#E-812

NXL103 (Linopristin/Flopristin) Activity Against Pathogens Isolated from Patients in Canadian Hospitals: CANWARD 2009

J.A. Karlowsky, P. Lagacé-Wiens, A. Wierzbowski, D.J. Hoban, G.G. Zhanel
University of Manitoba, Health Sciences Centre, Winnipeg, Canada

George G. Zhanel
Health Sciences Centre
MS673-820 Sherbrook St.
Winnipeg, Manitoba R3A 1R9
Ph: (204) 787-4902
Fax: (204) 787-4699
Email: ggzhanel@pcs.mb.ca

ABSTRACT

Background: NXL103 is a novel, orally active, semi-synthetic streptogramin combination (linopristin/flopristin) with potential to treat pathogens associated with community-acquired pneumonia (CAP) and acute bacterial skin and soft tissue infections. NXL103 has also demonstrated activity against resistant organisms, such as community-associated (CA) and healthcare-associated (HA) methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). We determined the *in vitro* activity of NXL103 against Gram-positive pathogens and *Haemophilus influenzae* recently isolated from patients in medical and surgical wards, intensive care units, clinics, and emergency rooms at 15 Canadian hospitals from January to December 2009.

Methods: Antimicrobial susceptibility testing was performed using broth microdilution panels following the recommended CLSI method.

Results: The activity of NXL103 and comparators is summarized below.

Organism (n)	MIC$_{50}$/MIC$_{90}$ (μg/mL)						
	NXL103	CLR	CLI	LNZ	LVX	SXT	VAN
MSSA (871)	0.12/0.12	0.25/>32	≤0.12/≤0.12	2/2	0.25/4	≤0.12/≤0.12	1/1
CA-MRSA (74)	0.12/0.12	>32/>32	≤0.12/>8	2/2	4/8	≤0.12/≤0.12	1/1
HA-MRSA (151)	0.25/0.5	>32/>32	>8/>8	2/2	>32/>32	≤0.12/≤0.12	1/1
MSSE (83)	0.06/0.12	>32/>32	≤0.12/>8	0.5/1	0.25/>32	≤0.12/8	1/2
MRSE (17)	0.12/0.25	>32/>32	>8/>8	1/1	16/>32	4/8	2/2
S. pneumoniae (209)	0.12/0.12	≤0.03/1	≤0.12/≤0.12	0.5/1	1/1	≤0.12/0.5	0.25/0.25
Pen-NS *S. pneumoniae* (25)	0.12/0.12	1/>32	≤0.12/0.5	0.5/1	1/1	0.5/>8	0.25/0.25
Macrolide-NS *S. pneumoniae* (33)	0.12/0.12	2/16	≤0.12/0.5	0.5/1	1/1	0.25/8	0.25/0.25
E. faecalis (127)	1/2	>32/>32	>8/>8	2/2	2/>32	NA	1/2
E. faecium (43)	0.12/0.5	>32/>32	>8/>8	2/2	>32/>32	NA	1/>32
VRE (16)	0.25/0.5	>32/>32	>8/>8	2/2	>32/>32	NA	>32/>32
S. pyogenes (103)	≤0.03/≤0.03	≤0.03/0.5	≤0.12/≤0.12	0.5/1	0.5/0.5	NA	0.25/0.5
H. influenzae (159)	0.25/1	8/16	NA	8/16	≤0.015/0.03	≤0.12/4	NA

NA, not applicable; NS, non-susceptible; MSSA, methicillin-susceptible *S. aureus*, MSSE, methicillin-susceptible *S. epidermidis*; MRSE, methicillin-resistant *S. epidermidis*; CLR, clarithromycin; CLI, clindamycin; LNZ, linezolid; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin.

Conclusions: NXL103 demonstrated potent *in vitro* activity against pathogens commonly associated with skin and soft tissue infections (including community- and healthcare-associated MRSA and *S. pyogenes*), respiratory tract infections (penicillin- and macrolide-non-susceptible *S. pneumoniae*, *S. pyogenes*, and *H. influenzae*), as well as against VRE and MRSE.

BACKGROUND

NXL103 (formerly XRP 2868) is an orally active, semisynthetic streptogramin combination (70:30 ratio of linopristin [RPR 132552, Group A, PII component] and flopristin [RPR 202868, Group B, PI component]) for potential therapeutic use in the treatment of patients with community-acquired pneumonia (CAP), acute bacterial skin and soft tissue infections, as well as infections attributable to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).

NXL103 has been previously reported to inhibit staphylococci at *in vitro* concentrations ≤1 μg/mL and all non-pneumococcal streptococci at ≤0.25 μg/mL, and to be four-fold more potent than quinupristin-dalfopristin against *S. aureus* and *Enterococcus faecium* (1). NXL103 has also demonstrated potent *in vitro* activity against Gram-positive anerobic bacteria (2), has been reported to not be affected by current macrolide resistance mechanisms, and, to date, has been evaluated in a single phase II CAP clinical trial (3).

METHODS

From January 2009-December 2009, 15 sentinel Canadian hospital laboratories were asked to submit consecutive bacterial pathogens (1 per patient) from blood, respiratory, urine, and wound infections. In total, 5,375 isolates were submitted and 4,546 isolates (1,871 Gram-positive; 2,675 Gram-negative) were tested for antimicrobial susceptibilities. Yeasts, non-speciated coagulase-negative staphylococci, *Streptococcus agalactiae*, viridans streptococci, *Moraxella catarrhalis*, and species with fewer than 10 isolates were not tested for antimicrobial susceptibilities. Isolates were tested for antimicrobial susceptibilities using in-house prepared (Department of Clinical Microbiology, Health Sciences Centre, Winnipeg, Canada) 96-well broth microdilution panels according to CLSI M100-S19 (2009) guidelines. Minimum inhibitory concentrations (MICs) were interpreted using CLSI M100-S19 (2009) guidelines, where available.

DISCUSSION

- Against methicillin-susceptible *S. aureus* (MSSA), NXL103 demonstrated an MIC$_{90}$ of 0.12 μg/mL with an MIC range of ≤0.03–4 μg/mL. Against MRSA, specifically, isolates of healthcare-associated MRSA, NXL103 had a higher MIC$_{90}$ (0.5 μg/mL) than MSSA; community-associated MRSA had an MIC$_{90}$ of 0.12 μg/mL, identical to MSSA (Table 1).
- NXL103 appeared equally potent against *S. aureus* and *S. epidermidis* (Table 1).
- NXL103 showed greater *in vitro* potency against *S. pyogenes* (MIC$_{90}$, 0.03 μg/mL) than against *S. pneumoniae* (MIC$_{90}$, 0.12 μg/mL), *E. faecium* (MIC$_{90}$, 0.5 μg/mL), and *E. faecalis* (MIC$_{90}$, 2 μg/mL) (Table 1).
- *S. aureus* non-susceptible to clarithromycin or clindamycin (MIC$_{90}$, 0.5 μg/mL) had NXL103 MIC$_{90}$s two doubling dilutions higher than did clarithromycin- or clindamycin-susceptible isolates (MIC$_{90}$, 0.12 μg/mL) (Table 2). Concurrent resistance to clarithromycin or clindamycin in *S. pneumoniae* did not appear to affect NXL103 activity (MIC$_{90}$, 0.12 μg/mL). NXL103 *in vitro* activity was also not affected by resistance to other commonly used, mechanistically unrelated, antimicrobial agents (data not shown).
- NXL103 was active against *H. influenzae* (MIC$_{90}$, 1 μg/mL) and demonstrated similar activity against both clarithromycin-susceptible (MIC$_{90}$, 0.5 μg/mL) and non-susceptible isolates (MIC$_{90}$, 1 μg/mL).

CONCLUSION

NXL103 demonstrates potent *in vitro* activity against pathogens commonly associated with skin and soft tissue infections (including community- and healthcare-associated MRSA and *S. pyogenes*), respiratory tract infections (penicillin- and macrolide-non-susceptible *S. pneumoniae*, *S. pyogenes*, and *H. influenzae*), as well as against VRE and MRSE collected from patients attending hospitals across Canada in 2009.

ACKNOWLEDGMENTS

Funding for the CANWARD study was provided in part by the University of Manitoba, National Microbiology Laboratory, and AstraZeneca (Macclesfield, UK). The medical centers (investigators) that participated in CANWARD 2009 are listed at http://www.canr.info/.

REFERENCES

1. Eliopoulos GM, Ferraro MJ, Wennersten CB, Moellering RC. Antimicrob Agents Chemother 2005; 49: 3034–3039.
2. Goldstein EJC, Citron DM, Merriam V et al. Antimicrob Agents Chemother 2005; 49: 408–413.
3. Politano AD, Sawyer RG. Current Opin Investig Drugs 2010; 1: 225–236.

RESULTS

TABLE 1. ***In vitro*** **activities of NXL103 and comparative agents against Gram-positive pathogens**

Organism (no. tested)/antimicrobial agent	MIC (μg/mL)					
	50%	90%	Range	% S	% I	% R
MSSA (871)						
NXL103	0.12	0.12	≤0.03-4	NA[a]	NA	NA
Clarithromycin	0.25	>32	≤0.03->32	75.9	0.1	24
Clindamycin	≤0.12	≤0.12	≤0.12->8	92.1	0.5	7.5
Levofloxacin	0.25	4	≤0.06->32	89.3	0.3	10.3
Linezolid	2	2	≤0.12-4	100	NA	0
Vancomycin	1	1	0.5-2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	99.7	NA	0.3
MRSA (232)[b]						
NXL103	0.12	0.5	0.06-2	NA	NA	NA
Clarithromycin	>32	>32	0.12->32	14.2	0	85.8
Clindamycin	≤0.12	>8	≤0.12->8	53.4	0	46.6
Levofloxacin	>32	>32	0.12->32	19.8	0	80.2
Linezolid	2	2	0.5-4	100	NA	0
Vancomycin	1	1	0.5-2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	95.3	NA	4.7
Community-associated MRSA (74)[b]						
NXL103	0.12	0.12	0.12-0.5	NA	NA	NA
Clarithromycin	>32	>32	0.12->32	28.4	0	71.6
Clindamycin	≤0.12	>8	≤0.12->8	89.2	0	10.8
Levofloxacin	4	8	0.12-8	47.3	0	52.7
Linezolid	2	2	2-Jan	100	NA	0
Vancomycin	1	1	0.5-2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12-0.25	100	NA	0
Healthcare-associated MRSA (151)[b]						
NXL103	0.25	0.5	0.06-2	NA	NA	NA
Clarithromycin	>32	>32	0.12->32	4.6	0	95.4
Clindamycin	>8	>8	≤0.12->8	34.4	0	65.6
Levofloxacin	>32	>32	0.25->32	3.3	0	96.7
Linezolid	2	2	0.5-4	100	NA	0
Vancomycin	1	1	0.5-2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	92.7	NA	7.3
MSSE (83)						
NXL103	0.06	0.12	≤0.03-1	NA	NA	NA
Clarithromycin	>32	>32	≤0.03->32	38.6	3.6	57.8
Clindamycin	≤0.12	>8	≤0.12->8	60.2	1.2	38.6
Levofloxacin	0.25	>32	0.12->32	56.6	0	43.4
Linezolid	0.5	1	≤0.12-2	100	NA	NA
Vancomycin	1	2	≤0.12-2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12-8	71.1	NA	28.9
MRSE (17)						
NXL103	0.12	0.25	≤0.03-0.25	NA	NA	NA
Clarithromycin	>32	>32	≤0.03->32	17.6	0	82.4
Clindamycin	>8	>8	≤0.12->8	17.6	0	82.4
Levofloxacin	16	>32	1->32	5.9	5.9	88.2
Linezolid	1	1	0.5-1	100	NA	NA
Vancomycin	2	2	2-Jan	100	0	0
Trimethoprim-sulfamethoxazole	4	8	≤0.12->8	26.3	NA	73.7
Streptococcus pneumoniae (209)						
NXL103	0.12	0.12	≤0.03-0.5	NA	NA	NA
Clarithromycin	≤0.03	1	≤0.03->32	84.1	3.8	12
Clindamycin	≤0.12	≤0.12	≤0.12-2	96.6	2.4	1
Ceftriaxone	≤0.12	≤0.12	≤0.12-4	99	0.5	0.5
Levofloxacin	1	1	≤0.06-8	99.5	0	0.5
Linezolid	0.5	1	≤0.12-1	100	NA	NA
Vancomycin	0.25	0.25	≤0.12-0.5	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12-8	96.2	1.1	2.7
Penicillin-susceptible *S. pneumoniae* (184)						
NXL103	0.12	0.12	≤0.03-0.25	NA	NA	NA
Clarithromycin	≤0.03	0.06	≤0.03-16	91.3	2.2	6.6
Clindamycin	≤0.12	≤0.12	≤0.12-0.5	99.5	0.5	0
Ceftriaxone	≤0.12	≤0.12	≤0.12-0.25	100	0	0
Levofloxacin	1	1	≤0.06-8	99.5	0	0.6
Linezolid	0.5	1	≤0.12-1	100	NA	NA
Vancomycin	0.25	0.25	≤0.12-0.5	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12-8	96.2	1.1	2.7
Penicillin non-susceptible *S. pneumoniae* (25)						
NXL103	0.12	0.12	0.06-0.5	NA	NA	NA
Clarithromycin	1	>32	≤0.03->32	32	16	52
Clindamycin	≤0.12	0.5	≤0.12-2	76	16	8
Ceftriaxone	≤0.12	1	≤0.12-4	92	4	4
Levofloxacin	1	1	0.5-2	100	0	0
Linezolid	0.5	1	≤0.12-1	100	NA	NA
Vancomycin	0.25	0.25	≤0.12-0.25	100	0	0
Trimethoprim-sulfamethoxazole	0.5	>8	≤0.12->8	52	12	36
Streptococcus pyogenes (103)						
NXL103	≤0.03	≤0.03	≤0.03-0.12	NA	NA	NA
Clarithromycin	≤0.03	0.5	≤0.03->32	87.4	5.8	6.8
Clindamycin	≤0.12	≤0.12	≤0.12	100	0	0
Ceftriaxone	≤0.12	≤0.12	≤0.12	100	NA	NA
Levofloxacin	0.5	0.5	0.12-2	100	0	0
Linezolid	0.5	1	0.25-1	100	NA	NA
Vancomycin	0.25	0.5	≤0.12-0.5	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12-8	NA	NA	NA
Enterococcus faecalis (127)						
NXL103	1	2	0.12-4	NA	NA	NA
Clarithromycin	>32	>32	≤0.03->32	NA	NA	NA
Clindamycin	>8	>8	0.25->8	NA	NA	NA
Levofloxacin	2	>32	0.5->32	63.8	0.8	35.4
Linezolid	2	2	2-Jan	100	0	0
Vancomycin	1	2	0.5-4	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12-8	NA	NA	NA
Enterococcus faecium (43)[c]						
NXL103	0.12	0.5	0.06-2	NA	NA	NA
Clarithromycin	>32	>32	1->32	NA	NA	NA
Clindamycin	>8	>8	≤0.12->8	NA	NA	NA
Levofloxacin	>32	>32	2->32	2.3	0	97.7
Linezolid	2	2	0.5-4	97.9	2.3	0
Vancomycin	1	>32	0.25->32	79.1	0	20.9
Trimethoprim-sulfamethoxazole	2	>8	≤0.12->8	NA	NA	NA
VRE (16)						
NXL103	0.25	0.5	0.12->16	NA	NA	NA
Clarithromycin	>32	>32	1->32	NA	NA	NA
Clindamycin	>8	>8	1->8	NA	NA	NA
Levofloxacin	>32	>32	>32	0	0	100
Linezolid	2	2	2-Jan	100	0	0
Vancomycin	>32	>32	>32	0	0	100
Trimethoprim-sulfamethoxazole	0.25	>8	≤0.12->8	NA	NA	NA

[a] NA, not available.
[b] The 232 MRSA (*mecA* positive) included 74 community-associated isolates (CMRSA7 [USA400] and CMRSA10 [USA300]), 151 healthcare-associated isolates (one of the other 10 Canadian MRSA epidemic pulsed-field gel electrophoresis patterns), and 7 *mecA* positive isolates with unique pulsed-field gel electrophoresis patterns.
[c] All vancomycin-resistant isolates were *vanA* positive.

TABLE 2. ***In vitro*** **activities of NXL103 and comparative agents against Gram-positive isolates with clarithromycin-resistant and clindamycin-resistant phenotypes**

Organism (no. tested)/antimicrobial agent	MIC (μg/mL)					
	50%	90%	Range	% S	% I	% R
S. aureus clarithromycin-susceptible (694)						
NXL103	0.12	0.12	≤0.03-0.25	NA[a]	NA	NA
Clindamycin	≤0.12	≤0.12	≤0.12-1	99.4	0.6	0
Linezolid	2	2	≤0.12-2	100	NA	NA
S. aureus clarithromycin non-susceptible (409)						
NXL103	0.12	0.5	0.06-4	NA	NA	NA
Clindamycin	≤0.12	>8	≤0.12->8	57.7	0	42.3
Linezolid	2	2	0.5-4	100	NA	NA
S. aureus clindamycin-susceptible (926)						
NXL103	0.12	0.12	≤0.03-0.25	NA	NA	NA
Clarithromycin	0.25	>32	≤0.03->32	74.5	0.1	25.4
Linezolid	2	2	≤0.12-4	100	NA	NA
S. aureus clindamycin non-susceptible (177)						
NXL103	0.25	0.5	0.06-4	NA	NA	NA
Clarithromycin	>32	>32	0.25->32	2.3	0	97.7
Linezolid	2	2	0.5-4	100	NA	NA
S. pneumoniae clarithromycin-susceptible (175)						
NXL103	0.12	0.12	≤0.03-0.12	NA	NA	NA
Clindamycin	≤0.12	≤0.12	≤0.12	100	0	0
Linezolid	0.5	1	≤0.12-1	100	NA	NA
S. pneumoniae clarithromycin non-susceptible (33)						
NXL103	0.12	0.12	0.06-0.5	NA	NA	NA
Clindamycin	≤0.12	0.5	≤0.12-2	78.8	15.2	6.1
Linezolid	0.5	1	≤0.12-1	100	NA	NA
S. pneumoniae clindamycin-susceptible (201)						
NXL103	0.12	0.12	≤0.03-0.25	NA	NA	NA
Clarithromycin	≤0.03	0.5	≤0.03-16	87.1	4	9
Linezolid	0.5	1	≤0.12-1	100	NA	NA
S. pneumoniae clindamycin non-susceptible (7)						
NXL103	0.12	0.5	0.06-0.5	NA	NA	NA
Clarithromycin	16	>32	4->32	0	0	100
Linezolid	0.5	0.5	0.25-0.5	100	NA	NA

[a] NA, not available.

TABLE 3. ***In vitro*** **activities of NXL103 and comparative agents against *H. influenzae***

Organism (no. tested)/antimicrobial agent	MIC (μg/mL)					
	50%	90%	Range	% S	% I	% R
Haemophilus influenzae (159)						
NXL103	0.25	1	≤0.03-2	NA[a]	NA	NA
Clarithromycin	8	16	0.25-32	74.8	22	3.1
Cefuroxime	2	4	≤0.25-16	93.7	5.7	0.6
Amoxicillin-Clavulanate	0.5	2	≤0.06-4	100	NA	0
Ampicillin	≤0.25	16	≤0.25->128	82.4	1.9	15.7
Ciprofloxacin	≤0.015	≤0.015	≤0.015-0.03	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12->8	80	4.8	15.2
Haemophilus influenzae ampicillin-susceptible (131)						
NXL103	0.25	1	≤0.03-1	NA	NA	NA
Clarithromycin	8	16	0.25-32	73.3	22.9	3.8
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12->8	81.7	6.1	12.2
Haemophilus influenzae ampicillin-resistant (25)						
NXL103	0.25	0.5	≤0.03-1	NA	NA	NA
Clarithromycin	8	16	0.25-32	80	20	0
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12->8	80	0	20
Haemophilus influenzae clarithromycin-susceptible (119)						
NXL103	0.25	0.5	≤0.03-1	NA	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12-8	84.9	4.2	10.9
Haemophilus influenzae clarithromycin non-susceptible (40)						
NXL103	1	1	≤0.03-1	NA	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12-2	80	20	0

[a] NA, not available.

Presented at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, September 12–15, 2010