P1824

Activity of Debio 1452 against *Staphylococcus* spp. collected in 2015 / 2016

Stephen Hawser[1], Melinda Gueny[1], Isabelle Rochat[1], Ian Morrissey[1], Sophie Magnet[1], Guennaëlle Dieppois*[2]

[1]IHMA Europe Sàrl,Route de l'Ile-au-Bois 1A, 1870 Monthey, Switzerland; [2]Debiopharm International SA, Forum "après-demain", Chemin Messidor 5-7, 1006 Lausanne, Switzerland

IHMA Europe Sàrl
Route de l'Ile-au-Bois 1A
Monthey 1870, Switzerland
e-mail: shawser@ihma.com

Abstract

Background. Debio 1452 is the active moiety of the prodrug afabicin (Debio 1450), which is currently in Phase II clinical development for staphylococcal infections. Afabicin is an oral and IV first-in-class antibiotic specifically targeting *Staphylococcus* species through FabI inhibition. The current study evaluated the activity of Debio 1452 and comparator antibiotics against *Staphylococcus* spp. collected from various geographical locations during 2015-2016.

Materials/methods. A total of 758 clinical isolates collected during 2015 and 2016 from European, North American, Latin America and Asian hospitals were tested. Of these, 363, 228, 80 and 87 were MRSA, MSSA, *S. epidermidis* and other *Staphylococcus* species, respectively. Minimal inhibitory concentrations (MICs) were determined following CLSI guidelines.

Results. The table below summarizes results for Debio 1452. Debio 1452 was the most active agent tested with MIC_{90} for all *S. aureus*, all MRSA and all MSSA of 0.015, 0.008 and 0.015 mg/L, respectively. The overall range for all *S. aureus* was 0.002 – 0.25 mg/L. Debio 1452 showed similar activity against all *S. aureus*, MRSA and MSSA sub-groups with respect to geographical origin. Against *S. epidermidis*, Debio 1452 was again the most active agent with an MIC_{90} and MIC range of 0.03 and 0.004 – 0.25 mg/L, respectively. Similar MIC_{90} values were observed with MRSE and MSSE isolates. Against other *Staphylococcus* species (a total of 12 species identified) an MIC_{90} of 0.06 and an MIC range of 0.004 – 0.12 mg/L was observed. Activity was not affected by resistance to comparator antimicrobials.

	Debio 1452 MIC (mg/L)			
Organism	**MIC_{50}**	**MIC_{90}**	**Min**	**Max**
***S. aureus* (591)**	**0.008**	**0.015**	**0.002**	**0.25**
MRSA (363)	**0.008**	**0.008**	**0.004**	**0.25**
MSSA (228)	0.008	0.015	0.002	0.25
S. epidermidis (80)	0.015	0.03	0.004	0.25
MRSE (53)	0.015	0.03	0.004	0.25
MSSE (27)	0.015	0.015	0.004	0.06
Other staphylococci (87)	0.015	0.06	0.004	0.12

Conclusion. Consistent with historical data, Debio 1452 exhibited excellent *in vitro* activity against all staphylococci tested in the study. The in vitro activity of Debio 1452 was superior to other agents with no cross-resistance.

Introduction

Debio 1452 (previously known as AFN-1252) is the active moiety of afabicin (Debio 1450 previously known as AFN-1720), an IV and oral first in class antibiotic specifically targeting *Staphylococcus* species (through FabI inhibition) which is currently in Phase 2 clinical development. *In vivo*, afabicin is rapidly converted into its active moiety Debio 1452, which displays excellent and selective potency against *Staphylococcus* species.

The current study evaluated the *in vitro* activity of Debio 1452, against staphylococci clinical isolates, including methicillin-resistant (MRSA), methicillin-susceptible (MSSA) and other staphylococci collected during 2015 – 2016.

Materials & Methods

A total of 758 clinical isolates collected during the period 2015 – 2016 were tested. Of these, 363, 228, 80 and 87 were methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA), *S. epidermidis* and other *Staphylococcus*. *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were tested as quality control (QC) organisms.

MIC tests were performed by broth microdilution (final volume 100 µl) against all isolates in line with CLSI susceptibility testing standards (1,2). For Debio 1452, DMSO was used as both solvent and diluent according to CLSI guidelines for drug with low aqueous solubility (Direct Method for insoluble compounds CLSI).

Results

Table 1. Summary susceptibility data for Debio 1452 and comparators against all *S. aureus* (n = 591)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	<=1 | 2 | >=4	591	96.3	2.7	1.0	0.5	1	0.06	16
Clindamycin	<=0.5 | 1-2 | >=4	591	80.9	0.2	19.0	0.12	> 32	<= 0.03	> 32
Daptomycin	<=1 | -- | --	591	99.8	0.0	0.2	0.25	0.5	0.12	2
Debio 1452	**NB**	**591**	**-**	**-**	**-**	**0.008**	**0.015**	**0.002**	**0.25**
Doxycycline	<=4 | 8 | >=16	591	93.6	5.8	0.7	0.12	2	0.06	16
Linezolid	<=4 | -- | >=8	591	100.0	0.0	0.0	2	2	0.5	2
Oxacillin	<=2 | -- | >=4	591	38.6	0.0	61.4	> 8	> 8	0.12	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	591	96.5	0.0	3.6	0.06	0.12	<= 0.03	> 32
Vancomycin	<=2 | 4-8 | >=16	591	100.0	0.0	0.0	1	1	0.25	2

NB, no breakpoint available; %Susc, %Int, %Res, % of isolates susceptible, intermediate or resistant, respectively

Table 2. Summary susceptibility data for Debio 1452 and comparators against all MRSA (n = 363)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	<=1 | 2 | >=4	363	93.9	4.4	1.7	1	1	0.12	16
Clindamycin	<=0.5 | 1-2 | >=4	363	71.6	0.0	28.4	0.12	> 32	0.06	> 32
Daptomycin	<=1 | -- | --	363	99.7	0.0	0.3	0.25	0.5	0.12	2
Debio 1452	**NB**	**363**	**-**	**-**	**-**	**0.008**	**0.008**	**0.004**	**0.25**
Doxycycline	<=4 | 8 | >=16	363	90.9	8.0	1.1	0.12	4	0.06	16
Linezolid	<=4 | -- | >=8	363	100.0	0.0	0.0	2	2	0.5	2
Oxacillin	<=2 | -- | >=4	363	0.0	0.0	100.0	> 8	> 8	4	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	363	94.5	0.0	5.5	0.06	0.25	<= 0.03	> 32
Vancomycin	<=2 | 4-8 | >=16	363	100.0	0.0	0.0	1	1	0.25	2

NB, no breakpoint available; %Susc, %Int, %Res, % of isolates susceptible, intermediate or resistant, respectively

Table 3. Summary susceptibility data for Debio 1452 and comparators against all MSSA (n = 228)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	<=1 | 2 | >=4	228	100.0	0.0	0.0	0.25	0.5	0.06	0.5
Clindamycin	<=0.5 | 1-2 | >=4	228	95.6	0.4	4.0	0.12	0.12	<= 0.03	> 32
Daptomycin	<=1 | -- | --	228	100.0	0.0	0.0	0.25	0.5	0.12	1
Debio 1452	**NB**	**228**	**-**	**-**	**-**	**0.008**	**0.015**	**0.002**	**0.25**
Doxycycline	<=4 | 8 | >=16	228	97.8	2.2	0.0	0.12	0.5	0.06	8
Linezolid	<=4 | -- | >=8	228	100.0	0.0	0.0	2	2	0.5	2
Oxacillin	<=2 | -- | >=4	228	100.0	0.0	0.0	0.5	0.5	0.12	2
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	228	99.6	0.0	0.4	0.06	0.06	<= 0.03	16
Vancomycin	<=2 | 4-8 | >=16	228	100.0	0.0	0.0	1	1	0.5	2

NB, no breakpoint available; %Susc, %Int, %Res, % of isolates susceptible, intermediate or resistant, respectively

Table 4. Summary susceptibility data for Debio 1452 and comparators against all *S. epidermidis* (n = 80)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	NB	80	-	-	-	0.25	0.5	<= 0.03	2
Clindamycin	<=0.5 | 1-2 | >=4	80	72.5	0.0	27.5	0.12	> 32	<= 0.03	> 32
Daptomycin	<=1 | -- | --	80	100.0	0.0	0.0	0.25	0.5	0.12	1
Debio 1452	**NB**	**80**	**-**	**-**	**-**	**0.015**	**0.03**	**0.004**	**0.25**
Doxycycline	<=4 | 8 | >=16	80	96.3	2.5	1.3	0.5	1	<= 0.03	16
Linezolid	<=4 | -- | --	80	98.8	0.0	1.3	1	1	0.12	> 16
Oxacillin	<=0.25 | -- | >=0.5	80	33.8	0.0	66.3	2	> 8	0.06	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	80	63.8	0.0	36.3	0.25	8	<= 0.03	16
Vancomycin	<=4 | 8-16 | >=32	80	100.0	0.0	0.0	1	2	1	2

NB, no breakpoint available; %Susc, %Int, %Res, % of isolates susceptible, intermediate or resistant, respectively

Table 5. Summary susceptibility data for Debio 1452 and comparators against other *Staphylococcus* spp (n=87)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	NB	87	-	-	-	0.25	1	<= 0.03	2
Clindamycin	<=0.5 | 1-2 | >=4	87	70.1	0.0	29.9	0.12	> 32	<= 0.03	> 32
Daptomycin	<=1 | -- | --	87	98.9	0.0	1.2	0.25	1	0.06	2
Debio 1452	**NB**	**87**	**-**	**-**	**-**	**0.015**	**0.06**	**0.004**	**0.12**
Doxycycline	<=4 | 8 | >=16	87	95.4	2.3	2.3	0.12	2	<= 0.03	16
Linezolid	<=4 | -- | --	87	100.0	0.0	0.0	1	1	0.25	2
Oxacillin	<=0.25 | -- | >=0.5	80	53.8	0.0	46.3	0.25	> 8	0.06	> 8
Oxacillin*	<=2 | -- | >=4	7	100.0	0.0	0.0	1	1	0.5	1
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	87	79.3	0.0	20.7	0.12	16	<= 0.03	> 32
Vancomycin	<=4 | 8-16 | >=32	87	100.0	0.0	0.0	1	2	0.25	2

NB, no breakpoint available; %Susc, %Int, %Res, % of isolates susceptible, intermediate or resistant, respectively; **Oxacillin breakpoint for *S. lugdunensis*

Figure 1. Cumulative MIC distributions for Debio 1452 and comparators against all *S. aureus* (n = 591)

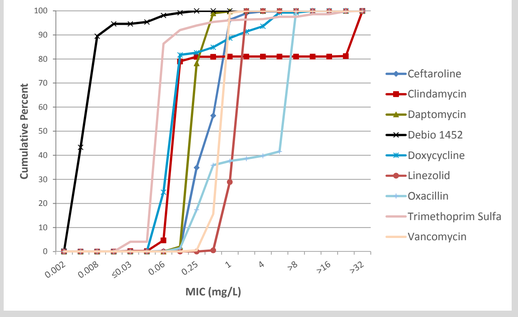


Figure 2. Cumulative MIC distributions for Debio 1452 and comparators against MRSA (n = 363)

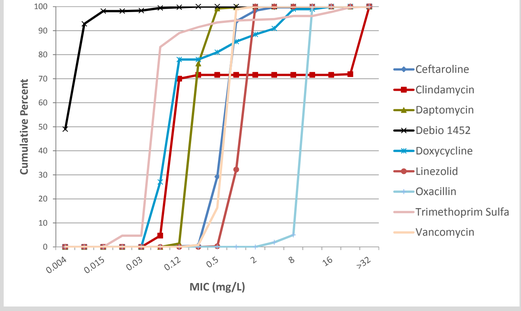


Figure 3. Cumulative MIC distributions for Debio 1452 and comparators against MSSA (n = 228)

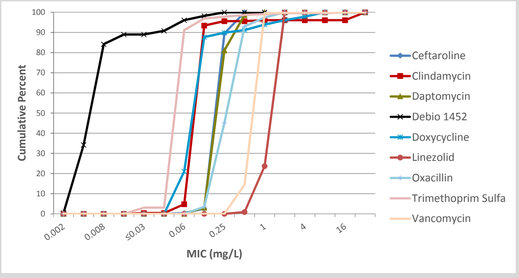


Figure 4. Cumulative MIC distributions for Debio 1452 and comparators against *S. epidermidis* (n = 80)

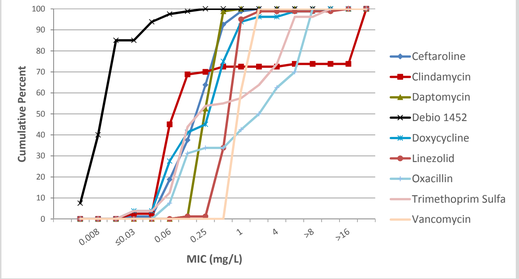
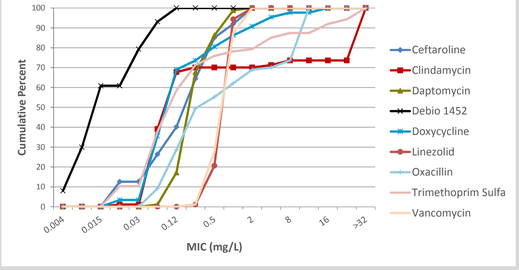


Figure 5. Cumulative MIC distributions for Debio 1452 and comparators against other staphylococci (n = 87)



Results Summary

- Debio 1452 was the most potent agent tested with MIC_{90} for all *S. aureus* (n = 591), all MRSA (n = 363) and all MSSA (n = 228) of 0.015, 0.008 and 0.015 mg/L, respectively (Tables 1-3).
- Against *S. epidermidis* (n = 80), Debio 1452 was again the most active agent with an MIC_{90} and MIC range of 0.03 and 0.004 – 0.25 mg/L, respectively (Table 4). Activity of Debio 1452 was the same against MRSE species (n = 87; a total ofand MSSE.
- Against other *Staphylococcus* 11 species), MIC_{90} and MIC range of 0.06 and 0.004 – 0.12 mg/L, respectively. (Table 5).
- The overall range for all staphylococci was 0.002 – 0.25mg/L (Figures 1-5).
- Debio 1452 showed similar activity againts staphylococci exhibiting a resistance to the other comparators.
- Debio 1452 activity for all staphylococci was not affected by geographical origin (data not shown).

Conclusions

- Consistent with historical data, Debio 1452 exhibited excellent *in vitro* activity against all staphylococci tested in the study. The highest MIC was 0.25 mg/L.
- The activity of Debio 1452 was superior to other agents with no cross-resistance.
- Further studies are warranted in support of clinical development of afabicin for the treatment of staphylococcal infection.

References and Acknowledgment:

1. Clinical and Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility test for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition. M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA, USA.
2. Clinical and Laboratory Standards Institute. 2016. Performance Standards for Antimicrobial Susceptibility testing; twenty-Fifth Informational Supplement. M100-S26. Clinical and Laboratory Standards Institute, Wayne, PA, USA.

This study was sponsored by a grant from Debiopharm International SA