxacin-resistant strains compared to levofloxacin-susceptible strains, however, with an MIC_{90} of 0.5 µg/ml (both MRSA and MSSA), JNJ-Q2 retained good potency against the levofloxacin-resistant subpopulation.
- JNJ-Q2 demonstrated excellent activity (MIC_{90}, 0.015 µg/ml) against 569 isolates of beta-haemolytic streptococci (including 278 *S. pyogenes* and 161 *S. agalactiae*).
- These favorable results support the further clinical development of JNJ-Q2 to treat ABSSSI including those caused by levofloxacin-resistant MRSA.

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