Poster P1826

Activity Profile of MBN-101: a Novel Antimicrobial Agent with Broad-Spectrum Activity against Bacteria, Including ESKAPE Pathogens

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Abstract

Background: MBN-101, a novel antimicrobial, is undergoing development for the topical/local treatment of chronic wound and tissue infection including diabetic foot ulcer (DFI) and orthopedic device-related infections. Chronic and deep tissue infections may be severe and are often polymicrobial, involving aerobes and anaerobes, including ESKAPE pathogens, thereby warranting broad-spectrum coverage that includes activity against resistant organisms. Ineffective management may lead to prolonged morbidity and increased risk of amputation. We herein present the *in vitro* activity of MBN-101 against an array of pathogens.

Materials/methods: We evaluated non-duplicate clinical isolates (N=826) of gram-positive and gram-negative aerobes and anaerobes by determining their susceptibility to MBN-101 and relevant comparators by broth microdilution/agar dilution testing per CLSI guidelines (M07/M11/M100).

Results: The activity profile of MBN-101 (mg/L) is summarized below:

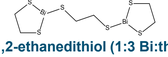
Gram-positive Aerobes			Gram-negative Aerobes			Obligate Anaerobes		
Organism (N)	MIC Range	$MIC_{50/90}$	Organism (N)	MIC Range	$MIC_{50/90}$	Organism (N)	MIC Range	$MIC_{50/90}$
S. aureus (155)	≤0.03-1	0.25/0.5	*E. coli* (55)	0.5-2	2/2	Gram-positive (33)	≤0.015-4	1/4
S. epidermidis (100)	≤0.03-0.25	0.06/0.12	*K. pneumoniae* (58)	1-8	4/8	*Clostridium* spp. (10)	0.25-4	2/4
S. pyogenes (53)	0.03-0.5	0.25/0.5	*P. aeruginosa* (56)	0.5-8	1/4	*P. acnes* (9)	≤0.03-4	1/-
S. agalactiae (55)	0.25->16	8/16	*A. baumannii* (29)	0.5-4	2/2	*Peptostreptococcus* spp. (4)	0.25-4	-/-
S. pneumoniae (7)	0.25-1	1/-						
E. faecalis (104)	0.12-2	1/2				Gram-negative (19)	≤0.015-4	0.25/2
E. faecium (102)	0.5-2	1/2				*Bacteroides* spp. (9)	0.03-4	0.5/-

MBN-101 had an $MIC_{50/90}$ (mg/L) of 0.25/0.5 against methicillin-resistant *Staphylococcus aureus* (n=105) and 1/2 against vancomycin-resistant enterococci (n=53 *E. faecalis* and n=52 *E. faecium*), which was identical to that observed with susceptible subpopulations. MBN-101 maintained potent activity against multidrug-resistant strains of *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*, macrolide-resistant β-hemolytic streptococci, and extended-spectrum β-lactamase/carbapenemase producing Enterobacteriaceae.

Conclusions: MBN-101 demonstrated potent broad-spectrum activity *in vitro* against aerobic/anaerobic bacteria commonly isolated from human infections, including DFI and orthopedic infections. The activity of MBN-101 was not affected by antibiotic-resistance phenotype. These results highlight the potential of MBN-101 for the topical/local treatment of infections for which broad-spectrum coverage is indicated.

Introduction

- **MBN-101** is an aqueous suspension of a novel bismuth thiol ("BisEDT") currently undergoing clinical development for the topical treatment of chronic wound and tissue infections including diabetic foot ulcer infections (DFI) and orthopedic device infections.
- Although acute DFI and orthopedic infections typically involve Gram-positive cocci, the epidemiology of moderate and severe tissue infections is often polymicrobial involving Gram-negative bacilli and anaerobic bacteria.
- Antibiotic resistant pathogens are becoming increasingly common and pathogens for which there are limited therapeutic options (e.g. ESKAPE pathogens) have emerged.
- As a result, the continued development of new agents with broad-spectrum activity that covers resistant pathogens is necessary to address treatment of complicated infections such as DFI and orthopedic device related infections.



Bismuth-1,2-ethanedithiol (1:3 Bi:thiol molar ratio)

Objective

- **To evaluate the in vitro activity of BisEDT, the active pharmaceutical ingredient (API) in MBN-101 aqueous suspension formulation, against prevalent clinical pathogens focusing on those relevant to chronic wound and tissue infections, including ESKAPE pathogens with important resistance phenotypes.**

Materials and Methods

- **Evaluated organisms consisted of 826 non-duplicate clinical isolates alongside relevant ATCC quality control isolates (CLSI M100).**
- **Resistance phenotypes among the test isolates included methicillin-resistant staphylococci (MRSA/MRSE), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceae (CRE), and multi-drug resistant (MDR) isolates based on resistance to ≥3 different classes of antibiotic.**
- **MIC values were determined in accordance with CLSI guidelines for the susceptibility testing of aerobes by broth microdilution (CLSI M07) and anaerobes by agar dilution (CLSI M11). MIC values as reported reflect the activity of BisEDT, the API of the MBN-101 formulation, which was used during susceptibility testing.**

Results

IN VITRO ACTIVITY AGAINST GRAM-POSITIVE AEROBES

- **As shown in Table 1, BisEDT had potent activity by $MIC_{50/90}$ (mg/L) against *S. aureus* (0.5/0.5 for MSSA, 0.25/0.5 for MRSA) and *S. epidermidis* (0.06/0.12 for MSSE, 0.06/0.25 for MRSE); for 50 community-acquired MRSA, BisEDT had an $MIC_{50/90}$ of 0.25/0.5 mg/L.**
- **BisEDT was also active against enterococci with $MIC_{50/90}$ (mg/L) values of 2/2 and 1/1 against vancomycin (VAN)-susceptible and –resistant *E. faecalis*, respectively, and 1/2 against both VAN-susceptible and –resistant *E. faecium* (Table 2).**
- **BisEDT activity against staphylococci and enterococci was not impacted by methicillin-resistance (Figure 1A) or vancomycin-resistance (Figure 2A), respectively.**
- **By cumulative susceptibility, BisEDT was the most potent agent against staphylococci (Figure 1B) and *E. faecium* (Figure 2B); BisEDT, imipenem (IPM), and daptomycin (DAP) were the most potent against *E. faecalis* (Figure 2B).**
- **As shown in Table 3 and Figure 3A, BisEDT had potent activity against *S. pyogenes* ($MIC_{50/90}$= 0.25/0.5 mg/L) and was comparatively less active against *S. agalactiae* ($MIC_{50/90}$= 8/16 mg/L).**
- **Against multidrug-resistant (MDR) *S. pneumoniae* (N=7), BisEDT was active with MIC values of 0.25-1 mg/L (Table 3).**

IN VITRO ACTIVITY AGAINST GRAM-NEGATIVE AEROBES

- **As shown in Table 4, BisEDT was active by $MIC_{50/90}$ (mg/L) against *E. coli* (2/2), *K. pneumoniae* (4/8), *P. aeruginosa* (1/4), and *A. baumannii* (2/2). In no instance was an MIC > 8 mg/L observed for BisEDT against the evaluated Gram-negative bacilli.**
- **The activity of BisEDT against Enterobacteriaceae was not impacted by ceftazidime (CAZ)-resistance (Figure 4A) with an $MIC_{50/90}$ (mg/L) of 2/2 and 1/2 for CAZ-susceptible and –resistant *E. coli*, respectively, and 4/8 mg/L for CAZ-susceptible and –resistant *K. pneumoniae*; BisEDT maintained activity against 2 NDM-1 and 5 KPC isolates (MIC= 1-4 mg/L).**
- **BisEDT was more potent than CAZ, ciprofloxacin (CIP), and gentamicin (GM) by MIC_{90} against Enterobacteriaceae (Table 4, Figure 4B).**
- **BisEDT activity against *P. aeruginosa* and *A. baumannii* was not impacted by multidrug-resistance (Figure 5A) with an $MIC_{50/90}$ (mg/L) of 1/2 and 2/2 for non-MDR and MDR *P. aeruginosa*, respectively, and 2/2 for non-MDR and MDR *A. baumannii*.**
- **BisEDT was at least 4-fold more potent overall than CAZ, IPM, CIP, and GM by MIC_{90} against *P. aeruginosa* and by $MIC_{50/90}$ against *A. baumannii* (Table 4), and the increased activity of BisEDT against isolates with a high degree of resistance to the evaluated comparators was apparent by cumulative susceptibility (Figure 5B).**

Table 1. In vitro activity of BisEDT and comparators against staphylococci

Organism	Drug	Type (n)	MIC Range	MIC_{50}	MIC_{90}	%S	%R
S. aureus (155)	BisEDT	MSSA (50)	≤0.03-1	0.5	0.5	-	-
		MRSA (105)	≤0.06-1	0.25	0.5	-	-
	Vancomycin	MSSA (50)	0.5-2	1	1	100	0.0
		MRSA (105)	0.25-2	1	2	100	0.0
	Linezolid	MSSA (50)	2-4	2	4	100	0.0
		MRSA (100)	2-4	2	4	100	0.0
	Daptomycin	MSSA (50)	0.25-0.5	0.5	0.5	100	-
		MRSA (100)	0.25-1	0.5	0.5	100	-
	Imipenem	MSSA (50)	≤0.008-0.03	0.015	0.03	100	0.0
		MRSA (100)	0.12->8	1	>8	0.0	100
	Ciprofloxacin	MSSA (50)	0.12->32	0.25	1	90.0	4.0
		MRSA (105)	0.25->32	16	>32	32.4	65.7
	Gentamicin	MSSA (50)	0.25->32	0.5	1	96.0	4.0
		MRSA (105)	0.12->32	0.5	1	96.2	3.8
S. epidermidis (100)	BisEDT	MSSE (50)	≤0.03-0.25	0.06	0.12	-	-
		MRSE (50)	≤0.06-0.25	0.06	0.25	-	-
	Vancomycin	MSSE (50)	0.25-8	2	4	98.0	0.0
		MRSE (50)	1-4	2	2	100	0.0
	Linezolid	MSSE (50)	0.5-2	2	2	100	0.0
		MRSE (50)	1-4	2	2	100	0.0
	Daptomycin	MSSE (50)	0.12-16	0.5	1	96.0	-
		MRSE (50)	0.25-1	0.5	0.5	100	-
	Imipenem	MSSE (50)	≤0.008-0.25	0.015	0.015	100	0.0
		MRSE (50)	0.06->8	>8	>8	0.0	100
	Ciprofloxacin	MSSE (50)	0.12->32	0.25	>32	76.0	22.0
		MRSE (50)	0.12->32	>32	>32	32.4	65.7
	Gentamicin	MSSE (50)	≤0.03->32	0.12	0.12	96.0	4.0
		MRSE (50)	≤0.03->32	32	>32	32.0	68.0

MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; MSSE: methicillin-susceptible *S. epidermidis*, MRSE: methicillin-resistant *S. epidermidis*, %S: percent susceptible, %R: percent resistant
NOTE: linezolid, daptomycin, and imipenem were not tested against 5 MRSA/MDR *S. aureus*

Table 2. In vitro activity of BisEDT and comparators against enterococci

Organism (N)	Drug	Type (n)	MIC Range	MIC_{50}	MIC_{90}	%S	%R
E. faecalis (104)	BisEDT	VSE (51)	0.12-2	2	2	-	-
		VRE (53)	0.25-2	1	1	-	-
	Vancomycin	VSE (51)	0.5-4	1	4	100	0.0
		VRE (53)	32->64	>64	>64	0.0	100
	Linezolid	VSE (51)	2-4	2	4	84.3	0.0
		VRE (50)	1-32	2	2	94.0	6.0
	Daptomycin	VSE (51)	0.25-2	1	2	100	-
		VRE (50)	0.25-2	1	2	100	-
	Imipenem	VSE (51)	0.5->8	1	2	-	-
		VRE (50)	0.5->8	1	2	-	-
	Ciprofloxacin	VSE (51)	0.25->32	2	>32	47.1	43.1
		VRE (53)	32->32	>32	>32	0.0	100
	Gentamicin	VSE (51)	0.06->32	16	>32	-	-
		VRE (53)	4->32	>32	>32	-	-
E. faecium (102)	BisEDT	VSE (50)	0.5-2	1	2	-	-
		VRE (52)	0.5-2	1	2	-	-
	Vancomycin	VSE (50)	0.5-2	1	1	100	0.0
		VRE (52)	32->64	>64	>64	0.0	100
	Linezolid	VSE (50)	1-4	2	2	94.0	0.0
		VRE (50)	2-32	2	2	94.0	2.0
	Daptomycin	VSE (50)	0.5-8	2	4	98.0	-
		VRE (50)	1-4	2	4	100	-
	Imipenem	VSE (50)	0.5->8	>8	>8	-	-
		VRE (50)	>8	>8	>8	-	-
	Ciprofloxacin	VSE (50)	0.12->32	>32	>32	14.0	82.0
		VRE (52)	2->32	>32	>32	0.0	96.2
	Gentamicin	VSE (50)	2->32	16	>32	-	-
		VRE (52)	4->32	16	>32	-	-

VSE: vancomycin-susceptible enterococci, VRE: vancomycin-resistant enterococci, %S: percent susceptible, %R: percent resistant
NOTE: linezolid, daptomycin, and imipenem were not tested against 3 VRE/MDR *E. faecalis* and 2 VRE/MDR *E. faecium*

Figure 1A. BisEDT MIC distribution against staphylococci

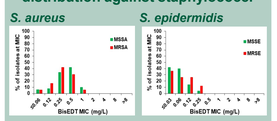


Figure 1B. Cumulative in vitro susceptibility of staphylococci to BisEDT and comparators

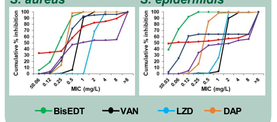
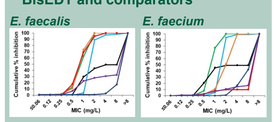


Figure 2A. BisEDT MIC distribution against enterococci

Figure 2B. Cumulative in vitro susceptibility of enterococci to BisEDT and comparators



IN VITRO ACTIVITY AGAINST ANAEROBES

- **As shown in Table 5, BisEDT had potent activity against the evaluated Gram-positive and Gram-negative anaerobes, with MIC values of ≤0.015 – 4 mg/L.**
- **Based on MIC ranges overall and by species, BisEDT was more potent than both clindamycin (CLI) and metronidazole (MTZ) for which there were multiple instances where MIC values were >16 mg/L. In contrast, for BisEDT there were no instances where the MIC value exceeded 4 mg/L.**

Table 3. In vitro activity of BisEDT and comparators against streptococci

Organism (N)	Drug	MIC Range	MIC_{50}	MIC_{90}	%S	%R
S. pyogenes (53)	BisEDT	0.03-0.5	0.25	0.5	-	-
	Vancomycin	0.25-1	0.5	0.5	100	0.0
	Linezolid[a]	0.5-2	1	2	100	-
	Daptomycin[a]	0.06-1	0.12	0.25	100	-
	Imipenem[b]	≤0.008-8	≤0.008	8	-	-
	Ciprofloxacin	0.12-2	0.5	2	84.9[c]	0.0
	Gentamicin[a]	2-16	4	8	-	-
S. agalactiae (55)	BisEDT	0.25->16	8	16	-	-
	Vancomycin	0.5-4	0.5	0.5	100	0.0
	Linezolid[a]	1-2	1	2	100	-
	Daptomycin[a]	0.25-4	0.5	1	96.0	-
	Imipenem[b]	≤0.008-1	0.015	0.015	-	-
	Ciprofloxacin	0.5-2	1	1	-	-
	Gentamicin[a]	4->32	32	32	-	-
S. pneumoniae (7)	BisEDT	0.25-1	1	-	-	-
	Vancomycin	0.25-0.5	0.25	-	100	0.0
	Penicillin	0.12-4	4	-	0.0[c]	71.4
	Clindamycin	>8	>8	-	0.0	100
	Erythromycin	>8	>8	-	0.0	100
	Ciprofloxacin	0.5-32	2	-	42.9[b]	28.6
	Meropenem	0.03-1	1	-	28.6	57.1

%S: percent susceptible, %R: percent resistant
[a] 4 macrolide-resistant *S. pyogenes* and 5 macrolide-resistant *S. agalactiae* not tested for these agents
[b] interpreted using FDA breakpoints
[c] interpreted using oral non-meningitidis breakpoints

Table 4. In vitro activity of BisEDT and comparators against Gram-negative aerobes

Organism (N)	Drug	MIC Range	MIC_{50}	MIC_{90}	%S	%R
E. coli (55)	BisEDT	0.5-2	2	2	-	-
	Ceftazidime	0.12->32	1	>32	72.7	25.5
	Imipenem[a]	0.06-1	0.25	0.25	100	0.0
	Ciprofloxacin	0.008->4	0.25	>4	52.7	47.3
	Gentamicin	0.25->16	1	>16	78.2	20.0
K. pneumoniae (58)	BisEDT	1-8	4	8	-	-
	Ceftazidime	0.25->32	1	>32	55.2	37.9
	Imipenem[a]	0.12->16	0.25	8	84.0	16.0
	Ciprofloxacin	0.015->4	0.12	>4	60.3	37.9
	Gentamicin	0.25->16	0.5	>16	74.1	20.7
P. aeruginosa (56)	BisEDT	0.5-8	1	4	-	-
	Ceftazidime	2->32	8	>32	58.9	35.7
	Imipenem[a]	0.5->16	1	16	58.0	34.0
	Ciprofloxacin	0.06->4	0.5	>4	55.4	37.5
	Gentamicin	0.12->16	2	16	75.0	10.7
A. baumannii (29)	BisEDT	0.5-4	2	2	-	-
	Ceftazidime	2->32	16	>32	37.9	48.3
	Imipenem[a]	0.12->16	8	>16	45.8	54.2
	Ciprofloxacin	0.03->4	>4	>4	34.5	65.5
	Gentamicin	0.12->16	>16	>16	34.5	58.6

%S: percent susceptible, %R: percent resistant
[a] imipenem was not tested for 5 *E. coli* (1 non-ESBL, 3 ESBL, 1 NDM), 8 *K. pneumoniae* (2 ESBL, 5 KPC, 1 NDM), 6 *P. aeruginosa* (1 non-MDR, 5 MDR), and 5 *A. baumannii* (1 non-MDR, 4 MDR)

Table 5. In vitro activity of BisEDT and comparators against anaerobes

Organism (N)	MIC Range		
	BisEDT	CLI	MTZ
Gram-positive			
C. difficile (8)	0.25-1	4->64	0.5->64
C. perfringens (2)	0.5-4	2->16	2
Peptostreptococcus spp. (4)	0.25-4	0.25->16	1->16
P. acnes (11)	≤0.03-2	0.06->16	NT
E. lenta (1)	0.25	2	2
Bifidobacterium spp. (4)	≤0.015-0.12	≤0.015-0.06	0.5-4
Lactobacillus spp. (3)	1	0.25-4	>16
Gram-negative			
B. fragilis (3)	0.25-1	1-4	0.5-1
Bacteroides spp. (non-*fragilis*) (6)	0.03-4	0.12->16	0.5->16
Prevotella spp. (4)	0.03-2	0.12->16	0.5->16
Fusobacterium spp. (2)	≤0.015	0.06->16	≤0.015-0.03
F. asaccharolytica (2)	0.06	0.12	1-2
E. corrodens (1)	0.06	>16	8
V. parvula (1)	0.25	>16	>16

Figure 3A. BisEDT MIC distribution against β-hemolytic streptococci

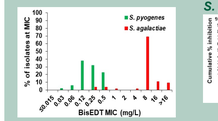


Figure 3B. Cumulative in vitro susceptibility of β-hemolytic streptococci to BisEDT and comparators

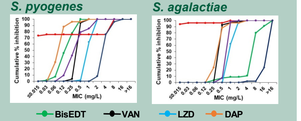


Figure 4A. BisEDT MIC distribution against *E. coli* and *K. pneumoniae*

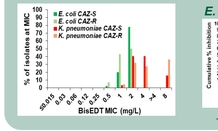


Figure 4B. Cumulative in vitro susceptibility of *E. coli* and *K. pneumoniae* to BisEDT and comparators

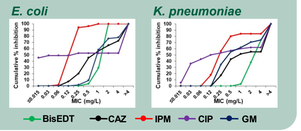


Figure 5A. BisEDT MIC distribution against *P. aeruginosa* and *A. baumannii*

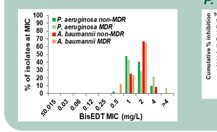
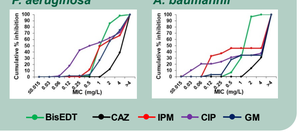


Figure 5B. Cumulative in vitro susceptibility of *P. aeruginosa* and *A. baumannii* to BisEDT and comparators



Conclusions

- **BisEDT demonstrated broad spectrum *in vitro* activity against the evaluated Gram-positive and Gram-negative aerobic and anaerobic isolates.**
- **BisEDT maintained potent activity against resistant isolates including phenotypes associated with ESKAPE pathogens (MRSA, VRE, ESBL/CRE, and MDR).**
- **The broad-spectrum activity of BisEDT (the API in MBN-101), its activity against pathogens with challenging resistance phenotypes, and the antibiofilm activity associated with bismuth thiols as a class (Folsom et al, JAM 2011;111:989) highlight the potential of MBN-101 for the treatment of device-related and chronic wound infections.**

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