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In Vitro Activity of Lactone Ketolide WCK 4873 When Tested Against Contemporary Community-Acquired Bacterial Pneumonia Pathogens from a Global Surveillance Program

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Abstract

Background: WCK 4873 is a novel antimicrobial agent of the lactone ketolide class currently in clinical development for the treatment of community acquired bacterial pneumonia (CABP). It has completed SAD and MAD Phase 1 studies in Europe and intra-pulmonary pharmacokinetic study in US. WCK 4873 was awarded QIDP status in 2015. In this study, WCK 4873 was tested against contemporary CABP clinical isolates collected in medical centers worldwide as part of the 2014 SENTRY Antimicrobial Surveillance Program.

Methods: A total of 1,512 contemporary (2014) CABP clinical isolates from the United States, 1,505 from Europe, 558 from Asia-Pacific, and 558 from Latin America, as part of the SENTRY Program, were susceptibility (S) tested against WCK 4873 and multiple comparator agents by reference broth microdilution methods and interpretive criteria.

Results: WCK 4873 was very active ($MIC_{50/90}$, 0.015/0.06 µg/mL) against 1,911 *Streptococcus pneumoniae* (SPN) and inhibited all strains at MIC values ≤0.25 µg/mL. Telithromycin (TEL) S (CLSI) was 99.9% against SPN, and WCK4873 was up to eight-fold more potent than TEL ($MIC_{50/90}$, 0.015/0.5 µg/mL). Overall, 37.9% of SPN were resistant (R) to erythromycin (ERY) and 19.7% were R to clindamycin (CLI). WCK 4873 retained good activity against ERY-R/CLI-S strains ($MIC_{50/90}$, 0.03/0.06 µg/mL) and ERY-R/CLI-R strains ($MIC_{50/90}$, 0.03/0.12 µg/mL). Against 716 *Staphylococcus aureus* (SA), 88.5% of isolates were inhibited by WCK 4873 at the CLSI TEL S breakpoint of ≤1 µg/mL ($MIC_{50/90}$, 0.06/>2 µg/mL). MIC_{90} values for WCK 4873 were elevated for methicillin-resistant (MR) compared to methicillin-susceptible (MS) SA (MRSA, $MIC_{50/90}$, 0.06/>2 µg/mL; MSSA, $MIC_{50/90}$, 0.06/0.06 µg/mL). WCK 4873 ($MIC_{50/90}$, 4/4 µg/mL) demonstrated similar activity to TEL ($MIC_{50/90}$, 2/4 µg/mL; 97.9% S, CLSI) against 1,002 *Haemophilus influenzae* (HI) isolates. WCK 4873 ($MIC_{50/90}$, 0.12/0.25 µg/mL) exhibited similar activity to TEL ($MIC_{50/90}$, 0.12/0.12 µg/mL; 99.6% S, EUCAST) against 504 *M. catarrhalis* (MC) isolates.

Conclusions: WCK 4873 showed a broad range of potent *in vitro* activity against contemporary (2014) global CABP pathogens (SPN, SA, HI and MC). These results support the continued clinical development of WCK 4873 for CAPB.

Introduction

WCK 4873 (Nafithromycin) is a novel antimicrobial agent of the lactone ketolide class currently in clinical development for the treatment of community acquired bacterial pneumonia (CABP). It has completed single ascending dose (SAD) and multiple ascending dose (MAD) Phase 1 studies in Europe and intra-pulmonary pharmacokinetic study in the United States (USA). WCK 4873 was awarded Qualified Infectious Disease Product (QIDP) status in 2015 by the USA Food and Drug Administration.

In this study, we report WCK 4873 and comparator antimicrobial agent activities, measured by reference Clinical and Laboratory Standards Institute (CLSI) methods, tested against a large collection (4,133 isolates) of contemporary CABP clinical isolates collected in medical centers worldwide as part of the 2014 SENTRY Antimicrobial Surveillance Program.

Methods

Organism collection and specimen source: A total of 4,133 non-duplicate isolates were collected prospectively during 2014 from 147 medical institutions located in USA (68), EU (42), LA (20) and APAC (17). Only clinically significant isolates were included in the study (one per patient episode). The number of species tested by geographical region is shown in **Table 1**. Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) when following manufacturer instructions.

Table 1. Distribution of species tested by geographical region.

Organism	USA	EU	APAC	LA	Total
S. aureus	205	203	154	154	716
S. pneumoniae	712	698	251	250	1,911
H. influenzae	398	402	102	100	1,002
M. catarrhalis	197	202	51	54	504
Total	1,512	1,505	558	558	4,133

Susceptibility testing: MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods as described in CLSI document M07-A10 (2015). For WCK 4873 and telithromycin, MIC results were obtained using validated broth microdilution panels produced by JMI Laboratories (North Liberty, Iowa). For other antimicrobial agents, panels were used that were manufactured by ThermoFisher Scientific (formerly TREK Diagnostics Systems/Sensititre; Cleveland, Ohio, USA). Validation of the MIC values was performed by concurrent testing of the following quality control (QC) reference strains: *Streptococcus pneumoniae* American Type Culture Collection (ATCC) 49619, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213, and *Haemophilus influenzae* ATCC 49247. All WCK 4873 and telithromycin MIC values were within the QC ranges recommended by CLSI. MIC interpretations were based on CLSI and EUCAST breakpoint criteria.

Results

S. pneumoniae

- WCK 4873 was very active ($MIC_{50/90}$, 0.015/0.06 µg/mL) against 1,911 *S. pneumoniae* isolates with all isolates inhibited at MIC values of 0.25 µg/mL or less (**Table 2**). Similar $MIC_{50/90}$ values were observed in each of the four geographic regions sampled (data not shown).
- Overall, telithromycin susceptibility was 99.9/89.3% (CLSI/EUCAST criteria; **Table 3**). Using MIC_{50} results, WCK 4873 had an identical potency (0.015 µg/mL) to telithromycin, however using the MIC_{90}, WCK 4873 (0.06 µg/mL) was eight-fold more potent than telithromycin (0.5 µg/mL; **Table 3**).
- WCK 4873 ($MIC_{50/90}$, 0.015/0.06 µg/mL), telithromycin ($MIC_{50/90}$, 0.015/0.5 µg/mL; 99.9% susceptible), vancomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/1 µg/mL; 100.0% susceptible) were the most active antimicrobial agents tested against *S. pneumoniae* (**Table 3**).
- Using CLSI breakpoints, resistance to oral penicillin V was 16.7% overall (**Table 3**); Erythromycin, tetracycline, and trimethoprim-sulfamethoxazole resistance rates were high overall (37.9, 28.4, and 24.5%, respectively; **Table 3**).

H. influenzae

- WCK 4873 demonstrated moderate activity ($MIC_{50/90}$, 4/4 µg/mL) against *H. influenzae* (**Table 2**). $MIC_{50/90}$ results were similar (4/4 µg/mL) for each of the four geographical regions (data not shown and regardless of β-lactamase production among tested *H. influenzae* (**Table 2**). WCK 4873 activity ($MIC_{50/90}$, 4/4 µg/mL) showed equal or two-fold less potency than telithromycin ($MIC_{50/90}$, 2/4 µg/mL; **Table 3**) against *H. influenzae*.

M. catarrhalis

- WCK 4873 exhibited good activity ($MIC_{50/90}$, 0.12/0.25 µg/mL) against *M. catarrhalis* isolates (**Table 2**). $MIC_{50/90}$ results for WCK 4873 were similar (0.12-0.25/0.25 µg/mL) for each of the four geographical regions (data not shown). WCK 4873 ($MIC_{50/90}$, 0.12/0.25 µg/mL) demonstrated a potency comparable to telithromycin ($MIC_{50/90}$, 0.12/0.12 µg/mL; **Table 3**).

S. aureus

- WCK 4873 demonstrated bimodal activity ($MIC_{50/90}$, 0.06/>2 µg/mL) distributions against 716 *S. aureus* (**Table 2**). Regardless of methicillin resistance (MRSA) profile, WCK 4873 showed limited activity (MIC >2 µg/mL) against most (80/83) telithromycin-resistant (n=80) and telithromycin-intermediate (n=3) strains that were also clindamycin-resistant, i.e. constitutively resistant to macrolides (**Table 2**). Conversely, WCK 4873 activity was high ($MIC_{50/90}$, 0.06/0.06 µg/mL) against telithromycin-susceptible strains (**Table 2**), as well as against erythromycin-resistant strains that were susceptible to clindamycin (n=85) and strains with inducible (D-test positive, n=110) clindamycin resistance (data not shown).
- The activity of WCK 4873 against *S.aureus* varied by geographical region with activity being greater in EU ($MIC_{50/90}$, 0.06/0.06 µg/mL, data not shown) and APAC ($MIC_{50/90}$, 0.06/0.12 µg/mL, data not shown) compared to USA ($MIC_{50/90}$, 0.06/>2 µg/mL, data not shown) and LA ($MIC_{50/90}$, 0.06/>2 µg/mL, data not shown). However, the overall MIC distribution was similar (bimodal) in each of these regions and the lower MIC_{90} values observed in EU and APAC were reflective of the lower rates of telithromycin resistance in these regions; 6.9% and 8.4%, respectively, when compared to 12.2% in USA and 18.2% in LA (data not shown).
- Against all 716 *S.aureus* isolates, WCK 4873 ($MIC_{50/90}$, 0.06/>2 µg/mL) demonstrated a potency most similar to telithromycin ($MIC_{50/90}$, 0.06/>2 µg/mL, 88.4% susceptible; **Table 3**). Overall, resistance rates were higher for oxacillin (MRSA, 34.6%), erythromycin (33.1-37.2% [CLSI/EUCAST]), ciprofloxacin (25.1-27.1% [CLSI/EUCAST]), and clindamycin (11.9%; **Table 3**). No resistance was observed when *S. aureus* were tested against linezolid and vancomycin (**Table 3**); and susceptibility to daptomycin was 100.0% (data not shown).

Table 2. Cumulative frequency distributions of WCK 4873 MIC results when tested against 4,133 bacterial isolates from patients with community-acquired pneumonia.

Organism/phenotype	No. of isolates	No. of isolates (cumulative %) inhibited at WCK 4873 MIC (µg/mL) of:													
		≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>*	MIC_{50}	MIC_{90}
S. pneumoniae	1911	1 (0.1)	20 (1.1)	396 (21.8)	1014 (74.9)	224 (86.6)	162 (95.1)	88 (99.7)	6 (100.0)	--	--	--	--	--	--	--	0.015	0.06
H. influenzae	1002	--	--	--	--	--	--	2 (0.2)	4 (0.4)	6 (1.0)	42 (5.2)	428 (47.9)	455 (93.3)	56 (98.9)	5 (99.4)	6 (100.0)	4	4
β-lactamase-positive	210	--	--	--	--	--	--	--	--	5 (2.4)	90 (45.2)	99 (92.4)	14 (99.0)	1 (99.5)	1 (100.0)	4	4	
β-lactamase-negative	792	--	--	--	--	--	--	2 (0.3)	2 (0.5)	6 (1.3)	37 (5.9)	338 (48.6)	356 (93.6)	42 (98.9)	4 (99.4)	5 (100.0)	4	4
M. catarrhalis	504	--	1 (0.2)	6 (1.4)	1 (1.6)	6 (2.8)	58 (14.3)	265 (66.9)	159 (98.4)	8 (100.0)	--	--	--	--	--	--	0.12	0.25
S. aureus	716	--	--	--	1 (0.1)	39 (5.6)	562 (84.1)	27 (87.8)	3 (88.3)	2 (88.5)	0 (88.5)	2 (88.8)	--	--	--	80 (100.0)	0.06	>2
MSSA	468	--	--	--	--	28 (6.0)	409 (93.4)	20 (97.6)	1 (97.9)	2 (98.3)	0 (98.3)	2 (98.7)	--	--	--	6 (100.0)	0.06	0.06
MRSA	248	--	--	--	1 (0.4)	11 (4.8)	153 (66.5)	7 (69.4)	2 (70.2)	0 (70.2)	0 (70.2)	0 (70.2)	--	--	--	74 (100.0)	0.06	>2
Telithromycin-S (MIC, ≤1 µg/mL)	633	--	--	--	1 (0.2)	39 (6.3)	562 (95.1)	27 (99.4)	3 (99.8)	1 (100.0)	--	--	--	--	--	--	0.06	0.06
Telithromycin-I (MIC, 2 µg/mL)	3	--	--	--	--	--	--	--	--	1 (33.3)	0 (33.3)	0 (33.3)	--	--	--	2 (100.0)	>2	--
Telithromycin-R (MIC, ≥4 µg/mL)	80	--	--	--	--	--	--	--	--	--	--	2 (2.5)	--	--	--	78 (100.0)	>2	>2

a. Greater than the highest dilution tested, which was 16 µg/mL for *H. influenzae* and 2 µg/mL for all other organisms.
Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; S; susceptible; I = intermediate; R = resistant; ERY = erythromycin; CLI = clindamycin; PEN = penicillin; NS, non-susceptible.

Table 3. Activity of WCK 4873 and comparators when tested against bacterial pathogens recovered as part of the global surveillance program for 2014.

Organism/agent	MIC (µg/mL)		Range	CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}		%S	%I	%R	%S	%I	%R
***S. pneumoniae* (1,911 isolates)**									
WCK 4873	0.015	0.06	≤0.002 — 0.25	-[b]	-	-	-	-	-
Telithromycin	0.015	0.5	≤0.002 — 2	99.9	0.1	0.0	89.3	8.9	1.8
Erythromycin	≤0.12	>16	≤0.12 — >16	61.4	0.7	37.9	61.4	0.7	37.9
Clindamycin	≤0.25	>2	≤0.25 — >2	79.4	0.9	19.7	80.3	-	19.7
Amoxicillin-clavulanate	≤1	4	≤1 — >8	87.6	4.0	8.4[c]	-	-	-
Penicillin	≤0.06	2	≤0.06 — >8	59.9	23.3	16.7[d]	59.9	-	40.1[e]
				59.9	-	40.1[e]	59.9	32.3	7.8[f]
				92.2	7.0	0.8[f]	-	-	-
Ceftriaxone	≤0.06	1	≤0.06 — >8	78.6	12.0	9.3[g]	78.6	19.9	1.4
				90.7	7.9	1.4[f]	-	-	-
Linezolid	1	1	≤0.12 — 2	100.0	-	-	100.0	0.0	0.0
Tetracycline	≤0.5	>8	≤0.5 — >8	71.2	0.4	28.4	71.2	0.4	28.4
TMP-SMX	≤0.5	>4	≤0.5 — >4	64.9	10.6	24.5	71.4	4.1	24.5
Vancomycin	0.25	0.5	≤0.12 — 1	100.0	-	-	100.0	-	0.0
***H. influenzae* (1,002 isolates)**									
WCK 4873	4	4	0.12 — >16	-	-	-	-	-	-
Telithromycin	2	4	0.12 — >16	97.9	1.2	0.9	0.2	98.9	0.9
Azithromycin	0.5	1	≤0.03 — >4	99.3	-	-	2.7	96.6	0.7
Clarithromycin	4	8	≤0.12 — >16	95.7	3.0	1.3	2.8	97.2	0.0
Amoxicillin-clavulanate	≤1	2	≤1 — 8	96.6	-	0.4	97.7	-	2.3
Ampicillin	≤0.25	>8	≤0.25 — >8	76.9	2.0	21.1	76.9	-	23.1[b]
Ceftriaxone	≤0.06	≤0.06	≤0.06 — 0.25	100.0	-	-	99.6	-	0.4
Ciprofloxacin	≤0.03	≤0.03	≤0.03 — >4	99.6	-	-	99.1	-	0.9
Tetracycline	0.5	0.5	≤0.12 — >16	98.4	0.1	1.5	98.3	0.1	1.6
TMP-SMX	≤0.5	>4	≤0.5 — >4	66.7	6.1	27.2	66.7	1.7	31.6
***M. catarrhalis* (504 isolates)**									
WCK 4873	0.12	0.25	0.004 — 0.5	-	-	-	-	-	-
Telithromycin	0.12	0.12	0.004 — 0.5	-	-	-	99.6	0.4	0.0
Azithromycin	≤0.03	0.06	≤0.03 — 0.12	100.0	-	-[b]	100.0	0.0	0.0
Clarithromycin	≤0.12	≤0.12	≤0.12 — 0.5	100.0	-	-[b]	99.6	0.4	0.0
Amoxicillin-clavulanate	≤1	≤1	≤1 — ≤1	100.0	-	0.0[b]	100.0	-	0.0
Ceftriaxone	0.25	0.5	≤0.06 — 2	100.0	-	-[b]	99.8	0.2	0.0
Tetracycline	≤0.12	0.25	≤0.12 — >16	99.8	0.0	0.2[b]	99.8	0.0	0.2
TMP-SMX	≤0.5	≤0.5	≤0.5 — 2	95.4	4.6	0.0[b]	95.4	3.0	1.6

Organism/agent	MIC (µg/mL)		Range	CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}		%S	%I	%R	%S	%I	%R
***S. aureus* (716 isolates)**									
WCK 4873	0.06	>2	0.015 — >2	-	-	-	-	-	-
Telithromycin	0.06	>2	0.03 — >2	88.4	0.4	11.2	-	-	-
Erythromycin	0.25	>16	≤0.12 — >16	60.9	6.0	33.1	61.3	1.5	37.2
Oxacillin	0.5	>2	≤0.25 — >2	65.4	-	34.6	65.4	-	34.6
Clindamycin	≤0.25	>2	≤0.25 — >2	88.1	0.0	11.9	87.6	0.6	11.9
Linezolid	1	1	0.25 — 2	100.0	-	0.0	100.0	-	0.0
Ciprofloxacin	0.5	>4	0.06 — >4	72.9	2.0	25.1	72.9	-	27.1
Tetracycline	≤0.5	2	≤0.5 — >8	91.1	0.6	8.4	89.8	0.4	9.8
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	98.7	-	1.3	98.7	0.3	1.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
MSSA (468 isolates)									
WCK 4873	0.06	0.06	0.03 — >2	-	-	-	-	-	-
Telithromycin	0.06	0.12	0.03 — >2	98.1	0.4	1.5	-	-	-
Erythromycin	0.25	>16	≤0.12 — >16	77.5	5.6	16.7	78.2	1.7	20.1
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	97.9	0.0	2.1	97.6	0.2	2.1
Linezolid	1	1	0.25 — 2	100.0	-	0.0	100.0	-	0.0
Ciprofloxacin	0.25	0.5	0.06 — >4	92.7	1.9	5.3	92.7	0.0	7.3
Tetracycline	≤0.5	≤0.5	≤0.5 — >8	93.8	0.9	5.3	92.7	0.2	7.1
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	99.8	-	0.2	99.8	0.2	0.0
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0
MRSA (248 isolates)									
WCK 4873	0.06	>2	0.015 — >32	-	-	-	-	-	-
Telithromycin	0.12	>2	0.03 — >2	70.2	0.4	29.4	-	-	-
Erythromycin	>16	>16	≤0.12 — >16	29.0	6.9	64.1	29.4	1.2	69.4
Clindamycin	≤0.25	>2	≤0.25 — >2	69.8	0.0	30.2	68.5	1.2	30.2
Linezolid	1	1	0.25 — 2	100.0	-	0.0	100.0	-	0.0
Ciprofloxacin	>4	>4	0.12 — >4	35.5	2.0	62.5	35.5	-	64.5
Tetracycline	≤0.5	>8	≤0.5 — >8	85.9	0.9	14.1	84.3	0.8	14.9
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	96.8	-	3.2	96.8	0.4	2.8
Vancomycin	1	1	0.5 — 2	100.0	0.0	0.0	100.0	-	0.0

a. Criteria as published by CLSI [2015] and EUCAST [2015]
b. "-" = breakpoints not available to interpret
c. Using Non-Meningitis breakpoints
d. Using Oral breakpoints
e. Using Parenteral, Meningitis breakpoints
f. Using Parenteral, Non-Meningitis breakpoints
g. Using EUCAST "infections other than meningitis" breakpoints
h. As published in CLSI M45 3rd Edition 2015

Conclusions

- **WCK 4873 was very active ($MIC_{50/90}$, 0.015/0.06 µg/mL) against all 1,911 *S. pneumoniae* isolates with 100.0% of isolates inhibited at MIC values of 0.25 µg/mL or less. Using the MIC_{50}, WCK 4873 demonstrated identical potency (0.015 µg/mL) to that of telithromycin, however using MIC_{90}, WCK 4873 (0.06 µg/mL) was eight-fold more potent than telithromycin (0.5 µg/mL).**
- **WCK 4873 had moderate activity ($MIC_{50/90}$, 4/4 µg/mL) against *H. influenzae* and approximately a two-fold lower potency than telithromycin ($MIC_{50/90}$, 2/4 µg/mL).**
- **WCK 4873 demonstrated activity ($MIC_{50/90}$, 0.12/0.25 µg/mL) against *M. catarrhalis* similar to that of telithromycin ($MIC_{50/90}$, 0.12/0.12 µg/mL).**
- **WCK 4873 was shown to be as active as the comparator ketolide, telithromycin (88.4% susceptible) against the global collection of *S. aureus* isolates cultured during 2014. The activities of WCK 4873 and telithromycin were considerably lowered against *S. aureus* strains demonstrating a constitutively expressed macrolide-resistant phenotype.**
- **WCK 4873 showed a broad range of potent *in vitro* activity against contemporary (2014) global CABP pathogens. These results support the continued clinical development of WCK 4873 for CAPB.**

Acknowledgements

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