CEM-102 (Fusidic Acid) Maintains Potency against Resistant MRSA and Prevalent Hospital Acquired, Community Acquired, and Epidemic MRSA Clones

C.M. Pillar[1], M.K. Torres[1], D.F. Sahm[1] and P. Fernandes[2]

[1]Eurofins Medinet, Chantilly, VA, [2]Cempra Pharmaceuticals, Chapel Hill, NC

CM Pillar, Eurofins Medinet
14100 Park Meadow Dr., Ste 110
Chantilly, VA
703-480-2535

Abstract

Background: MRSA, a prevalent pathogen of hospital and community acquired infections, can be difficult to treat due to resistance. Recently, resistance has emerged to commonly utilized anti-MRSA agents (e.g. linezolid [LZD], daptomycin [DAP], and vancomycin [VAN]) illustrating the need for new agents. CEM-102 (fusidic acid) is currently undergoing clinical development for the treatment of skin infections in the US. This study evaluates the *in vitro* activity of CEM-102 against prevalent community-acquired, hospital-acquired, and epidemic clones including isolates non-susceptible (NS) to anti-MRSA agents.

Methods: 56 MRSA from the NARSA and Eurofins Medinet repositories were tested for susceptibility to CEM-102 and comparators by broth microdilution according to current CLSI guidelines. Isolates included those with rare resistance phenotypes (VISA/VRSA [n=10], LZD and DAP NS isolates [n=20]) and isolates from prevalent community (USA300/400 [n=10]), hospital (USA100/800 [n=10]), and epidemic clones (e.g. Iberian, UK-EMRSA 15/16 [n=5]).

Results: Against the selected resistant MRSA, CEM-102 had an MIC range of 0.06-8 mg/mL with an MIC_{50} and MIC_{90} of 0.12 mg/mL. With the exception of 1 VISA isolate (with an MIC of 1 mg/mL), 2 DAP NS isolates (with MICs of 4 mg/mL), and 1 LZD NS isolate (with an MIC of 8 mg/mL), CEM-102 MICs were 0.06-0.12 mg/mL against MRSA with rare but emerging resistance phenotypes. Against a subset of 10 community, 10 hospital, and 5 epidemic clones, CEM-102 MICs were 0.06-0.12 mg/mL.

Conclusions: CEM-102 had potent *in vitro* activity against MRSA NS to currently utilized agents (VAN, LZD, and DAP). CEM-102 was also active against USA100 and USA300 MRSA, clones of MRSA most likely to be encountered clinically in the US today. Based on its potency and activity against established and emerging resistance phenotypes among MRSA, these results highlight the potential of CEM-102 for the treatment of MRSA in the US.

Introduction

•*S. aureus* is the most prevalent pathogen of both community and hospital acquired skin and skin structure infections (SSSI)

•MRSA are commonly encountered clinically and, though rare, *S. aureus* with reduced susceptibility to other commonly utilized Gram-positive agents (vancomycin/linezolid/daptomycin) have emerged

•Fusidic acid is approved for use in Europe and is currently under development in the US for the treatment of acute bacterial SSSI (ABSSSI) as CEM-102, utilizing a novel oral dosing regimen designed to maximize bioavailability to increase coverage and minimize resistance development

•This study evaluates the *in vitro* activity of CEM-102 and other Gram-negative agents against select resistant *S. aureus* isolates (e.g. VISA/VRSA, linezolid/daptomycin non-susceptible) and prevalent MRSA clones (e.g. USA100 and USA300)

Materials and Methods

•Clinical *S. aureus* isolates non-susceptible to currently utilized Gram-positive agents (vancomycin/linezolid/daptomycin) were selected from the Eurofins Medinet Repository (Chantilly, VA) and the repository for the Network on Antimicrobial Resistance in *S. aureus* (NARSA, developed and supported by NIAID)

•Genetically characterized MRSA consisting of prevalent community-acquired isolates (PFGE type USA300/400), hospital-acquired isolates (PFGE type USA100/600/800), and epidemic clones (PFGE type Iberian, Brazilian/Hungarian, etc.) were also selected from The Eurofins and NARSA repositories

•With the exception of 5 isolates (2 Japanese, 3 European) selected for their rare resistance phenotypes and 7 global epidemic strains, all isolates were of US origin

•Selected resistant *S. aureus* isolates were tested for susceptibility to CEM-102 and comparator agents by broth microdilution in accordance with CLSI M7-A8 and CLSI M100-S20

Results

Table 1. CEM-102 and comparator activity against select resistant *S. aureus* from the NARSA and Eurofins repositories (N=56)

Antimicrobial	MIC (µg/mL) Range	Mode	MIC_{50}	MIC_{90}	%S[A]	%I	%R
CEM-102 (Fusidic Acid)	0.06-8	0.12	0.12	0.12	94.6	-	5.4
Daptomycin	0.25-2	0.5	0.5	2	87.5	-	-
Linezolid	1->4	2	2	>4	87.5	-	12.5
Vancomycin	1->32	2	2	8	71.4	19.6	8.9
Azithromycin	0.25->8	>8	>8	>8	28.6	0.0	71.4
Clindamycin	0.06->4	0.12	0.25	>4	57.1	5.4	37.5
Gentamicin	≤0.06->16	0.25	0.5	>16	71.4	1.8	26.8
Ciprofloxacin	0.25->4	>4	>4	>4	25.0	3.6	71.4
Tetracycline	0.12->32	0.25	0.5	32	73.2	1.8	25.0
SXT	≤0.5->4	≤0.5	≤0.5	>4	89.3	-	10.7
Oxacillin	2->4	>4	>4	>4	1.8	-	98.2

[A]CLSI M100-S20 interpretive criteria applied with the exception of CEM-102 (EUCAST breakpoints applied)

Figure 1. Distribution of CEM-102 MICs against resistant *S. aureus* (A) overall and (B) by phenotype/genotype

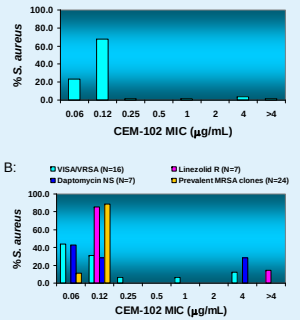

Figure 2. Cumulative susceptibility of resistant *S. aureus* to CEM-102 and comparators

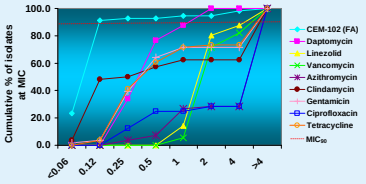

Table 2. Antibiogram of CEM-102 and comparators against *S. aureus* with reduced susceptibility to glycopeptides

Pre-Selected Phenotype	Strain ID	MIC (µg/mL) and Interpretation[A] CEM-102	Daptomycin	Linezolid	Vancomycin	Azithromycin	Clindamycin	Gentamicin	Ciprofloxacin	Tetracycline	SXT
VISA	VISA (Mu50)	NRS1	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	>16 (R)	>4 (R)	>32 (R)	≤0.5 (S)
VISA	hVISA (Mu3)	NRS2	0.06 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	>16 (R)	>4 (R)	>32 (R)	≤0.5 (S)
VISA	VISA	NRS3	0.06 (S)	1 (S)	1 (S)	8 (I)	>8 (R)	>4 (R)	>16 (R)	>4 (R)	1 (S)	≤0.5 (S)
VISA	VISA	NRS4	0.12 (S)	0.5 (S)	2 (S)	4 (I)	>8 (R)	>4 (R)	0.5 (S)	>4 (R)	0.5 (S)	≤0.5 (S)
VISA	VISA	NRS17	1 (S)	1 (S)	2 (S)	8 (I)	8 (R)	0.06 (S)	16 (R)	0.25 (S)	2 (S)	≤0.5 (S)
VISA	VISA	NRS22	0.06 (S)	1 (S)	2 (S)	4 (I)	>8 (R)	>4 (R)	8 (I)	>4 (R)	0.12 (S)	≤0.5 (S)
VISA	VISA	NRS73	0.06 (S)	2 (NS)	1 (S)	8 (I)	1 (S)	0.12 (S)	>16 (R)	>4 (R)	32 (R)	>4 (R)
VISA	VISA	NRS74	0.06 (S)	1 (S)	2 (S)	8 (I)	>8 (R)	>4 (R)	>16 (R)	>4 (R)	0.25 (S)	≤0.5 (S)
VISA	VISA	NRS79	0.25 (S)	1 (S)	2 (S)	4 (I)	>8 (R)	>4 (R)	0.5 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
VISA	2861091	4 (R)	2 (NS)	4 (S)	4 (I)	>8 (R)	0.12 (S)	>16 (S)	>4 (R)	0.5 (S)	≤0.5 (S)	
VISA	2861092	0.12 (S)	0.5 (S)	>4 (R)	4 (I)	>8 (R)	0.12 (S)	>16 (R)	>4 (R)	1 (S)	≤0.5 (S)	
VISA	2861094	4 (R)	2 (NS)	2 (S)	4 (I)	1 (S)	0.5 (S)	≤0.06 (S)	0.5 (S)	0.5 (S)	≤0.5 (S)	
VISA	2861095	0.12 (S)	2 (NS)	1 (S)	2 (S)	>8 (R)	0.12 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)	
VISA	2861118	0.06 (S)	2 (NS)	1 (S)	8 (I)	>8 (R)	>4 (R)	0.5 (S)	>4 (R)	0.12 (S)	≤0.5 (S)	
VISA	2861126	0.06 (S)	1 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	>16 (S)	>4 (R)	32 (R)	>4 (R)	
VRSA	NRS128	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	1 (S)	1 (S)	>16 (S)	>4 (R)	32 (R)	>4 (R)	
VRSA	NRS120	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	1 (S)	1 (S)	>16 (S)	>4 (R)	32 (R)	>4 (R)	
VRSA	NRS121	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	2 (S)	1 (S)	0.25 (S)	>4 (R)	32 (R)	≤0.5 (S)	
VRSA	NRS127	0.12 (S)	0.25 (S)	4 (S)	2 (S)	>8 (R)	0.06 (S)	0.25 (S)	>4 (R)	16 (R)	≤0.5 (S)	
VRSA	NRS271	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	1 (S)	0.5 (S)	0.12	>4 (R)	0.5 (S)	≤0.5 (S)	
VRSA	2861090	8 (R)	0.25 (S)	>4 (R)	2 (S)	1 (S)	0.25 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)	
VRSA	2861092	0.12 (S)	0.5 (S)	>4 (R)	4 (I)	>8 (R)	0.12 (S)	1 (S)	>4 (R)	1 (S)	1 (S)	
VRSA	2861125	0.06 (S)	0.25 (S)	4 (S)	2 (S)	0.25 (S)	0.5 (S)	0.25 (S)	>4 (R)	1 (S)	≤0.5 (S)	
VRSA	2861127	0.12 (S)	0.25 (S)	>4 (R)	2 (S)	>8 (R)	>4 (R)	>16 (S)	>4 (R)	0.25 (S)	≤0.5 (S)	
VRSA	2861128	0.12 (S)	0.5 (S)	4 (S)	2 (S)	0.25 (S)	0.5 (S)	0.25 (S)	>4 (R)	1 (S)	≤0.5 (S)	

[A]CLSI M100-S20 interpretive criteria applied with the exception of CEM-102 (EUCAST breakpoints applied)

Table 3. Antibiogram of CEM-102 and comparators against daptomycin and linezolid non-susceptible *S. aureus*

Pre-Selected Phenotype	Strain ID	MIC (µg/mL) and Interpretation[A] CEM-102	Daptomycin	Linezolid	Vancomycin	Azithromycin	Clindamycin	Gentamicin	Ciprofloxacin	Tetracycline	SXT
Daptomycin NS	NRS73	0.06 (S)	2 (NS)	1 (S)	8 (I)	1 (S)	0.12 (S)	>16 (S)	>4 (R)	32 (R)	>4 (R)
Daptomycin NS	NRS74	0.06 (S)	1 (S)	2 (S)	8 (I)	>8 (R)	>4 (R)	>16 (S)	>4 (R)	0.25 (S)	≤ 0.5 (S)
Daptomycin NS	NRS79	0.25 (S)	1 (S)	2 (S)	4 (I)	>8 (R)	>4 (R)	0.5 (S)	>4 (R)	0.25 (S)	≤ 0.5 (S)
Daptomycin NS	2861089	0.06 (S)	2 (NS)	2 (S)	2 (S)	>8 (R)	0.12 (S)	1 (S)	0.5 (S)	0.25 (S)	≤ 0.5 (S)
Daptomycin NS	2861091	4 (R)	2 (NS)	4 (S)	4 (I)	>8 (R)	0.12 (S)	>16 (S)	>4 (R)	0.5 (S)	≤ 0.5 (S)
Daptomycin NS	2861093	0.12 (S)	2 (NS)	2 (S)	2 (S)	>8 (R)	>4 (R)	0.5 (S)	>4 (R)	1 (S)	≤ 0.5 (S)
Daptomycin NS	2861094	4 (R)	2 (NS)	2 (S)	4 (I)	1 (S)	0.5 (S)	≤0.06 (S)	0.5 (S)	0.5 (S)	≤ 0.5 (S)
Daptomycin NS	2861095	0.12 (S)	2 (NS)	1 (S)	2 (S)	>8 (R)	0.12 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤ 0.5 (S)
Daptomycin NS	2861118	0.06 (S)	2 (NS)	1 (S)	8 (I)	>8 (R)	>4 (R)	0.5 (S)	>4 (R)	0.12 (S)	≤ 0.5 (S)
Daptomycin NS	2861126	0.06 (S)	1 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	>16 (S)	>4 (R)	32 (R)	>4 (R)
Linezolid R	NRS128	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	1 (S)	1 (S)	>16 (S)	>4 (R)	32 (R)	>4 (R)
Linezolid R	NRS120	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	1 (S)	1 (S)	>16 (S)	>4 (R)	32 (R)	>4 (R)
Linezolid R	NRS121	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	2 (S)	1 (S)	0.25 (S)	>4 (R)	32 (R)	≤ 0.5 (S)
Linezolid R	NRS127	0.12 (S)	0.25 (S)	4 (S)	2 (S)	>8 (R)	0.06 (S)	0.25 (S)	>4 (R)	16 (R)	≤ 0.5 (S)
Linezolid R	NRS271	0.12 (S)	0.5 (S)	>4 (R)	2 (S)	1 (S)	0.5 (S)	0.12	>4 (R)	0.5 (S)	≤ 0.5 (S)
Linezolid R	2861090	8 (R)	0.25 (S)	>4 (R)	2 (S)	1 (S)	0.25 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤ 0.5 (S)
Linezolid R	2861092	0.12 (S)	0.5 (S)	>4 (R)	4 (I)	>8 (R)	0.12 (S)	1 (S)	>4 (R)	1 (S)	1 (S)
Linezolid R	2861125	0.06 (S)	0.25 (S)	4 (S)	2 (S)	0.25 (S)	0.5 (S)	0.25 (S)	>4 (R)	1 (S)	≤ 0.5 (S)
Linezolid R	2861127	0.12 (S)	0.25 (S)	>4 (R)	2 (S)	>8 (R)	>4 (R)	>16 (S)	>4 (R)	0.25 (S)	≤ 0.5 (S)
Linezolid R	2861128	0.12 (S)	0.5 (S)	4 (S)	2 (S)	0.25 (S)	0.5 (S)	0.25 (S)	>4 (R)	1 (S)	≤ 0.5 (S)

[A]CLSI M100-S20 interpretive criteria applied with the exception of CEM-102 (EUCAST breakpoints applied)

Table 4. Antibiogram of CEM-102 and comparators against prevalent MRSA clones

	PFGE Type	Strain ID	MIC (µg/mL) and Interpretation[A] CEM-102	Daptomycin	Linezolid	Vancomycin	Azithromycin	Clindamycin	Gentamicin	Ciprofloxacin	Tetracycline	SXT
Global epidemic	UK-EMRSA-15	2861097	0.12 (S)	0.25 (S)	2 (S)	1 (S)	0.5 (S)	0.12 (S)	0.5 (S)	0.25 (S)	0.5 (S)	≤0.5 (S)
Global epidemic	UK-EMRSA-16	2861098	0.12 (S)	0.5 (S)	2 (S)	1 (S)	>8 (R)	0.12 (S)	0.25 (S)	>4 (R)	0.5 (S)	≤0.5 (S)
Global epidemic	Iberian	2861099	0.06 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	1 (S)	0.25 (S)	>32 (R)	≤0.5 (S)
Global epidemic	Brazilian/ Hungarian	2861100	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	1 (S)	0.25 (S)	>32 (R)	>4 (R)
Global epidemic	Berlin	2861101	0.06 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
Global epidemic	S. German	2861102	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	>16 (R)	>4 (R)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS382	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	0.25 (S)	>4 (R)	0.5 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS642	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS660	0.12 (S)	0.5 (S)	2 (S)	2 (S)	1 (S)	0.12 (S)	0.25 (S)	0.5 (S)	>32 (R)	≤0.5 (S)
HA-MRSA	USA100	NRS670	0.12 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS680	0.12 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	>4 (R)	0.5 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS695	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	>4 (R)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS708	0.12 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA100	NRS720	0.12 (S)	0.25 (S)	2 (S)	2 (S)	1 (S)	0.12 (S)	0.25 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA600	NRS22	0.06 (S)	1 (S)	2 (S)	4 (I)	>8 (R)	>4 (R)	8 (I)	>4 (R)	0.12 (S)	>4 (R)
HA-MRSA	USA800	NRS387	0.12 (S)	0.5 (S)	1 (S)	2 (S)	1 (S)	0.12 (S)	0.25 (S)	0.25 (S)	0.25 (S)	≤0.5 (S)
HA-MRSA	USA800	NRS384	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	2 (I)	32 (R)	>4 (R)
CA-MRSA	USA300	NRS643	0.12 (S)	0.5 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	>4 (R)	0.25 (S)	≤0.5 (S)
CA-MRSA	USA300	NRS662	0.12 (S)	0.5 (S)	2 (S)	1 (S)	>8 (R)	0.12 (S)	0.5 (S)	0.25 (S)	0.25 (S)	≤0.5 (S)
CA-MRSA	USA300	NRS677	0.12 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	>4 (R)	0.5 (S)	≤0.5 (S)
CA-MRSA	USA300	NRS683	0.12 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	0.5 (S)	0.25 (S)	≤0.5 (S)
CA-MRSA	USA300	NRS702	0.12 (S)	0.25 (S)	1 (S)	2 (S)	>8 (R)	0.12 (S)	0.5 (S)	2 (I)	0.25 (S)	≤0.5 (S)
CA-MRSA	USA300	NRS707	0.12 (S)	0.25 (S)	2 (S)	2 (S)	>8 (R)	0.12 (S)	0.25 (S)	0.5 (S)	0.25 (S)	≤0.5 (S)
CA-MRSA	USA400	NRS123	0.12 (S)	0.5 (S)	2 (S)	2 (S)	1 (S)	0.12 (S)	0.25 (S)	0.5 (S)	0.5 (S)	≤0.5 (S)
CA-MRSA	USA400	NRS192	0.12 (S)	0.5 (S)	2 (S)	2 (S)	0.5 (S)	0.12 (S)	0.5 (S)	0.5 (S)	32 (R)	≤0.5 (S)
CA-MRSA	USA400	NRS193	0.12 (S)	0.25 (S)	2 (S)	2 (S)	1 (S)	0.12 (S)	0.25 (S)	0.25 (S)	0.25 (S)	≤0.5 (S)

[A]CLSI M100-S20 interpretive criteria applied with the exception of CEM-102 (EUCAST breakpoints applied)

•Against the pre-selected resistant *S. aureus* evaluated, CEM-102 had an overall MIC_{50} and MIC_{90} of 0.12 µg/mL, several fold lower than the other evaluated agents (**Table 1**)

•Among the pre-selected resistant *S. aureus* and MRSA clones; 20% were VISA, 9% were VRSA, 13% were daptomycin non-susceptible and 13% were linezolid resistant (**Table 1**)

•Based on overall MIC distribution (**Figure 1A**), CEM-102 typically had an MIC of ≤ 0.12 mg/mL (91%), with few isolates (5%) having MICs > 1 µg/mL, and no isolates having a CEM-102 MIC exceeding 8 µg/mL (10-fold lower than the 80 µg/mL maintained in the serum during the proposed CEM-102 dosing regimen)

•The CEM-102 MIC distribution was not notably altered by evaluated resistance phenotype or genotype (**Figure 1B**), though for the three isolates with CEM-102 MICs of 4-8 µg/mL, two were daptomycin non-susceptible and one was linezolid resistant (**Table 3**)

•The increased potency of CEM-102 relative to the other agents against the evaluated isolates was apparent by plotting cumulative susceptibility against MIC (**Figure 2**)

•Evaluated VISA/VRSA isolates (**Table 2**), though largely susceptible to CEM-102, were commonly resistant to other evaluated classes of agents

•Hospital-acquired (HA-MRSA), community-acquired (CA-MRSA), and epidemic clones were 100% susceptible to CEM-102, including isolates with resistance across several classes of evaluated agents (e.g. USA100/600) (**Table 4**)

Conclusions

•CEM-102 (Fusidic acid) had potent *in vitro* activity against selected *S. aureus* with resistance to currently utilized Gram-positive active agents

•CEM-102 was also active against clinical isolates of prevalent epidemic, hospital-acquired, and community-acquired clones of MRSA

•The activity profile of CEM-102 which includes commonly encountered clinical CA-MRSA and HA-MRSA and also MRSA with challenging resistance phenotypes (e.g. VISA/VRSA, daptomycin/linezolid non-susceptible) highlights the potential clinical utility of this agent for the oral treatment of skin and skin structure infections

Acknowledgements

This study was supported by a grant from Cempra Pharmaceuticals. Eurofins would like to acknowledge Parveen Grover and Dinesh Shah for their contributions to this study, and would also like to acknowledge the NARSA program for providing many of the *S. aureus* utilized in this study.