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In Vitro Activity of WCK 4873 (Nafithromycin) against Resistant Subsets of *Streptococcus pneumoniae* From a Global Surveillance Program (2014)

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Abstract

Background: WCK 4873 (INN: Nafithromycin) is a novel lactone ketolide, currently in clinical development for the treatment of community acquired bacterial pneumonia (CABP). WCK 4873 has completed SAD and MAD Phase 1 studies in Europe and an intra-pulmonary pharmacokinetic study in USA. WCK 4873 was awarded QIDP status in 2015. In this study, WCK 4873 was tested against contemporary *Streptococcus pneumoniae* (SPN) clinical isolates (including resistant subsets) collected in medical centers worldwide as part of the 2014 SENTRY Antimicrobial Surveillance Program.

Methods: A total of 1,911 SPN, were tested for susceptibility (S) against WCK 4873 and multiple comparator agents by reference broth microdilution methods and interpretive criteria. Number of isolates by geography (country or region) were as follows: USA (712), Europe (698, 23 countries), Asia Pacific (251, 8 countries) and Latin America (250, 11 countries).

Results: Against all 1,911 SPN, WCK 4873 was very active ($MIC_{50/90}$, 0.015/0.06 µg/mL) with all strains inhibited at MIC values ≤0.25 µg/mL (Table). Telithromycin (TEL) S (CLSI/EUCAST) rates were 99.9/89.3% and WCK 4783 was up to eight-fold more potent than TEL ($MIC_{50/90}$, 0.015/0.5 µg/mL). Using the EUCAST S breakpoint for TEL of ≤0.25 µg/mL, 204 strains were non-S to TEL and all 204 strains demonstrated WCK 4873 MIC values of ≤0.25 µg/mL ($MIC_{50/90}$, 0.06/0.12 µg/mL). WCK 4873 was four-fold less active against penicillin (PEN) -intermediate and -resistant (R) strains compared to PEN-S strains with WCK 4783 $MIC_{50/90}$ values of 0.06/0.12, 0.06/0.12 and 0.015/0.03 µg/mL, respectively. Ceftriaxone (CRO) non-S was 9.3% using CLSI non-meningitis breakpoints. Erythromycin (ERY) R was 37.9%, and 19.7% were R to clindamycin (CLI). WCK 4783 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).

Conclusions: WCK 4873 demonstrated potent activity against contemporary (2014) global SPN isolates and retained good activity against strains with lower activity to TEL (including 204 strains non-S by EUCAST breakpoints), PEN, CRO, ERY, and CLI.

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 SAD and 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 by the United States Food and Drug Administration (USA-FDA) in 2015.

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 (1,911 isolates) of contemporary *Streptococcus pneumoniae* isolates (including resistant subsets) collected in medical centers worldwide as part of the 2014 SENTRY Antimicrobial Surveillance Program.

Methods

Organism collection and specimen source: A total of 1,911 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 isolates 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.

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 used 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 strain: *S. pneumoniae* American Type Culture Collection (ATCC) 49619. MIC interpretations were based on CLSI and EUCAST breakpoint criteria.

Results

- WCK 4873 was very active ($MIC_{50/90}$, 0.015/0.06 µg/mL) against 1,911 *S. pneumonaie* isolates with all isolates inhibited at MIC values of 0.25 µg/mL or less (**Tables 1** and **2**). Similar $MIC_{50/90}$ values were observed in each of the four geographic regions sampled (**Table 1**).
- Overall, telithromycin susceptibility was 99.9/89.3% (CLSI/EUCAST criteria; **Table 1**). 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 1**). Against 394 erythromycin and clindamycin resistant pneumococci (constitutively macrolide resistant), MIC_{50} and MIC_{90} of WCK 4873 was 0.03 and 0.12 µg/mL, respectively.
- Using the EUCAST susceptibility breakpoint for telithromycin of ≤0.25 µg/mL, 204 *S. pneumonaie* strains were non-susceptible to telithromycin and all strains demonstrated WCK 4873 MIC values of ≤0.25 µg/mL ($MIC_{50/90}$, 0.06/0.12 µg/mL; **Table 2**).
- Erythromycin (ERY)-resistance (R) was 37.9% and 19.7% were R to clindamycin (CLI). WCK 4783 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; **Table 2**).
- WCK 4873 ($MIC_{50/90}$, 0.015/0.06 µg/mL), telithromycin ($MIC_{50/90}$, 0.015/0.5 µg/mL; 99.9% susceptible), tigecycline ($MIC_{50/90}$, 0.03/0.06 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 SPN (**Table 1**).
- Overall, tetracycline, and trimethoprim-sulfamethoxazole resistance rates were high (28.4 and 24.5%, respectively; **Table 1**).
- Using CLSI breakpoints, resistance to oral penicillin V was 16.7% overall, ranging from 11.9% in Europe to 29.1% in Asia-Pacific (**Table 1**). Among USA isolates of *S. pneumoniae*, penicillin resistance was at 13.6% and was 26.8% in Latin American isolates (**Table 1**). Using non-meningitis CLSI breakpoints, ceftriaxone resistance was highest in the Asia-Pacific region (4.8%) and was lower in Latin America (0.8%), Europe (1.0%) and the USA (0.8%, **Table 1**). WCK 4873 was four-fold less active against penicillin-intermediate and -resistant strains compared to penicillin-susceptible strains with WCK 4783 $MIC_{50/90}$ values of 0.06/0.12, 0.06/0.12 and 0.015/0.03 µg/mL, respectively (**Table 2**).

Table 2. Cumulative frequency distributions of WCK 4873 MIC results when tested against 1,911 *S. pneumoniae* isolates.

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	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
PEN-S (MIC, ≤2 µg/mL)	1762	1 (0.1)	20 (1.2)	392 (23.4)	994 (79.9)	200 (91.2)	127 (98.4)	25 (99.8)	3 (100.0)	0.015	0.03
PEN-I (MIC, 4 µg/mL)	133	--	--	4 (3.0)	18 (16.5)	21 (32.3)	29 (54.1)	59 (98.5)	2 (100.0)	0.06	0.12
PEN-R (MIC, ≥8 µg/mL)	16	--	--	--	2 (12.5)	3 (31.2)	6 (68.8)	4 (93.8)	1 (100.0)	0.06	0.12
ERY-S (MIC, ≤0.25 µg/mL) and CLI-S (MIC, ≤0.25 µg/mL)	1173	--	19 (1.6)	371 (33.2)	765 (98.5)	14 (99.7)	3 (99.9)	1 (100.0)	--	0.015	0.015
ERY-R (MIC, ≥0.5 µg/mL) and CLI-S (MIC, ≤0.25 µg/mL)	344	1 (0.3)	1 (0.6)	11 (3.8)	121 (39.0)	114 (72.1)	88 (97.7)	8 (100.0)	--	0.03	0.06
ERY-R (MIC, ≥0.5 µg/mL) and CLI-R (MIC, ≥0.5 µg/mL)	394	--	--	14 (3.6)	128 (36.0)	96 (60.4)	71 (78.4)	79 (98.5)	6 (100.0)	0.03	0.12
Telithromycin-S (MIC, ≤0.25 µg/mL)	1707	1 (0.1)	20 (1.2)	396 (24.4)	1014 (83.8)	209 (96.1)	64 (99.8)	3 (100.0)	--	0.015	0.03
Telithromycin-NS (MIC, ≥0.5 µg/mL)	204	--	--	--	15 (7.4)	98 (55.4)	85 (97.1)	6 (100.0)	0.06	0.06	0.12

Abbreviations: S; susceptible; I = intermediate; R = resistant; NS, non-susceptible; ERY = erythromycin; CLI = clindamycin; PEN = penicillin.

Table 1. Activity of WCK 4873 and comparator antimicrobial agents by geographic region when tested against 1,911 isolates of *Streptococcus pneumoniae*.

Geographic region (no. tested) / antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Overall (1,911)									
WCK 4873	0.015	0.06	≤0.002 — 0.25	-	-	-	-	-	-
Telithromycin	0.015	0.5	≤0.002 — 2	99.9	0.1	0.0	89.3	8.9	1.8
Amox-clav	≤1	4	≤1 — >8	87.6	4.0	8.4[b]	-	-	-
Ceftriaxone	≤0.06	1	≤0.06 — >8	78.6 90.7	12.0 7.9	9.3[c] 1.4[b]	78.6 -	19.9 -	1.4 -
Clindamycin	≤0.25	>2	≤0.25 — >2	79.4	0.9	19.7	80.3	-	19.7
Erythromycin	≤0.12	>16	≤0.12 — >16	61.4	0.7	37.9	61.4	0.7	37.9
Linezolid	1	1	≤0.12 — 2	100.0	-	-	100.0	0.0	0.0
Penicillin	≤0.06	2	≤0.06 — >8	59.9 59.9 92.2	23.3 - 7.0	16.7[d] 40.1[e] 0.8[f]	59.9 59.9 -	- 32.3 -	40.1[c] 7.8[b] -
Tetracycline	≤0.5	>8	≤0.5 — >8	71.2	0.4	28.4	71.2	0.4	28.4
Tigecycline	0.03	0.06	≤0.015 — 0.12	99.9	-	-[g]	-	-	-
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
USA (712)									
WCK 4873	0.015	0.06	0.004 — 0.25	-	-	-	-	-	-
Telithromycin	0.015	0.5	0.004 — 2	99.9	0.1	0.0	82.7	14.6	2.7
Amox-clav	≤1	4	≤1 — >8	88.5	4.4	7.2[b]	-	-	-
Ceftriaxone	≤0.06	1	≤0.06 — 8	81.6 93.7	12.1 5.5	6.3[c] 0.8[b]	81.6 -	17.6 -	0.8 -
Clindamycin	≤0.25	>2	≤0.25 — >2	82.2	1.3	16.6	83.4	-	16.6
Erythromycin	0.25	>16	≤0.12 — >16	50.0	1.0	49.0	50.0	1.0	49.0
Linezolid	1	1	≤0.12 — 2	100.0	-	-	100.0	0.0	0.0
Penicillin	≤0.06	2	≤0.06 — 8	58.1 58.1 93.5	28.2 - 5.9	13.6[d] 41.9[e] 0.6[f]	58.1 58.1 -	- 35.4 -	41.9[c] 6.5[b] -
Tetracycline	≤0.5	>8	≤0.5 — >8	76.0	0.4	23.6	76.0	0.4	23.6
Tigecycline	0.03	0.06	≤0.015 — 0.06	100.0	-	-[g]	-	-	-
TMP-SMX	≤0.5	>4	≤0.5 — >4	67.8	12.1	20.1	75.4	4.5	20.1
Vancomycin	0.25	0.5	≤0.12 — 1	100.0	-	-	100.0	-	0.0
European Region (698)									
WCK 4873	0.015	0.03	≤0.002 — 0.25	-	-	-	-	-	-
Telithromycin	0.015	0.12	≤0.002 — 2	99.9	0.1	0.0	94.8	4.2	1.0
Amox-clav	≤1	2	≤1 — >8	92.6	2.3	5.2[b]	-	-	-
Ceftriaxone	≤0.06	1	≤0.06 — >8	84.2 92.8	8.6 6.2	7.2[c] 1.0[b]	84.2 -	14.8 -	1.0 -
Clindamycin	≤0.25	>2	≤0.25 — >2	80.8	1.0	18.2	81.8	-	18.2
Erythromycin	≤0.12	>16	≤0.12 — >16	74.1	0.6	25.4	74.1	0.6	25.4
Linezolid	1	1	≤0.12 — 2	100.0	-	-	100.0	0.0	0.0
Penicillin	≤0.06	2	≤0.06 — >8	68.5 68.5 95.0	19.6 - 4.3	11.9[d] 31.5[e] 0.7[f]	68.5 68.5 -	- 26.5 -	31.5[c] 5.0[b] -
Tetracycline	≤0.5	>8	≤0.5 — >8	75.1	0.0	24.9	75.1	0.0	24.9
Tigecycline	0.03	0.06	≤0.015 — 0.12	99.9	-	-[g]	-	-	-
TMP-SMX	≤0.5	>4	≤0.5 — >4	70.6	9.3	20.1	76.1	3.9	20.1
Vancomycin	0.25	0.5	≤0.12 — 0.5	100.0	-	-	100.0	-	0.0
Asia-W. Pacific Region (251)									
WCK 4873	0.015	0.06	0.004 — 0.12	-	-	-	-	-	-
Telithromycin	0.015	0.25	0.004 — 0.5	100.0	0.0	0.0	91.2	8.8	0.0
Amox-clav	≤1	8	≤1 — >8	79.7	4.0	16.3[b]	-	-	-
Ceftriaxone	0.12	2	≤0.06 — >8	64.1 80.5	16.3 14.7	19.5[c] 4.8[b]	64.1 -	31.1 -	4.8 -
Clindamycin	≤0.25	>2	≤0.25 — >2	68.5	0.8	30.7	69.3	-	30.7
Erythromycin	≤0.12	>16	≤0.12 — >16	57.0	0.8	42.2	57.0	0.8	42.2
Linezolid	1	1	≤0.12 — 2	100.0	-	-	100.0	0.0	0.0
Penicillin	≤0.06	4	≤0.06 — >8	51.8 51.8 84.5	19.1 - 13.1	29.1[d] 48.2[e] 2.4[f]	51.8 51.8 -	- 32.7 -	48.2[c] 15.5[b] -
Tetracycline	≤0.5	>8	≤0.5 — >8	55.8	0.8	43.4	55.8	0.8	43.4
Tigecycline	0.03	0.03	≤0.015 — 0.06	100.0	-	-[g]	-	-	-
TMP-SMX	≤0.5	>4	≤0.5 — >4	56.6	8.8	34.7	64.5	0.8	34.7
Vancomycin	0.25	0.5	≤0.12 — 0.5	100.0	-	-	100.0	-	0.0
Latin America Region (250)									
WCK 4873	0.015	0.06	0.004 — 0.12	-	-	-	-	-	-
Telithromycin	0.015	0.25	0.004 — 1	100.0	0.0	0.0	90.8	6.0	3.2
Amox-clav	≤1	8	≤1 — >8	79.2	8.0	12.8[b]	-	-	-
Ceftriaxone	0.12	2	≤0.06 — 8	69.2 86.4	17.2 12.8	13.6[c] 0.8[b]	69.2 -	30.0 -	0.8 -
Clindamycin	≤0.25	>2	≤0.25 — >2	78.4	0.0	21.6	78.4	-	21.6
Erythromycin	≤0.12	>16	≤0.12 — >16	62.8	0.0	37.2	62.8	0.0	37.2
Linezolid	1	1	0.25 — 2	100.0	-	-	100.0	0.0	0.0
Penicillin	0.12	4	≤0.06 — 8	49.2 49.2 88.4	24.0 - 11.2	26.8[d] 50.8[e] 0.4[f]	49.2 49.2 -	- 39.2 -	50.8[c] 11.6[b] -
Tetracycline	≤0.5	>8	≤0.5 — >8	62.4	0.8	36.8	62.4	0.8	36.8
Tigecycline	0.03	0.03	≤0.015 — 0.12	99.6	-	-[g]	-	-	-
TMP-SMX	1	>4	≤0.5 — >4	48.8	11.6	39.6	53.6	6.8	39.6
Vancomycin	0.25	0.5	≤0.12 — 0.5	100.0	-	-	100.0	-	0.0

a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Using Non Meningitis breakpoints.
c. Using Meningitis breakpoints.
d. Using Oral breakpoints.
e. Using Parenteral, Meningitis breakpoints.
f. Using Parenteral, Non Meningitis breakpoints.
g. Breakpoints from FDA Package Insert revised 12/2014.

Abbreviations: Amox-clav = Amoxicillin-clavulanate; TMP-SMX = Trimethoprim-sulfamethoxazole

Conclusions

- **WCK 4873 was very active ($MIC_{50/90}$, 0.015/0.06 µg/mL) against a global collection of contemporary (2014) *S. pneumoniae* isolates with 100.0% of 1,911 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} values, WCK 4873 (0.06 µg/mL) was eight-fold more potent than telithromycin (0.5 µg/mL).**
- **Interestingly, WCK 4873 was highly active against constitutively macrolide resistant pneumococci (MIC_{50} and MIC_{90} being 0.03 and 0.12 µg/mL) including telithromycin non-susceptible strains (MIC_{50} and MIC_{90} being 0.06 and 0.12 µg/mL).**
- **WCK 4783 retained good activity against telithromycin non-susceptible, ERY-R/CLI-S and ERY-R/CLI-R strains.**

Acknowledgements

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