

AFN-1252, a FabI Inhibitor, Demonstrates a Staphylococcus-Specific Spectrum of Activity[∇]

James A. Karlowsky,^{1*} Nachum Kaplan,² Barry Hafkin,² Daryl J. Hoban,¹ and George G. Zhanel¹

Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada,¹ and Affinium Pharmaceuticals, Inc., Toronto, Ontario, Canada²

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AFN-1252, a potent inhibitor of enoyl-acyl carrier protein reductase (FabI), inhibited all clinical isolates of *Staphylococcus aureus* (n = 502) and *Staphylococcus epidermidis* (n = 51) tested, including methicillin (methicillin)-resistant isolates, at concentrations of ≤ 0.12 $\mu\text{g/ml}$. In contrast, AFN-1252 was inactive (MIC₉₀, >4 $\mu\text{g/ml}$) against clinical isolates of *Streptococcus pneumoniae*, beta-hemolytic streptococci, *Enterococcus* spp., *Enterobacteriaceae*, nonfermentative gram-negative bacilli, and *Moraxella catarrhalis*. These data support the continued development of AFN-1252 for the treatment of patients with resistant staphylococcal infections.

AFN-1252 is an investigational inhibitor of staphylococcal FabI, an essential enzyme that catalyzes the reduction of *trans*-2-enoyl-acyl carrier protein (*trans*-2-enoyl-ACP) to acyl-ACP, the final step in each elongation cycle of bacterial fatty acid biosynthesis (1, 7, 10). Enoyl-ACP reductase is known to have four distinct enzyme forms: FabI, FabK, FabL, and FabV (8). FabI is the sole form of enoyl-ACP reductase present in *Staphylococcus aureus*, *Staphylococcus epidermidis*, and a few other bacterial species (6, 8, 9). No alternative enzyme or rescue pathway for FabI in staphylococci has been identified, suggesting that FabI is essential to *Staphylococcus* cell viability and that resistance to FabI inhibitors such as AFN-1252 will not readily emerge with therapy (1).

AFN-1252 is being developed by Affinium Pharmaceuticals, Inc. (Toronto, Canada), in both oral and intravenous formulations, for the treatment of antimicrobial-susceptible and -resistant staphylococcal infections, particularly infections caused by *S. aureus*. The structure of AFN-1252 has been described previously (9). AFN-1252 has demonstrated in vivo efficacy in a murine subcutaneous abscess model using a strain of methicillin (methicillin)-resistant *S. aureus* (12). The present study was undertaken to assess the in vitro activities of AFN-1252 against recent clinical isolates of staphylococci, as well as other gram-positive cocci and gram-negative bacilli, to demonstrate the full antibacterial spectrum of activity of AFN-1252.

Clinically relevant isolates were collected at 12 Canadian hospital laboratories from January to December 2007 as a part of the ongoing CANWARD in vitro surveillance study and shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) for identity confirmation and antimicrobial susceptibility testing. Multidrug-resistant staphylococci were defined as those isolates that were resistant to two or more of the agents ciprofloxacin, clindamycin, and gentamicin and included both methicillin-susceptible and methicillin-resistant isolates. Vancomycin-intermediate *S. aureus* and vanco-

mycin-resistant *S. aureus* isolates were obtained through the Network on Antimicrobial Resistance in *Staphylococcus aureus* program (supported under NIAID, NIH, contract no. N01-AI-95359) for testing against AFN-1252.

Clinical and Laboratory Standards Institute (CLSI)-specified broth microdilution testing was performed using frozen, in-house-prepared, 96-well panels containing AFN-1252 and comparative agents (3). Dimethyl sulfoxide was used as the solvent and diluent for AFN-1252. AFN-1252 was tested over a doubling-dilution concentration range of 0.008 to 4 $\mu\text{g/ml}$, and its MICs were recorded following 20 to 24 h of incubation at 35°C in ambient air. MICs were interpreted using CLSI M100-S17 guidelines (2). For the reference strain *S. aureus* ATCC 29213, AFN-1252 reproducibly demonstrated an MIC of 0.015 $\mu\text{g/ml}$.

AFN-1252 inhibited all isolates of methicillin-susceptible and methicillin-resistant *S. aureus* and *S. epidermidis* at concentrations of ≤ 0.12 $\mu\text{g/ml}$ (Table 1). AFN-1252 demonstrated MIC₉₀s for methicillin-resistant *S. aureus* and *S. epidermidis* and multidrug-resistant *S. aureus* and *S. epidermidis* (data not shown) of ≤ 0.008 $\mu\text{g/ml}$. AFN-1252 was less active in vitro against vancomycin-intermediate *S. aureus* isolates (n = 12; MIC₉₀, 0.12 $\mu\text{g/ml}$) and vancomycin-resistant *S. aureus* isolates (n = 12; MIC₉₀, 0.06 $\mu\text{g/ml}$) than against vancomycin-susceptible isolates (MIC₉₀, ≤ 0.008 $\mu\text{g/ml}$) (data not shown). AFN-1252 was inactive (MIC range, 4 to >4 $\mu\text{g/ml}$) against non-staphylococcal gram-positive pathogens and gram-negative pathogens (Table 1).

In this study, AFN-1252 demonstrated narrow-spectrum, staphylococcus-specific in vitro activity and was inactive against all nonstaphylococcal potential human pathogens tested, including streptococci, enterococci, species of *Enterobacteriaceae*, nonfermentative gram-negative bacilli, and *Moraxella catarrhalis*. AFN-1252's narrow-spectrum, staphylococcus-specific activity may be an attractive attribute for the treatment of patients with staphylococcal infections or the decolonization of patients with methicillin-resistant *S. aureus* because, compared to other treatment agents, it has a reduced risk of selecting for resistance in normal flora and other colonizing bacterial species and a reduced risk of altering normal flora

* Corresponding author. Mailing address: Department of Clinical Microbiology, Health Sciences Centre, MS673C, 820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada. Phone: (204) 787-4597. Fax: (204) 787-4699. E-mail: jkarlowsky@hsc.mb.ca.

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TABLE 1. Activities of AFN-1252 and comparator agents against staphylococci, nonstaphylococcal gram-positive pathogens, and gram-negative pathogens

Species or isolate group (no. of isolates)	Agent	MIC (µg/ml)			% of isolates classified by MIC as:		
		50%	90%	Range	Susceptible	Intermediate	Resistant
Methicillin-susceptible <i>S. aureus</i> (375)	AFN-1252	≤0.008	≤0.008	≤0.008–0.12			
	Cefazolin	≤0.5	1	≤0.5–8	100	0	0
	Ciprofloxacin	0.5	8	≤0.06–>16	83.8	4.2	12.0
	Clindamycin	≤0.12	≤0.12	≤0.12–>8	91.0	0.4	8.6
	Gentamicin	≤0.5	1	≤0.5–>32	96.7	0.1	3.2
	Linezolid	2	2	≤0.12–4	100	0	0
	Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	99.3		0.7
	Vancomycin	1	1	≤0.25–2	100	0	0
	Methicillin-resistant <i>S. aureus</i> (127)	AFN-1252	≤0.008	≤0.008	≤0.008–0.06		
Cefazolin		64	>128	32–>128	0	0	100
Ciprofloxacin		>16	>16	0.25–>16	10.1	0.3	89.6
Clindamycin		>8	>8	≤0.12–>8	37.9	0.3	61.8
Gentamicin		≤0.5	>32	≤0.5–>32	86.8	0	13.2
Linezolid		2	4	0.25–4	100	0	0
Trimethoprim-sulfamethoxazole		≤0.12	8	≤0.12–>8	87.8		12.2
Vancomycin		1	1	≤0.25–2	100	0	0
Methicillin-susceptible <i>S. epidermidis</i> (42)		AFN-1252	≤0.008	0.03	≤0.008–0.06		
	Cefazolin	1	4	≤0.5–8	100	0	0
	Ciprofloxacin	4	>16	≤0.06–>16	47.2	0	52.8
	Clindamycin	≤0.12	>8	≤0.12–>8	61.1	0	38.9
	Gentamicin	≤0.5	>32	≤0.5–>32	58.3	10.2	31.5
	Linezolid	0.5	1	≤0.12–2	100	0	0
	Trimethoprim-sulfamethoxazole	1	>8	≤0.12–>8	58.3		41.7
	Vancomycin	1	2	≤0.25–2	100	0	0
	Methicillin-resistant <i>S. epidermidis</i> (9)	AFN-1252	≤0.008	≤0.008	≤0.008		
Cefazolin		64	128	32–128	0	0	100
Ciprofloxacin		>16	>16	8–>16	0	0	100
Clindamycin		>8	>8	≤0.12–>8	10.0	0	90.0
Gentamicin		16	>32	≤0.5–>32	30.0	15.0	55.0
Linezolid		1	1	0.5–1	100	0	0
Trimethoprim-sulfamethoxazole		4	8	≤0.12–>8	25.0		75.0
Vancomycin		1	2	1–2	100	0	0
<i>Streptococcus pneumoniae</i> (489)		AFN-1252	>4	>4	4–>4		
	Penicillin	0.06	0.25	≤0.03–>8	79.3	15.7	5.0
	Levofloxacin	0.5	1	≤0.06–32	99.4	0	0.6
	Ceftriaxone	≤0.06	0.12	≤0.06–4	99.7	0.2	0.1
	Linezolid	0.5	1	≤0.12–2	100		
	Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8	86.3	6.7	7.0
	Vancomycin	≤0.25	≤0.25	≤0.25–0.5	100		
	<i>Streptococcus pyogenes</i> (73)	AFN-1252	>4	>4	>4		
Penicillin		≤0.03	≤0.03	≤0.03–0.12	100		
Ciprofloxacin		1	2	0.25–4			
Clindamycin		≤0.06	≤0.06	≤0.06–>8	97.3	0	2.7
Linezolid		1	1	0.5–2	100		
Trimethoprim-sulfamethoxazole		≤0.12	≤0.12	≤0.12–0.25			
Vancomycin		0.5	0.5	≤0.25–0.5	100		
<i>Streptococcus agalactiae</i> (86)		AFN-1252	>4	>4	>4		
	Penicillin	0.06	0.25	≤0.03–0.12	100		
	Ciprofloxacin	1	2	0.5–>16			
	Clindamycin	≤0.06	>8	≤0.06–>8	85.2	2.3	12.5
	Linezolid	1	1	≤0.12–2	100		
	Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–0.25			
	Vancomycin	≤0.25	≤0.25	≤0.25–0.5	100		
	<i>Enterococcus faecalis</i> (81)	AFN-1252	>4	>4	>4		
Cefazolin		32	128	0.5–>128			
Ciprofloxacin		2	>16	0.25–>16	38.3	26.6	35.1
Clindamycin		>8	>8	≤0.12–>8			
Linezolid		2	2	0.5–4	98.7	1.3	0
Trimethoprim-sulfamethoxazole		≤0.12	0.25	≤0.12–>8			
Vancomycin		1	2	0.5–4	100	0	0

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TABLE 1—Continued

Species or isolate group (no. of isolates)	Agent	MIC ($\mu\text{g/ml}$)			% of isolates classified by MIC as:		
		50%	90%	Range	Susceptible	Intermediate	Resistant
<i>Enterococcus faecium</i> (38)	AFN-1252	>4	>4	4->4			
	Cefazolin	>128	>128	32->128			
	Ciprofloxacin	>16	>16	1->16	12.1	5.2	82.7
	Clindamycin	>8	>8	≤ 0.12 ->8			
	Linezolid	2	2	1-4	91.4	8.6	0
	Trimethoprim-sulfamethoxazole	≤ 0.12	>8	≤ 0.12 ->8			
<i>E. coli</i> (599)	AFN-1252	4	>4	0.5->4			
	Cefazolin	2	64	≤ 0.5 ->128	82.1	3.8	14.1
	Ciprofloxacin	≤ 0.06	>16	≤ 0.06 ->16	75.2	0.3	24.5
	Gentamicin	≤ 0.5	16	≤ 0.5 ->32	88.9	0.5	10.6
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 -0.5	100	0	0
	Piperacillin-tazobactam	2	4	≤ 1 ->512	97.6	1.0	1.4
<i>K. pneumoniae</i> (199)	AFN-1252	>4	>4	2->4			
	Cefazolin	2	8	≤ 0.5 ->128	91.4	1.8	6.8
	Ciprofloxacin	≤ 0.06	0.5	≤ 0.06 ->16	92.5	0.9	6.6
	Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5 ->32	96.7	0.4	2.9
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 -0.25	100	0	0
	Piperacillin-tazobactam	2	8	≤ 1 ->512	96.7	1.3	2.0
<i>Klebsiella oxytoca</i> (32)	AFN-1252	>4	>4	2->4			
	Cefazolin	8	32	≤ 0.5 ->128	60.0	23.0	17.0
	Ciprofloxacin	≤ 0.06	0.12	≤ 0.06 ->16	95.0	2.0	3.0
	Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5 ->32	97.0	2.0	1.0
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 -0.12	100	0	0
	Piperacillin-tazobactam	2	16	≤ 1 ->512	90.0	1.0	9.0
<i>Enterobacter cloacae</i> (72)	AFN-1252	>4	>4	4->4			
	Cefazolin	128	>128	1->128	5.4	3.6	91.0
	Ciprofloxacin	≤ 0.06	0.5	≤ 0.06 ->16	91.6	0.6	7.8
	Gentamicin	≤ 0.5	1	≤ 0.5 ->32	96.4	0	3.6
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 -0.5	100	0	0
	Piperacillin-tazobactam	2	64	≤ 1 ->512	82.6	8.4	9.0
<i>Proteus mirabilis</i> (34)	AFN-1252	4	>4	2->4			
	Cefazolin	8	16	1-64	86.6	8.4	5.0
	Ciprofloxacin	≤ 0.06	2	≤ 0.06 ->16	82.4	8.4	9.2
	Gentamicin	1	2	≤ 0.5 ->32	95.8	0.8	3.4
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 -0.25	100	0	0
	Piperacillin-tazobactam	2	64	≤ 1 -2	100	0	0
<i>Serratia marcescens</i> (39)	AFN-1252	4	>4	2->4			
	Cefazolin	>128	>128	2->128	0.9	0	99.1
	Ciprofloxacin	0.12	2	≤ 0.06 -16	88.8	3.7	7.5
	Gentamicin	≤ 0.5	1	≤ 0.5 ->32	91.6	3.7	4.7
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 -2	100	0	0
	Piperacillin-tazobactam	2	8	≤ 1 -128	94.4	4.7	0.9
<i>Pseudomonas aeruginosa</i> (137)	AFN-1252	>4	>4	>4			
	Cefazolin	>128	>128	16->128			
	Ciprofloxacin	0.5	16	≤ 0.06 ->16	66.0	11.0	23.4
	Gentamicin	4	>32	≤ 0.5 ->32	60.1	19.0	20.9
	Meropenem	0.5	8	≤ 0.06 ->64	87.8	4.1	8.1
	Piperacillin-tazobactam	4	64	≤ 1 ->512	92.7	0	7.3
<i>Stenotrophomonas maltophilia</i> (26)	AFN-1252	>4	>4	>4			
	Cefazolin	>128	>128	128->128			
	Ciprofloxacin	4	>16	≤ 0.06 ->16			
	Gentamicin	32	>32	≤ 0.5 ->32			
	Meropenem	>64	>64	≤ 0.06 ->64			

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TABLE 1—Continued

Species or isolate group (no. of isolates)	Agent	MIC ($\mu\text{g/ml}$)			% of isolates classified by MIC as:		
		50%	90%	Range	Susceptible	Intermediate	Resistant
<i>Acinetobacter baumannii</i> (15)	Piperacillin-tazobactam		>512	16->512			
	Trimethoprim-sulfamethoxazole	1	>8	≤ 0.12 ->8	75.5		24.5
	AFN-1252	>4	>4	>4			
	Cefazolin	>128	>128	64->128			
	Ciprofloxacin	0.25	4	0.12->16	88.0	0	12.0
	Gentamicin	≤ 0.5	1	≤ 0.5 ->32	92.0	0	8.0
	Meropenem	0.5	4	≤ 0.06 -32	92.0	0	8.0
	Piperacillin-tazobactam	4	>512	≤ 1 ->512	76.0	12.0	12.0
<i>M. catarrhalis</i> (70)	Trimethoprim-sulfamethoxazole	≤ 0.12	>8	≤ 0.12 ->8	84.0		16.0
	AFN-1252	>4	>4	2->4			
	Penicillin	>8	>8	≤ 0.03 ->8			
	Ciprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06	100		
	Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5			
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06			
	Piperacillin-tazobactam	≤ 1	≤ 1	≤ 1			
	Trimethoprim-sulfamethoxazole	≤ 0.12	0.5	≤ 0.12 -1	94.0	6.0	0

and will potentially contribute minimally to the overall burden of resistance intrinsic with broad-spectrum agents.

Only one previously published study has described the in vitro activity of AFN-1252 (9). In that study, all 350 isolates of methicillin-susceptible and 154 isolates of methicillin-resistant *S. aureus* were inhibited by concentrations of AFN-1252 of $\leq 0.12 \mu\text{g/ml}$, results identical to the data presented in this study (Table 1). All methicillin-susceptible ($n = 50$) and methicillin-resistant ($n = 50$) *S. epidermidis* isolates were inhibited by concentrations of AFN-1252 of $\leq 0.5 \mu\text{g/ml}$ ($\text{MIC}_{90\%}$, 0.03 to 0.06 $\mu\text{g/ml}$) (9), two doubling dilutions higher than those reported in the present study (Table 1). AFN-1252 has been reported to be inactive in vitro against gram-positive anaerobes, including *Bifidobacterium* spp., *Clostridium perfringens*, *Clostridium difficile*, *Eubacterium lentum*, *Lactobacillus* spp., *Peptostreptococcus* spp., and *Propionibacterium acnes*, as well as gram-negative anaerobes, including *Bacteroides* spp., *Fusobacterium* spp., *Porphyrionomonas* spp., *Prevotella* spp., and *Veillonella parvula* (8).

Our data revealed that organisms other than staphylococci, specifically *M. catarrhalis*, *Escherichia coli*, and *Klebsiella pneumoniae*, that possess FabI as their sole enoyl-ACP reductase (10) were nonsusceptible to AFN-1252. Staphylococci, *E. coli*, *M. catarrhalis*, and *Haemophilus influenzae* have been shown previously to possess FabI and to lack an alternative enzyme or rescue pathway (1). We speculate that *M. catarrhalis*, *E. coli*, and *K. pneumoniae* are not susceptible to AFN-1252, despite possessing FabI as their sole enoyl-ACP reductase, because these gram-negative organisms may possess an efflux mechanism for or present a permeability barrier to AFN-1252. AFN-1252 may be a substrate for the *acrAB* efflux pump of *E. coli*, as the AFN-1252 MIC for an *acrAB*-deficient mutant (AG100a ΔacrAB) has been demonstrated previously to be 0.016 $\mu\text{g/ml}$ while the MIC for the parental strain (AG100) is $>32 \mu\text{g/ml}$ (8). The FabI active sites of these gram-negative bacteria have structural differences from the *S. aureus* active site used to direct the iterative structure-guided development of AFN-1252 (Affinium Pharmaceuticals, Inc., unpublished data). Alterna-

tively, FabI may be overexpressed in these species, as the overexpression of FabI in *S. aureus* has been reported to reduce the activity of triclosan, an agent whose mechanism of action also involves interaction with FabI (11).

In conclusion, escalating rates of resistance may limit the clinical utility of some currently marketed antibacterial agents and underlie the search for new classes of agents with novel mechanisms of action. AFN-1252 is a promising new agent with the potential to treat patients with staphylococcal infections known or suspected to be resistant to conventional antistaphylococcal therapies in both hospital and outpatient settings. These data support the continued development of AFN-1252 for the treatment of patients with resistant staphylococcal infections.

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