Activity of JNJ-Q2, a New Fluoroquinolone, Tested Against Contemporary Pathogens Isolated from Patients with Community-Acquired Bacterial Pneumonia

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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 treatment of community-acquired bacterial pneumonia (CABP).

Methods: This study included 3,757 contemporary (2010) respiratory pathogens from patients with CABP (89 centers in 27 countries). *S. pneumoniae* (SPN), *H. influenzae* (HI) and *M. catarrhalis* (MCAT) were susceptibility (S) tested by the CLSI broth microdilution method. S rates for comparator agents, including FQs, were determined using CLSI and EUCAST breakpoints.

Results: JNJ-Q2 was highly active against all three species inhibiting 96.9% of all 3,757 isolates at a MIC of ≤0.015 µg/ml. SPN resistances to penicillin, azithromycin, levofloxacin (LEV) and moxifloxacin (MOX) were 23.3, 40.3, 1.1 and 0.7%, respectively using CLSI criteria. Using MIC_{90}, JNJ-Q2 ($MIC_{50/90}$, 0.008/0.015 µg/ml) demonstrated 16-fold greater activity for SPN compared to MOX ($MIC_{50/90}$, 0.12/0.25 µg/ml), 64-fold greater activity than LEV ($MIC_{50/90}$, 1/1 µg/ml) and 128-fold greater activity than ciprofloxacin (CIP; $MIC_{50/90}$, 1/2 µg/ml). HI isolates were 21.9% ampicillin-resistant (CLSI). JNJ-Q2 ($MIC_{50/90}$, ≤0.004/0.015 µg/ml) was at least two-fold more active than MOX ($MIC_{50/90}$, 0.015/0.03 µg/ml) against HI. JNJ-Q2 ($MIC_{50/90}$, 0.015/0.015 µg/ml) was four-fold more active than MOX ($MIC_{50/90}$, 0.06/0.06 µg/ml) against MCAT.

Conclusions: JNJ-Q2 demonstrated very potent activity against these three common bacterial respiratory pathogens isolated from patients with CABP. JNJ-Q2 demonstrated greater activity compared to CIP, LEV and MOX against these species, including strains resistant to currently utilized FQs.

INTRODUCTION

JNJ-Q2 is a novel fluorinated 4-quinolone with potent activity against Gram-positive (including MRSA) and Gram-negative pathogens and has been shown to have balanced potency against both DNA gyrase and topoisomerase IV. JNJ-Q2 is in clinical development for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections.

The aims of this study were to determine comparative in vitro activity of JNJ-Q2 tested against clinical isolates collected in 2010 relevant to CABP, 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-Western Pacific 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 (MHB) for *Moraxella catarrhalis*, MHB with 2-5% lysed horse blood supplement for *Streptococcus pneumoniae* and Haemophilus Test Medium for *Haemophilus influenzae*. For all other comparator agents, the dry-form reference broth microdilution method was applied using trays 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 accurate test performances (CLSI, 2011). QC strains were tested daily using *H. influenzae* ATCC 49247 and 49766, and *S. pneumoniae* ATCC 49619.

Bacterial isolates. A total of 3,757 isolates obtained in the 2010 surveillance program. The dominant pathogen in this study collection was *S. pneumoniae* (2,137 strains), followed by *H. influenzae* (1,176 strains) and *M. catarrhalis* (444 strains). Isolates included a global collection of strains that were obtained from 89 medical centers in 27 countries in North America, Latin America, Europe and the Asia-West Pacific region. The distribution of medical centers by geographical region and country (number of centers) is shown in Table 1. Identification of bacterial species was confirmed at the reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) using colony morphology and growth patterns based upon appropriate media and incubation conditions as well as biochemical reactions and the bile solubility test (*S. pneumoniae*). β-lactamase testing was performed for all *H. influenzae* and *M. catarrhalis* isolates.

RESULTS

The spectrum of activity and potencies of JNJ-Q2 and comparator agents tested against 3,757 clinical isolates are presented in Tables 2, 3 and 4.

Activity of JNJ-Q2 against *S. pneumoniae.*

- JNJ-Q2 was the most active agent tested against *S. pneumoniae*, including strains that were multidrug resistant (MDR), defined as resistance to levofloxacin, ciprofloxacin and ≥two additional antimicrobial classes using both the CLSI and EUCAST breakpoint criteria (Tables 3 and 4).
- JNJ-Q2 had excellent activity ($MIC_{50/90}$, 0.008/0.015 µg/ml) against all 2,137 *S. pneumoniae* isolates with all but one isolate being inhibited at a MIC value of ≤0.25 µg/ml (Table 2). This single isolate was collected from Israel and had a reproducible JNJ-Q2 MIC value of 1 µg/ml with significantly elevated moxifloxacin (>8 µg/ml), levofloxacin (>4 µg/ml), and ciprofloxacin (>4 µg/ml) MIC values when compared to the wild-type population of this species.
- The JNJ-Q2 MIC_{90} value (0.015 µg/ml) was 128-fold lower than ciprofloxacin (2 µg/ml), 64-fold lower than levofloxacin (1 µg/ml) and 16-fold lower than moxifloxacin (0.25 µg/ml). These values were identical across all four geographic regions.
- Susceptibility to orally administered penicillin V was only 60.3% overall using both CLSI and EUCAST breakpoint criteria (Table 3), with resistance ranging from 17.3% in Europe to 39.4% in Asia-Western Pacific. Amoxicillin/clavulanate resistance was highest in Asia-Western Pacific (17.6%) and North America (12.0%) and was lower in Europe (3.4%) and Latin America (5.7%). Azithromycin, tetracycline, and trimethoprim/sulfamethoxazole resistance rates were high overall at 40.3, 32.7, and 27.5%, respectively (Table 3). Higher rates were observed in countries in the Asia-Western Pacific region (71.9, 72.2, and 52.0%, respectively).

Activity of JNJ-Q2 against *H. influenzae.*

- JNJ-Q2 was very active against *H. influenzae* isolates (MIC_{90}, 0.015 µg/ml) with all isolates being inhibited at a MIC of ≤1 µg/ml (Table 2). Levofloxacin, moxifloxacin and ciprofloxacin also demonstrated excellent activity against most isolates (>99.6% susceptibility).
- JNJ-Q2 was two-fold more active compared to moxifloxacin (MIC_{90}, 0.03 µg/ml); a comparison of activity with JNJ-Q2 was not possible for levofloxacin or ciprofloxacin because the MIC_{90} values were below the range tested.

Activity of JNJ-Q2 against *M. catarrhalis.*

- Against the collection of *M. catarrhalis* isolates, JNJ-Q2 demonstrated similar potency compared to the two other more commonly isolated community-acquired respiratory pathogens ($MIC_{50/90}$, 0.015 µg/ml) with inhibition of all isolates observed at a MIC value of ≤0.06 µg/ml (Table 2).
- JNJ-Q2, (MIC_{90}, 0.015 µg/ml) was four-fold more potent compared to moxifloxacin (MIC_{90}, 0.06 µg/ml).

Table 1. Distribution of medical centers by geographic region and country (number of centers).

Asia-Western Pacific (24)	Europe (26)		Latin America (12)	North America (27)
Australia (4)	Belgium (1)	Spain (3)	Argentina (2)	USA (27)
Korea (1)	France (5)	Sweden (2)	Brazil (4)	
Malaysia (1)	Germany (3)	Turkey (2)	Chile (2)	
New Zealand (2)	Greece (1)	UK (2)	Colombia (1)	
China and Hong Kong (11)	Ireland (2)		Mexico (3)	
Singapore (1)	Israel (1)			
South Africa (1)	Italy (2)			
Taiwan (3)	Poland (1)			
	Portugal (1)			

Table 2. MIC distribution of JNJ-Q2 compared to three comparator fluoroquinolones tested against the most common bacterial species associated with CABP.

Species (no. tested) /antimicrobial	No. (cumulative %) of isolates inhibited at antimicrobial MIC (µg/ml):												
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
S. pneumoniae (2,137)															
JNJ-Q2	81 (3.8)	1,758 (86.1)	266 (98.5)	7 (98.8)	17 (99.6)	5 (99.9)	2 (>99.9)	0 (>99.9)	1 (100.0)	-[b]	-	-	-	0.008	0.015
Moxifloxacin	NT[b]	4 (0.2)	1 (0.2)	9 (0.7)	199 (10.0)	1,593 (84.5)	304 (98.7)	5 (99.0)	1 (99.0)	5 (99.3)	11 (99.8)	3 (99.9)	2 (100.0)	0.12	0.25
Levofloxacin	NT	NT	NT	NT	NT	NT	NT	506 (23.7)	1,581 (97.7)	26 (98.9)	1 (98.9)	NT	NT	1	1
Ciprofloxacin	NT	NT	NT	3 (0.1)	1 (0.2)	0 (0.2)	14 (0.8)	340 (16.8)	1,338 (79.4)	380 (97.2)	33 (98.7)	NT	NT	1	2
H. influenzae (1,176)															
JNJ-Q2	655 (55.7)	340 (84.6)	106 (93.6)	35 (96.6)	22 (98.5)	13 (99.6)	1 (99.7)	3 (99.9)	1 (100.0)	-	NT	NT	NT	≤0.004	0.015
Moxifloxacin	NT	51 (4.3)	644 (59.1)	372 (90.7)	51 (95.1)	25 (97.2)	12 (98.2)	12 (99.2)	4 (99.6)	5 (100.0)	NT	NT	NT	0.015	0.03
Levofloxacin	NT	NT	NT	NT	NT	NT	NT	1,167 (99.2)	4 (99.6)	1 (99.7)	1 (99.7)	NT	NT	≤0.5	≤0.5
Ciprofloxacin	NT	NT	NT	1,116 (94.9)	9 (95.7)	21 (97.5)	9 (98.2)	3 (98.5)	13 (99.6)	1 (99.7)	0 (99.7)	NT	NT	≤0.03	≤0.03
M. catarrhalis (444)															
JNJ-Q2	5 (1.1)	152 (35.4)	279 (98.2)	6 (99.6)	2 (100.0)	-	-	-	-	-	-	-	-	0.015	0.015
Moxifloxacin	NT	2 (0.5)	1 (0.7)	33 (8.1)	396 (97.3)	10 (99.6)	1 (99.8)	1 (100.0)	-	-	NT	NT	NT	0.06	0.06
Levofloxacin	NT	NT	NT	NT	NT	NT	NT	442 (99.6)	2 (100.0)	-	-	NT	NT	≤0.5	≤0.5
Ciprofloxacin	NT	NT	NT	421 (94.8)	20 (99.3)	0 (99.3)	1 (99.6)	2 (100.0)	-	-	-	NT	NT	≤0.03	≤0.03

a. No values detected.
b. NT = Values not tested.

Table 3. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials against 3,757 CABP pathogens.

Organism (no. tested)/ Antimicrobial agent	MIC in µg/ml			CLSI[a] %S / %R	EUCAST[a] %S / %R
	MIC_{50}	MIC_{90}	Range		
S. pneumoniae (2,137)					
JNJ-Q2	0.008	0.015	≤0.004 – 1	- / -[b]	- / -
Moxifloxacin	0.12	0.25	0.008 – >8	99.0 / 0.7	99.0 / 1.0
Levofloxacin	1	1	≤0.5 – >4	98.9 / 1.1	98.9 / 1.1
Ciprofloxacin	1	2	≤0.03 – >4	- / -	0.2 / 2.9
Penicillin[c]	≤0.03	4	≤0.03 – >4	87.8 / 0.5	- / -
Penicillin[d]	≤0.03	4	≤0.03 – >4	60.3 / 23.3	60.3 / 12.2
Amoxicillin/clavulanate	≤1	4	≤1 – >8	86.6 / 9.8	- / -
Ceftriaxone	≤0.06	1	≤0.06 – 8	90.0 / 2.2	75.9 / 2.2
Cefuroxime	≤0.12	8	≤0.12 – >16	71.9 / 25.6	70.7 / 28.1
Azithromycin	≤0.25	>4	≤0.25 – >4	59.0 / 40.3	58.1 / 41.0
Clindamycin	≤0.25	>1	≤0.25 – >1	72.0 / 27.5	72.5 / 27.5
Tetracycline	0.5	>8	≤0.25 – >8	66.8 / 32.7	66.4 / 33.2
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	64.1 / 27.5	69.3 / 27.5
Linezolid	1	1	≤0.12 – 4	>99.9 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
H. influenzae (1,176)					
JNJ-Q2	≤0.004	0.015	≤0.004 – 1	- / -	- / -
Moxifloxacin	0.015	0.03	≤0.008 – >2	99.6 / -	99.2 / 0.8
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.7 / -	99.6 / 0.4
Ciprofloxacin	≤0.03	≤0.03	≤0.03 – >4	99.6 / -	98.5 / 1.5
Ampicillin	≤1	>8	≤1 – >8	76.7 / 21.9	76.7 / 23.3
Amoxicillin/clavulanate	≤1	2	≤1 – 8	99.9 / 0.1	89.0 / 11.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / -	99.8 / 0.2
Cefuroxime	1	2	≤0.12 – >16	98.8 / 0.2	77.6 / 5.7
Azithromycin	1	2	≤0.25 – >4	98.6 / -	0.2 / 1.4
Clarithromycin	8	16	≤0.25 – >32	81.4 / 2.3	1.1 / 0.8
Tetracycline	0.5	1	≤0.25 – >8	95.2 / 4.3	95.0 / 4.8
Tigecycline[e]	0.25	0.5	0.03 – 2	88.2 / -	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	65.9 / 30.9	65.9 / 32.9
M. catarrhalis (444)					
JNJ-Q2	0.015	0.015	≤0.004 – 0.06	- / -	- / -
Moxifloxacin	0.06	0.06	≤0.008 – 0.5	- / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0
Ciprofloxacin	≤0.03	≤0.03	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Ampicillin	≤1	4	≤1 – >8	- / -	61.3 / 38.7
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	99.8 / 0.2
Ceftriaxone	0.25	0.5	≤0.06 – 2	100.0 / -	98.6 / 0.0
Cefuroxime	1	2	≤0.12 – 8	99.8 / 0.0	76.1 / 2.0
Imipenem	≤0.12	≤0.12	≤0.12 – 0.25	- / -	100.0 / 0.0
Azithromycin	≤0.25	≤0.25	≤0.25 – >4	98.9 / -	99.5 / 0.5
Clindamycin	>1	>1	0.5 – >1	1.6 / 4.5	- / -
Tetracycline	≤0.25	0.5	≤0.25 – 8	98.9 / 1.1	98.6 / 1.1
Tigecycline[e]	0.06	0.25	≤0.03 – 0.5	- / -	- / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 4	95.0 / 1.4	95.0 / 2.3

a. Criteria as published by the CLSI (2011) and EUCAST (2011).
b. A dash indicates no breakpoint criteria have currently been established.
c. Criteria as published by the CLSI (2011) for penicillin parenteral (non-meningitis).
d. Criteria as published by the CLSI (2011) for penicillin (oral penicillin V).
e. US-FDA breakpoints were applied (Tygacil Product Insert, 2005).

Table 4. Activity of JNJ-Q2 and selected comparator antimicrobial agents when tested against 23 levofloxacin-resistant isolates of *S. pneumoniae*, including multidrug-resistant strains associated with community-acquired bacterial pneumonia[a].

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
JNJ-Q2	0.06	0.25	0.015 – 1	- / -[c]	- / -
Moxifloxacin	4	8	0.25 – >8	8.7 / 69.6	4.4 / 95.6
Levofloxacin	>4	>4	>4	0.0 / 100.0	0.0 / 100.0
Ciprofloxacin	>4	>4	>4	- / -	0.0 / 100.0
Penicillin[d]	0.25	4	≤0.03 - 4	78.3 / 0.0	- / -
Penicillin[e]	0.25	4	≤0.03 - 4	47.8 / 34.8	47.8 / 0.0
Cefuroxime[f]	0.5	16	≤0.12 - >16	52.2 / 43.5	52.2 / 43.5
Cefuroxime[g]	0.5	16	≤0.12 - >16	56.5 / 39.1	43.5 / 47.8
Azithromycin	>4	>4	≤0.25 - >4	21.7 / 78.3	21.7 / 78.3
Tetracycline	>8	>8	≤0.25 - >8	34.8 / 65.2	34.8 / 65.2
Trimethoprim/sulfamethoxazole	4	>4	≤0.5 - >4	30.4 / 65.2	34.8 / 65.2

a. Multidrug resistance was defined as resistance to levofloxacin, ciprofloxacin and ≥two additional antimicrobial classes.
b. Criteria as published by the CLSI (2011) and EUCAST (2011).
c. A dash indicates no breakpoint criteria have currently been established.
d. Criteria as published by the CLSI (2011) for penicillin parenteral (non-meningitis).
e. Criteria as published by the CLSI (2011) for penicillin (oral, penicillin V).
f. Criteria as published by the CLSI (2011) and EUCAST (2011) for parenteral cefuroxime.
g. Criteria as published by the CLSI (2011) and EUCAST (2011) for oral cefuroxime (cefuroxime axetil).

CONCLUSIONS

- JNJ-Q2 demonstrated excellent activity when tested against this global collection of contemporary CABP pathogens, including the most prevalent pathogen *S. pneumoniae.* Almost all isolates (99.9%) of pneumococci were inhibited at a MIC of ≤0.12 µg/ml.
- JNJ-Q2 demonstrated greater activity compared to ciprofloxacin, levofloxacin and moxifloxacin against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, including strains resistant to currently utilized FQs.

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