Poster #433

IN VITRO ACTIVITY OF OMIGANAN PENTAHYDROCHLORIDE AGAINST >1,600 CLINICAL TRIAL ISOLATES

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AMENDED ABSTRACT*

Background: Omiganan (OMI) is a rapidly bactericidal and fungicidal cationic peptide (CP) with broad spectrum, and with no identifiable resistance (R) mechanism. The objective of an ongoing Phase III clinical trial is to study the safety and efficacy of OMI 1% gel compared to "standard of care" in preventing intravascular catheter-site infections (CSI). We present a preliminary microbiology assessment of pathogen ranking and in vitro activity of OMI and comparator agents.

Methods: 2,118 isolates from 1,153 patients were submitted from trial sites in North America and Europe to a central laboratory for organism identification confirmation and susceptibility (S) testing by CLSI broth microdilution methods. Isolates originated from bloodstream (catheter line and peripheral samples), catheter insertion sites, and catheter tip and subcutaneous segments using roll plate and sonication methods. All isolates submitted from each patient (including duplicates) were in the analysis.

Results:

Organism (no.)	OMI MIC in µg/ml: MIC_{50}	MIC_{90}	Range
S. aureus (SA; 201)	16	32	8 - 32
Oxacillin (OX)-S (104)	16	16	8 - 32
OX-R (54)	32	32	8 - 32
Coagulase-negative staphylococci (CoNS; 1,258)	4	8	0.5 - 64
OX-S (274)	4	8	0.5 - 8
OX-R (696)	4	8	0.5 - 64
Enterococcus spp. (ENT; 169)	128	128	4 - 128
Candida spp. (73)	64	128	2 - 512
P. aeruginosa (PSA; 51)	128	256	64 - 512
Enterobacter spp. (EBS; 67)	128	256	32 - 512
Corynebacterium spp. (54)	2	4	0.5 - 4
Acinetobacter spp. (39)	64	64	≤4 - 128
E. coli (EC; 35)	32	64	16 - 64

Ranking pathogens (R-markers) included: CoNS (71.4% OX-R) > SA (39.8% OX-R) > ENT (1.2% vancomycin-R) > *Candida* spp. (16.4% fluconazole non-S) > EBS (35.8% ceftazidime-R > *Corynebacterium* spp. > PSA (11.8% meropenem-R) > *Acinetobacter* spp. (74.4% meropenem-resistant); see Table). ESBL-phenotypes for *Klebsiella* spp. and EC were 25.9 and 25.7%, respectively. OMI potency was unaffected by OX-R in CoNS and increased only 2-fold in OX-R SA. Mupirocin $MIC_{50/90}$ (% high-level R) results for CoNS and SA were ≤4/>256 (19.2%) and ≤4/≤4 µg/ml (3.0%), respectively. MIC_{50} results among yeast were *C. parapsilosis* (128 µg/ml) > *C. albicans* (64) > *C. tropicalis* (8).

Conclusion: At a clinical formulation of 1% (10,000 µg/ml), OMI inhibited all tested isolates (range, 0.5-512 µg/ml). OMI MICs were largely unaffected by prevailing R mechanisms, critical attributes for a topical CP agent being developed for prevention of CSI.

*Updated to include additional isolates

INTRODUCTION

Omiganan is a rapidly bactericidal and fungicidal cationic peptide analog of indolicidin that is known to significantly reduce normal skin flora counts following topical applications. This agent is being developed as a topical antimicrobic and is currently in a Phase III USA and European clinical trial for prevention of catheter-associated infections and in preclinical development for other indications. The compound has a broad spectrum of cidal activity including Gram-positive and -negative bacterial species and, importantly, yeast. The development of most catheter-related blood stream infections are thought to arise from colonization of the catheter and infection of tissues at the site of catheter placement; data from the National Nosocomial Infections Surveillance (NNIS) system has shown that the most commonly occurring organisms include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus* (including oxacillin- [methicillin]-resistant strains; MRSA), *Pseudomonas* spp., *Enterococcus* spp., Enterobacteriaceae and *Candida* spp., among others.

Given the importance of these pathogens in producing local catheter-site and catheter-related bloodstream infections, prevention of their occurrence can be expected to have significant impact on overall patient morbidity and mortality, and related health care costs (primarily extended hospital stays and additional treatment). The continued emergence of resistance among these pathogens further confounds this problem and poses special challenges in patient management.

The purpose of this study was to provide a preliminary assessment of the breadth of spectrum and potency of omiganan and comparator agents against organisms being recovered as part of a Phase III clinical trial. All organisms were recovered per protocol from peripheral or catheter blood draws, catheter insertion sites, or from cultured catheter segments using the roll plate and sonication techniques (upon meeting threshold criteria for significance).

MATERIALS AND METHODS

Organism collection studied: Studied isolates originated from bloodstream (catheter line and peripheral blood samples), catheter insertion sites, and catheter tip and subcutaneous segments using roll plate and sonication methods as published. A total of 2,118 isolates from 1,153 enrolled patients were submitted from trial sites in North America and Europe to a central laboratory (JMI Laboratories, North Liberty, Iowa) for organism identification confirmation and susceptibility (S) testing by CLSI broth microdilution methods. All isolates submitted from each patient were included in the analysis (see Table 1 for a listing of the top ranked species/organism groups recovered).

Susceptibility test methods: Broth microdilution MIC testing was performed according to Clinical and Laboratory Standards Institute (CLSI) methods (documents M7-A7 [2006]; M100-S17 [2007]; and M27-A2 [2002]). Panels were produced by JMI Laboratories using cation-adjusted Mueller-Hinton broth (with addition of 2 - 5 % lysed horse blood supplements for testing of fastidious species) and buffered RPMI 1640 for testing of yeasts (TREK Diagnostics, Cleveland, OH). Interpretive criteria for comparator agents, where available, were those as published by CLSI (M100-S17 [2007] and M27-S2 [2005]).

RESULTS

- The top ten ranked clinical trial pathogens (93.4% of the total) and key resistant markers included: coagulase-negative staphylococci (59.4%; 71.4% oxacillin-resistant) > *S. aureus* (9.5%; 39.8% oxacillin-resistant) > enterococci (8.0%; 1.2% vancomycin-resistant) > *Candida* spp. (3.4%; 16.4% fluconazole non-susceptible) > *Enterobacter* spp. (3.2%; 35.8% ceftazidime-resistant) > *Corynebacterium* spp. (2.5%) > *P. aeruginosa* (2.4%; 11.8% meropenem-resistant) > *Acinetobacter* spp. (1.8%; 74.4% meropenem-resistant) > *E. coli* (1.6%; 25.7% ESBL phenotype) > *Klebsiella* spp. (1.3%; 25.9% ESBL-phenotype).
- Among ranking pathogens, all Gram-positive isolates were inhibited by ≤128 µg/ml of omiganan, and Gram-negative species and yeasts by ≤512 µg/ml.
- Omiganan MIC_{50} potency was unaffected by oxacillin resistance in the coagulase-negative staphylococci compared with susceptible strains (both 8 µg/ml), and increased only two-fold (16 to 32 µg/ml) among oxacillin-resistant *S. aureus*.
- High level resistance to mupirocin was detected among both coagulase-negative staphylococci (19.2%) and *S. aureus* (3.0%).
- While >99% of oxacillin-susceptible coagulase negative staphylococci and *S. aureus* were susceptible to neomycin (breakpoint ≤10 µg/ml; one of the active components of triple antibiotic ointment), oxacillin-resistant strains were less so (87.4 and 15.0% susceptible, respectively).
- Neomycin was inactive against enterococci and variably active against Gram-negative species (*E. coli*, 88.6%; *Klebsiella* spp., 100.0%; *Enterobacter* spp., 98.5%, *P. aeruginosa*, 64.7% and *Acinetobacter* spp., 76.9%).
- Recovered *Candida* spp. were all susceptible to the marketed antifungal agents tested with the exceptions of *C. parapsilosis* (55.6% non-susceptible to fluconazole) and *C. tropicalis* (88.9% non-susceptible to itraconazole); all strains were inhibited by ≤256 µg/ml of omiganan.

Table 1. Cumulative percent inhibited at omiganan MIC values tested against species/groups of bacterial and fungal pathogens recovered as part of the a Phase III omiganan clinical trial (2,118 total isolates).

Organism group (no. tested)	Cumulative % inhibited at MIC values (µg/ml): ≤0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Coagulase-negative staphylococci (1,258)	<1	<1	3	65	99	>99	>99	100	-	-	-	-	-
Oxacillin-susceptible (360)	<1	<1	5	72	100	-	-	-	-	-	-	-	-
Oxacillin-resistant (898)	<1	<1	2	63	98	>99	>99	100	-	-	-	-	-
S. aureus (201)	0	0	0	0	17	77	100	-	-	-	-	-	-
Oxacillin-susceptible (121)	0	0	0	0	23	91	100	-	-	-	-	-	-
Oxacillin-resistant (80)	0	0	0	0	7	56	100	-	-	-	-	-	-
Enterococcus spp. (169)	0	0	0	4	7	8	9	42	100	-	-	-	-
Candida spp. (73)	0	0	0	0	7	8	18	70	99	100	-	-	-
Enterobacter spp. (67)	0	0	0	0	0	0	12	42	81	92	100	-	-
Corynebacterium spp.(54)	2	24	68	100	-	-	-	-	-	-	-	-	-
P. aeruginosa (51)	0	0	0	0	0	0	0	4	59	92	100	-	-
Acinetobacter spp. (39)	0	0	0	3	13	18	31	95	100	-	-	-	-
E. coli (35)	0	0	0	0	0	6	66	100	-	-	-	-	-
Klebsiella spp. (27)	0	0	0	0	0	7	48	63	74	93	100	-	-

Table 2. Activity of omiganan and comparator antimicrobial agents tested against ranking Gram-positive bacterial species recovered from catheter-associated infections.

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
S. aureus (201)				
Omiganan	16	32	8 - 32	- / -
Oxacillin	0.5	>2	≤0.25 - >2	60.2 / 39.8
Erythromycin	0.5	>8	0.12 - >8	53.2 / 42.3
Clindamycin	≤0.25	>4	≤0.25 - >4	69.7 / 30.3
Ciprofloxacin	0.5	>4	0.06 - >4	61.2 / 38.8
Tetracycline	≤2	>16	≤2 - >16	89.6 / 10.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 - 1	100.0 / 0.0
Neomycin	0.5	>16	≤0.12 - >16	65.7 / -
Mupirocin	≤4	≤4	≤4 - >256	- / -
Vancomycin	1	1	≤0.12 - 2	100.0 / 0.0
Coagulase-neg. staphylococci (1,258)				
Omiganan	4	8	0.5 - 64	- / -
Oxacillin	>2	>2	≤0.25 - >2	28.6 / 71.4
Erythromycin	>8	>8	≤0.06 - >8	37.4 / 62.0
Clindamycin	≤0.25	>4	≤0.25 - >4	68.0 / 31.0
Ciprofloxacin	4	>4	≤0.03 - >4	39.8 / 55.6
Tetracycline	≤2	8	≤2 - >16	89.4 / 9.6
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 - >2	66.5 / 33.5
Neomycin	≤0.12	8	≤0.12 - >16	90.9 / -
Mupirocin	≤4	>256	≤4 - >256	- / -
Vancomycin	1	2	0.25 - 4	100.0 / 0.0
Enterococcus spp. (169)				
Omiganan	128	128	4 - 128	- / -
Ampicillin	0.5	1	0.25 - >8	94.7 / 5.3
Ciprofloxacin	>4	>4	0.12 - >4	47.9 / 50.9
Erythromycin	>8	>8	0.12 - >8	10.1 / 68.0
Quinupristin/dalfopristin	>2	>2	0.5 - >2	4.7 / 87.6
Gentamicin (HL)	≤500	>500	≤500 - >500	55.0 / 45.0
Neomycin	>16	>16	2 - >16	1.8 / -
Mupirocin	256	256	≤4 - >256	- / -
Vancomycin	1	2	0.5 - >16	98.8 / 1.2
Corynebacterium spp. (54)				
Omiganan	2	4	0.5 - 4	- / -
Oxacillin	>2	>2	≤0.25 - >2	- / -
Erythromycin	>8	>8	≤0.06 - >8	- / -
Clindamycin	>4	>4	≤0.25 - >4	- / -
Ciprofloxacin	>4	>4	≤0.03 - >4	- / -
Tetracycline	≤2	16	≤2 - >16	- / -
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 - >2	- / -
Neomycin	>16	>16	≤0.12 - >16	- / -
Mupirocin	>256	>256	>256	- / -
Vancomycin	0.5	1	≤0.12 - 1	- / -

a. Susceptibility defined by the CLSI [2007]. β-lactam susceptibility should be directed by the oxacillin test results. Also the following criteria: mupirocin high level resistance at >256 µg/ml; neomycin at ≤ 10 µg/ml (susceptible); - = no interpretive criteria.

Table 3. Activity of omiganan and comparator antimicrobial agents tested against ranking Gram-negative bacterial species recovered from catheter-associated infections.

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
E. coli (35)				
Omiganan	32	64	16 - 64	- / -
Ampicillin	>16	>16	≤1 - >16	37.1 / 62.9
Ceftazidime	≤1	>16	≤1 - >16	77.1 / 22.9
Piperacillin/tazobactam	2	16	≤1 - >64	97.1 / 2.9
imipenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0
Ciprofloxacin	≤0.03	>4	≤0.03 - >4	71.4 / 28.6
Gentamicin	≤2	>8	≤2 - >8	77.1 / 22.9
Neomycin	2	>16	0.5 - >16	88.6 / -
Tetracycline	≤2	>8	≤2 - >8	54.3 / 45.7
Klebsiella spp. (27)				
Omiganan	64	256	16 - 512	- / -
Ampicillin	>16	>16	8 - >16	14.8 / 55.6
Ceftazidime	≤1	>16	≤1 - >16	74.1 / 25.9
Piperacillin/tazobactam	4	16	2 - 32	96.3 / 0.0
imipenem	≤0.12	≤0.12	≤0.12 - 0.25	100.0 / 0.0
Ciprofloxacin	≤0.03	>4	≤0.03 - >4	74.1 / 25.9
Gentamicin	≤2	≤2	≤2	100.0 / 0.0
Neomycin	4	4	0.25 - 8	100.0 / -
Tetracycline	≤2	≤2	≤2 - 4	100.0 / 0.0
Enterobacter spp. (67)				
Omiganan	128	256	32 - 512	- / -
Ampicillin	>16	>16	>16	0.0 / 100.0
Ceftazidime	4	>16	≤1 - >16	59.7 / 35.8
Piperacillin/tazobactam	8	>64	≤1 ->64	61.2 / 26.9
imipenem	≤0.12	0.5	≤0.12 - 1	100.0 / 0.0
Ciprofloxacin	≤0.03	>4	≤0.03 - >4	79.1 / 20.9
Gentamicin	≤2	>8	≤2 - >8	74.6 / 20.9
Neomycin	1	8	0.5 - 16	98.5 / -
Tetracycline	≤2	>8	≤2 - >8	71.6 / 26.9
P. aeruginosa (51)				
Omiganan	128	256	64 - 512	- / -
Ceftazidime	8	>16	2 - >16	52.0 / 30.0
Cefepime	4	>16	1 - >16	76.5 / 13.7
Piperacillin/tazobactam	8	>64	4 - >64	78.4 / 21.6
imipenem	2	16	≤0.12 - >16	54.9 / 11.8
Ciprofloxacin	0.25	>4	≤0.03 - >4	80.4 / 15.7
Gentamicin	≤2	>8	≤2 - >8	80.4 / 11.8
Neomycin	8	>16	4 - >16	64.7 / -
Acinetobacter spp. (39)				
Omiganan	64	64	≤4 - 128	- / -
Ceftazidime	>16	>16	≤1 - >16	15.4 / 79.5
Cefepime	>16	>16	≤0.12 - >16	23.1 / 74.4
Piperacillin/tazobactam	>64	>64	≤1 - >64	23.1 / 76.9
imipenem	>16	>16	≤0.12 - >16	25.6 / 74.4
Ciprofloxacin	>4	>4	≤0.03 - >4	20.5 / 79.5
Gentamicin	>8	>8	≤2 - >8	23.1 / 76.9
Neomycin	4	>16	0.25 - >16	76.9 / -

a. Susceptibility defined by the CLSI [2007] and the following criteria: neomycin at ≤10 µg/ml (susceptible only); - = no interpretive criteria.

Table 4. Activity of omiganan and comparator antimicrobial agents tested against ranking yeast species recovered from catheter-associated infections.

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
Candida spp. (73)				
Omiganan	64	128	8 - 256	- / -
Amphotericin B	0.5	1	0.06 - 1	- / -
Fluconazole	0.5	16	≤0.12 - 32	83.6 / 0.0
5-Flucytosine	0.06	0.12	≤0.03 - 1	100.0 / 0.0
Itraconazole	0.03	0.25	≤0.008 - 2	84.9 / 2.7
Voriconazole	≤0.008	0.25	≤0.008 - 0.5	100.0 / 0.0
Candida albicans (41)				
Omiganan	64	128	64 - 128	- / -
Amphotericin B	0.5	1	0.06 - 1	- / -
Fluconazole	0.25	0.5	≤0.12 - 1	100.0 / 0.0
5-Flucytosine	0.06	0.12	≤0.03 - 1	100.0 / 0.0
Itraconazole	0.015	0.03	≤0.008 - 0.06	100.0 / 0.0
Voriconazole	≤0.008	≤0.008	≤0.008 - 0.015	100.0 / 0.0
Candida parapsilosis (18)				
Omiganan	128	128	32 - 128	- / -
Amphotericin B	0.25	0.5	0.12 - 0.5	- / -
Fluconazole	16	32	0.25 - 32	44.4 / 0.0
5-Flucytosine	≤0.03	0.25	≤0.03 - 0.25	100.0 / 0.0
Itraconazole	0.06	0.12	0.03 - 0.12	100.0 / 0.0
Voriconazole	0.25	0.5	≤0.008 - 0.5	100.0 / 0.0
Candida tropicalis (9)				
Omiganan	8	-	8 - 32	- / -
Amphotericin B	1	-	0.5 - 1	- / -
Fluconazole	1	-	≤0.12 - 2	100.0 / 0.0
5-Flucytosine	0.12	-	0.06 - 0.25	100.0 / 0.0
Itraconazole	0.25	-	0.03 - 0.5	11.1 / 0.0
Voriconazole	0.03	-	≤0.008 - 0.12	100.0 / 0.0

a. Criteria as published by the CLSI [2006]; - = no interpretive criteria.

CONCLUSIONS

- Omiganan represents a 'first-in-class' agent that displays antimicrobial coverage of all major bacterial and fungal pathogens recovered during a clinical trial targeting prevention of local catheter-site and catheter-related bloodstream infections.
- At the clinical formulation concentration of 1% (topical gel; 10,000 µg/ml), omiganan is active against common skin microorganisms known to produce catheter-associated infections (highest documented MIC among ranking pathogens, 512 µg/ml), including strains with the most worrisome emerging resistance profiles.
- Ongoing surveillance of antimicrobial susceptibility of bacterial and fungal pathogens implicated in intravascular catheter-related infections is warranted to anticipate resistance trends, and susceptibility testing for omiganan should be included.

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