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AFABICIN DESPHOSPHONO *IN VITRO* ACTIVITY AGAINST *STAPHYLOCOCCUS* SPP.
Data From A Five-Year Susceptibility Surveillance Study (2018-2023)

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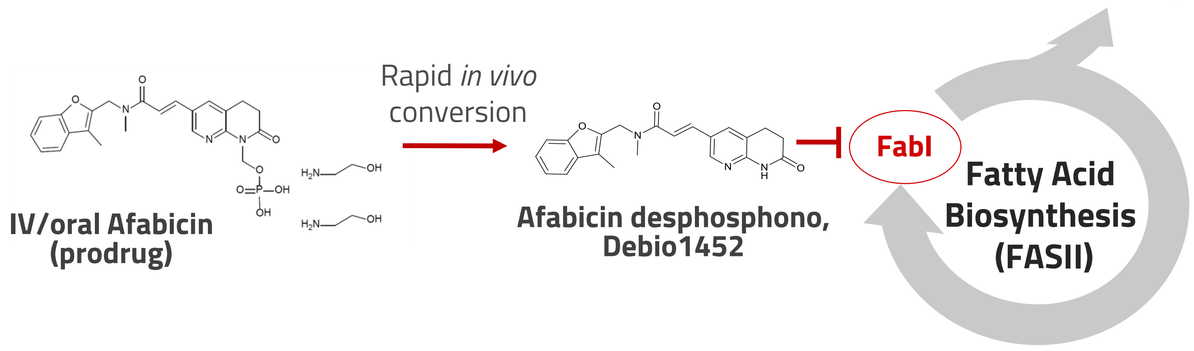
BACKGROUND

Afabicin is a novel first-in-class, narrow-spectrum antibacterial selectively targeting *Staphylococcus* spp. with the potential for sparing the gut microbiota (1). Afabicin is a prodrug that is converted to its active form afabicin desphosphono which inhibits the FabI enzyme in bacteria, crucially disrupting their fatty acid synthesis.



Promising safety and efficacy results have been obtained in Phase 2 trials in acute bacterial skin and skin structure infections (ABSSSI) (2) and bone and joint infections (BJI), following intravenous and oral administrations.

This surveillance study investigated the antibacterial activity of afabicin desphosphono and comparators against recent clinical *Staphylococcus* spp. isolates collected globally during 5 years of surveillance.

METHODS

A total of 602 clinical isolates were collected in Europe (37.9%), North America (33.9%), Latin-America (11.1%), Asia-Pacific (10.6%) and Africa/Middle East (6.5%) from staphylococcal infections affecting various body sites including skin and skin structure (30.0%), lower respiratory tract (23.4%), blood (19.4%), intra-abdominal sites (9.2%) and other sites (18.0%).

MIC determination and susceptibility testing was conducted by broth microdilution according to CLSI standards and clinical breakpoints (3,4).

RESULTS

- ✓ Afabicin desphosphono was the most active agent tested, with MIC_{90} of 0.008 mg/L against all *S. aureus* (Table 1).
- ✓ The tested isolates included 49.2% MRSA strains that were largely susceptible to the comparators with the exception of levofloxacin (52.4% resistant) and clindamycin (23.1% resistant) (MRSA data not shown in Tables).

Table 1. *In vitro* activity of afabicin desphosphono and comparators against *S. aureus* (N=423)

Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	% S	% I	% R
Afabicin [a]	**0.004**	**0.008**	**0.002-0.12**	-	-	-
Ceftaroline	0.25	0.5	≤0.12->4	98.8	0.9	0.2
Clindamycin	0.06	>4	≤0.03->4	87.5	0.2	12.3
Daptomycin	1	1	0.25-4	99.3	-	-
Doxycycline	0.12	1	≤0.03->4	96.0	4.0	0.0
Levofloxacin	0.25	>4	0.06->4	70.4	1.4	28.1
Linezolid	2	2	0.25-2	100.0	0.0	0.0
Omadacycline	0.5	1	0.25-4	-	-	-
Oxacillin	2	>8	0.12->8	50.8	-	49.2
Rifampin	0.008	0.015	≤0.004->0.12	100.0	0.0	0.0
Trimethoprim-Sulfamethoxazole	≤0.06	≤0.06	≤0.06->4	98.8	-	1.2
Vancomycin	1	1	0.25-2	100.0	0.0	0.0

a, Afabicin desphosphono; $MIC_{50/90}$, minimum inhibitory concentration (MIC) at which 50% and 90% of isolates are inhibited
S, susceptible; I, intermediate; R, resistant according to CLSI breakpoints M100 (2024)

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RESULTS continued

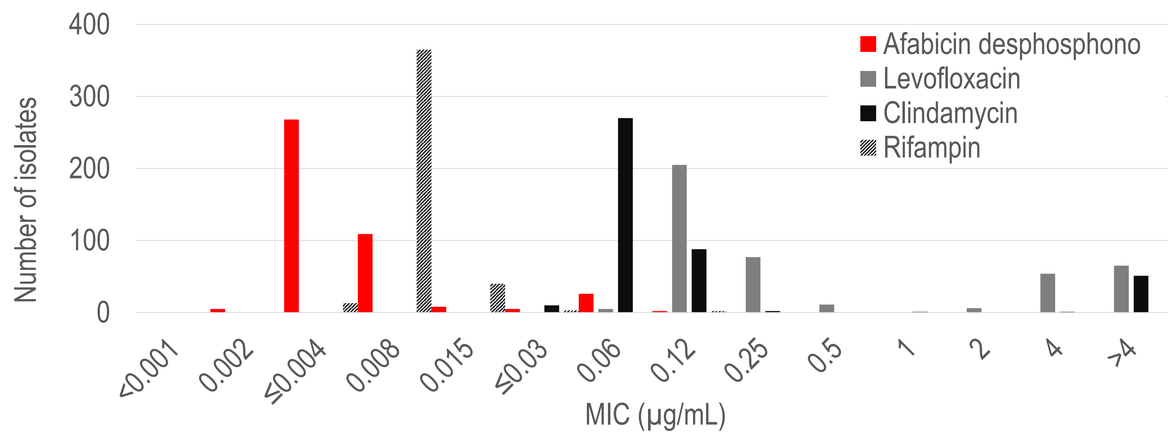
- ✓ Methicillin-, clindamycin- and levofloxacin-resistant *S. aureus* subsets remained fully sensitive to afabicin desphosphono (MIC_{90} values of 0.008 mg/L, Table 2, Figure 1).

Table 2. MIC_{90} (mg/L) of afabicin desphosphono and comparators against resistant *S. aureus* subsets

	N	Afabicin [a]	Cef-taroline	Dapto-mycin	Linezolid	Rifampin	Vanco-mycin
S. aureus, total	423	**0.008**	0.5	1	2	0.015	1
MRSA [b]	208	**0.008**	1	1	2	0.008	1
Clindamycin-resistant [b]	52	**0.008**	1	1	2	0.008	1
Levofloxacin-resistant [b]	119	**0.008**	1	1	2	0.015	1

a, Afabicin desphosphono; b, resistant isolates are subsets of the total *S. aureus* isolates tested
MRSA, methicillin-resistant *S. aureus*

Figure 1. MIC distribution of afabicin desphosphono and comparators against *S. aureus*



- ✓ When evaluated against coagulase-negative *Staphylococcus* spp. (CoNS), afabicin desphosphono was again the most potent agent (MIC_{90} of 0.06 mg/L, Table 3) and its activity was not affected by resistance to comparator antibacterials (data not shown).
- ✓ Overall, the MIC distributions were similar for isolates from different geographical origin (data not shown in Tables).

Table 3. *In vitro* activity of afabicin desphosphono and comparators against coagulase-negative *Staphylococcus* spp. (N=179)

Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)
Afabicin [a]	**0.015**	**0.06**	**≤0.001-0.25**
Ceftaroline	≤0.12	1	≤0.12-2
Clindamycin	0.06	>4	≤0.03->4
Daptomycin	0.5	1	0.12-4
Doxycycline	0.12	2	≤0.03->4
Levofloxacin	0.25	>4	≤0.03->4
Linezolid	1	1	0.25-2
Omadacycline	0.5	2	0.25-2
Oxacillin	1	>8	≤0.06->8
Rifampin	0.008	>0.12	≤0.004->0.12
Trimethoprim-Sulfamethoxazole	0.25	>4	≤0.06->4
Vancomycin	1	2	0.12-2

[a], Afabicin desphosphono

CONCLUSIONS

- ✓ **Afabicin desphosphono demonstrated potent *in vitro* antibacterial activity against all *S. aureus* and coagulase-negative *Staphylococcus* isolates**
- ✓ **The afabicin desphosphono activity was unaffected by resistance to other antibacterials, consistent with previous surveillance results** (5)
- ✓ **These results, together with the positive phase 2 clinical trial data in ABSSSI and in BJI, support the continued development of afabicin**

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