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Activity of Debio 1452 against *Staphylococcus* spp. collected in 2013 / 2014

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Revised Abstract

Background. Debio 1452 is the active moiety of the prodrug Debio 1450, which is currently in Phase 2 clinical development for staphylococcal infections. Debio 1450 is an IV and oral first in class antibiotic specifically targeting *Staphylococcus* species through FabI inhibition. Due to its unique mechanism of action, Debio 1450 should preserve the human microbiome and reduce antibiotic associated complications such as *Clostridium difficile* related colitis and diarrhea and candidiasis. The current study evaluated the activity of Debio 1452 against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA) and other staphylococci including coagulase negative staphylococci collected from various geographical locations during 2013 – 2014. **Materials/methods**. A total of 821 clinical isolates collected during the period 2013 / 2014 from European, North American, Latin America and Asian hospitals were tested. Of these, 402, 258, 95 and 66 were MRSA, MSSA, *S. epidermidis* and other *Staphylococcus* species, respectively. Minimal inhibitory concentrations (MICs) for Debio 1452 and eight antibiotic comparators were determined following CLSI guidelines. **Results.** Summary results for Debio 1452 are shown in the Table. Debio 1452 was the most potent agent tested with MIC_{90} for all *S. aureus* (n = 660), all MRSA (n = 402) and all MSSA (n = 258) of 0.008, 0.008 and 0.015 mg/L, respectively. The overall range for all *S. aureus* (n = 660) was ≤ 0.001 – 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* (n = 95), Debio 1452 was again the most active agent with an MIC_{90} and MIC range of 0.03 and 0.008 – 0.5 mg/L, respectively. Against other *Staphylococcus* species (a total of 11 species), MIC_{90} and MIC range were of 0.015 and 0.004 – 0.5 mg/L, respectively. Activity was not affected by resistance to comparator antimicrobials.

	Debio 1452 MIC (mg/L):			
Organism	MIC_{50}	MIC_{90}	Min	Max
S. aureus (660)	0.004	0.008	≤ 0.001	0.25
MRSA (402)	0.004	0.008	≤ 0.001	0.25
MSSA (258)	0.008	0.015	0.002	0.25
S. epidermidis (95)	0.015	0.03	0.008	0.5
Other staphylococci (66)	0.015	0.06	0.004	0.5

Conclusion. Debio 1452 exhibited excellent *in vitro* activity against all clinical isolates tested in the study. In the present study, Debio 1452 exhibited superior activity as compared with other agents and no cross-resistance to other antimicrobials was observed, consistent with historical data. Further studies are warranted in support of clinical development of Debio 1450 for staphylococcal infections.

Introduction

Debio 1452 (previously known as AFN-1252) is the active moiety of 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*, Debio 1450 is rapidly converted into its active moiety Debio 1452, which displays excellent and selective potency against *Staphylococcus* species.

The current study evaluated the activity of the active moiety of Debio 1450 (Debio 1452) against methicillin-resistant (MRSA), methicillin-susceptible (MSSA) and other staphylococci collected from various geographical locations during 2013 – 2014.

Materials & Methods

A total of 821 clinical isolates originating from skin and skin structure, blood or bone infections and collected in 2013 and 2014 were tested. Of these, 402, 258, 95 and 66 were methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA), *S. epidermidis* and other *Staphylococcus* spp., respectively. The 66 *Staphylococcus* spp. comprised *S. heamolyticus* (n = 15), *S. hominis* (n = 15), *S. lugdunensis* (n = 13), *S. capitis* (n = 8), *S. warneri* (n = 5), *S. simulans* (n = 3), *S. schleiferi* (n = 2) and one isolate each of non-speciated coagulase-negative staphylococci, *S. caprae*, *S. cohnii*, *S. intermedius* and *S. saprophyticus*.

MIC tests were performed by broth microdilution (final volume 100 µl) against all isolates in line with CLSI susceptibility testing standards (1, 2). *S. aureus* ATCC 29213 was tested as quality control (QC) organism.

Results

Table 1. Summary susceptibility data for Debio 1452 and comparators against all *S. aureus* (n = 660)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	<=1 | 2 | >=4	660	97.7	2.3	0.0	0.5	1	0.06	2
Clindamycin	<=0.5 | 1-2 | >=4	660	82.7	0.0	17.3	0.12	> 32	<= 0.03	> 32
Daptomycin	<=1 | -- | --	660	99.9	0.0	0.2	0.5	0.5	0.12	4
Debio 1452	**NB**	**660**	**-**	**-**	**-**	**0.008**	**0.008**	**<= 0.001**	**0.25**
Doxycycline	<=4 | 8 | >=16	660	95.5	3.8	0.8	0.12	1	<= 0.03	16
Linezolid	<=4 | -- | >=8	660	100.0	0.0	0.0	2	2	1	4
Oxacillin	<=2 | -- | >=4	660	39.1	0.0	60.9	> 8	> 8	0.12	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	660	97.7	0.0	2.3	0.06	0.12	<= 0.03	> 32
Vancomycin	<=2 | 4-8 | >=16	660	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 MRSA (n = 402)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	<=1 | 2 | >=4	402	96.3	3.7	0.0	0.5	1	0.12	2
Clindamycin	<=0.5 | 1-2 | >=4	402	73.6	0.0	26.4	0.12	> 32	0.06	> 32
Daptomycin	<=1 | -- | --	402	99.8	0.0	0.3	0.5	0.5	0.12	4
Debio 1452	**NB**	**402**	**-**	**-**	**-**	**0.004**	**0.008**	**<= 0.001**	**0.25**
Doxycycline	<=4 | 8 | >=16	402	93.8	5.0	1.2	0.12	1	0.06	16
Linezolid	<=4 | -- | >=8	402	100.0	0.0	0.0	2	2	1	4
Oxacillin	<=2 | -- | >=4	402	0.0	0.0	100.0	> 8	> 8	4	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	402	96.5	0.0	3.5	0.06	0.12	<= 0.03	> 32
Vancomycin	<=2 | 4-8 | >=16	402	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 MSSA (n = 258)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	<=1 | 2 | >=4	258	100.0	0.0	0.0	0.25	0.25	0.06	0.5
Clindamycin	<=0.5 | 1-2 | >=4	258	96.9	0.0	3.1	0.12	0.25	<= 0.03	> 32
Daptomycin	<=1 | -- | --	258	100.0	0.0	0.0	0.5	0.5	0.12	1
Debio 1452	**NB**	**258**	**-**	**-**	**-**	**0.008**	**0.015**	**0.002**	**0.25**
Doxycycline	<=4 | 8 | >=16	258	98.1	1.9	0.0	0.12	0.25	<= 0.03	8
Linezolid	<=4 | -- | >=8	258	100.0	0.0	0.0	2	4	1	4
Oxacillin	<=2 | -- | >=4	258	100.0	0.0	0.0	0.25	0.5	0.12	1
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	258	99.6	0.0	0.4	0.06	0.12	<= 0.03	4
Vancomycin	<=2 | 4-8 | >=16	258	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 4. Summary susceptibility data for Debio 1452 and comparators against *S. epidermidis* (n = 95)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	No Breakpoints Defined	95	0.0	0.0	0.0	0.25	0.5	<= 0.03	1
Clindamycin	<=0.5 | 1-2 | >=4	95	68.4	2.1	29.5	0.12	> 32	<= 0.03	> 32
Daptomycin	<=1 | -- | --	95	100.0	0.0	0.0	0.5	0.5	0.12	1
Debio 1452	**NB**	**95**	**-**	**-**	**-**	**0.015**	**0.03**	**0.008**	**0.5**
Doxycycline	<=4 | 8 | >=16	95	88.4	5.3	6.3	0.5	8	<= 0.03	16
Linezolid	<=4 | -- | --	95	97.9	0.0	2.1	1	1	0.25	> 16
Oxacillin	<=0.25 | -- | >=0.5	95	32.6	0.0	67.4	2	> 8	0.06	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	95	68.4	0.0	31.6	0.25	8	<= 0.03	16
Vancomycin	<=4 | 8-16 | >=32	95	100.0	0.0	0.0	2	2	0.25	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 staphylococci (n = 66)

Drug	Breakpoints (S|I|R)	N	% Susc	% Int	% Res	MIC_{50}	MIC_{90}	Min MIC	Max MIC
Ceftaroline	NB	66	-	-	-	0.12	2	<= 0.03	2
Clindamycin	<=0.5 | 1-2 | >=4	66	81.8	0.0	18.2	0.06	> 32	<= 0.03	> 32
Daptomycin	<=1 | -- | --	66	100.0	0.0	0.0	0.25	1	0.06	1
Debio 1452	**NB**	**66**	**-**	**-**	**-**	**0.015**	**0.06**	**0.004**	**0.5**
Doxycycline	<=4 | 8 | >=16	66	90.9	3.0	6.1	0.12	4	<= 0.03	16
Linezolid	<=4 | -- | --	66	100.0	0.0	0.0	1	2	0.5	4
Oxacillin	<=0.25 | -- | >=0.5	53	41.5	0.0	58.5	2	> 8	0.06	> 8
Oxacillin**	<=2 | -- | >=4	13	92.3	0.0	7.7	0.5	1	0.12	> 8
Trimethoprim Sulfa	<=2/38 | -- | >=4/76	66	77.3	0.0	22.7	0.25	16	<= 0.03	> 32
Vancomycin	<=4 | 8-16 | >=32	66	100.0	-	-	1	2	0.5	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 = 660)

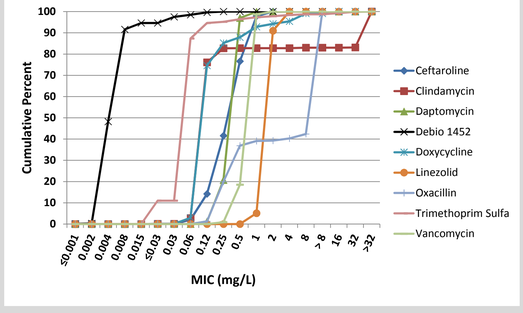


Figure 2. Cumulative MIC distributions for Debio 1452 and comparators against MRSA (n = 402)

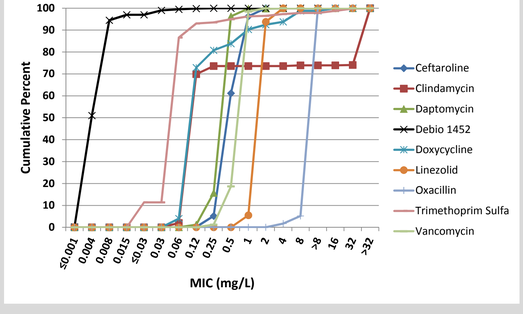


Figure 3. Cumulative MIC distributions for Debio 1452 and comparators against MSSA (n = 258)

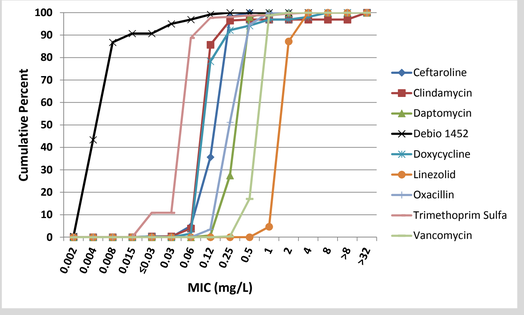


Figure 4. Cumulative MIC distributions for Debio 1452 and comparators against *S. epidermidis* (n = 95)

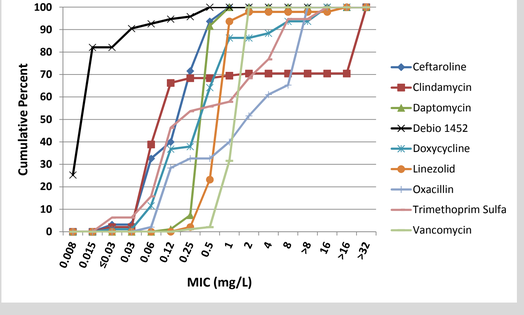
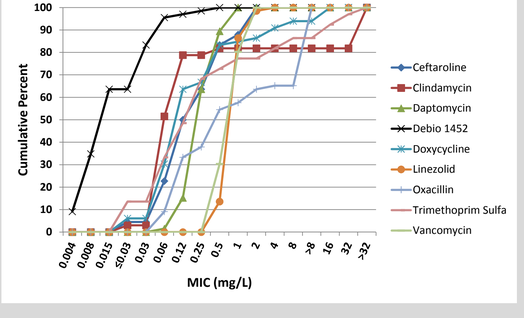


Figure 5. Cumulative MIC distributions for Debio 1452 and comparators against other staphylococci (n = 66)



Results Summary

- **Debio 1452 was the most potent agent tested with MIC_{90} for all *S. aureus* (n = 660), all MRSA (n = 402) and all MSSA (n = 258) of 0.008, 0.008 and 0.015 mg/L, respectively (Tables 1-3).**
- **Against *S. epidermidis* (n = 95), Debio 1452 was the most potent agent with an MIC_{90} and MIC range of 0.03 and 0.008 – 0.5 mg/L, respectively (Table 4).**
- **Against other *Staphylococcus* species, (a total of 11 species), MIC_{90} and MIC range were 0.015 and 0.004 – 0.5 mg/L, respectively (Table 5).**
- **The overall range for all staphylococci was ≤ 0.001 – 0.5 mg/L (Figures 1-5).**
- **Debio 1452 showed similar activity against MRSA and MSSA sub-groups and other staphylococci with respect to geographical origin (data not shown).**

Conclusions

- Debio 1452 exhibited excellent *in vitro* activity against all clinical isolates tested in the study. It was the most potent agent tested against the *Staphylococcus* species tested. The highest MIC was 0.5 mg/L.
- Activity of Debio 1452 was not, as expected from a novel mechanism of action, affected by resistance to other agents or classes.
- Further studies are warranted in support of the clinical development of Debio 1450 for staphylococcal infections.

References and Acknowledgment:

1. Clinical and Laboratory Standards Institute. 2012. Methods for Dilution Antimicrobial Susceptibility test for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition. M07-A9. Clinical and Laboratory Standards Institute, Wayne, PA, USA.
2. Clinical and Laboratory Standards Institute. 2014. Performance Standards for Antimicrobial Susceptibility testing; twenty-Fourth Informational Supplement. M100-S24. Clinical and Laboratory Standards Institute, Wayne, PA, USA.

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