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## Assessment of Eravacycline Against 3,467 Recent Gram-positive Bacteria, Including Multidrug-Resistant Isolates Collected From 2013-2014

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### Abstract

**Background** Eravacycline is a novel, fully synthetic fluorocycline antibiotic with broad-spectrum activity available in intravenous and oral formulations for the treatment of multidrug-resistant (MDR) infections. Eravacycline has completed enrollment in Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). The current study assessed the activity of eravacycline against 3,467 Gram-positive bacteria collected from 2013-2014, including multi-drug resistant (MDR) isolates.

**Methods:** A total of 3,467 Gram-positive clinical isolates comprising nine species and MDR isolates were tested. MDR was defined as resistant to 3 or more drug classes. MICs were determined by broth microdilution according to CLSI guidelines. Quality control testing was performed on each day of testing as specified by the CLSI.

**Results:** Eravacycline results, in µg/mL, are shown in the following Table:

	N	MIC <sub>50</sub>	MIC <sub>90</sub>	MIN	MAX
<i>E. faecalis</i>	501	0.06	0.06	0.008	0.5
<i>E. faecium</i>	459	0.06	0.06	0.008	1
<i>E. faecium</i> MDR	305	0.06	0.06	0.008	1
MRSA	493	0.06	0.12	0.015	1
MRSA MDR	37	0.12	1	0.06	1
MSSA	487	0.06	0.12	0.015	0.5
<i>S. epidermidis</i>	277	0.25	0.5	0.015	1
<i>S. haemolyticus</i>	157	0.12	0.5	0.015	1
<i>S. agalactiae</i>	199	0.015	0.03	0.008	0.06
<i>S. anginosus</i>	80	0.008	0.03	<= 0.001	0.06
<i>S. pneumoniae</i>	491	0.008	0.015	<= 0.001	0.03
<i>S. pneumoniae</i> MDR	46	0.008	0.015	0.002	0.015
<i>S. pyogenes</i>	323	0.015	0.015	0.004	0.06

MIN, minimum MIC; MAX, maximum MIC

**Conclusions:** Eravacycline was very active against Gram-positive clinical isolates, including MDR strains, with the highest eravacycline MIC at 1 µg/ml. MIC<sub>90</sub> ranged from 0.015 - 1 µg/ml. Overall, eravacycline showed promising activity against all strains tested including MDR isolates. Data from the recently completed Phase 3 trials will be used in determining the clinical breakpoints.

### Introduction

Eravacycline is a novel, fully synthetic fluorocycline antibiotic with broad-spectrum activity available in intravenous and oral formulations for the treatment of multidrug-resistant (MDR) infections, including those caused by MDR Gram-negative bacteria. Eravacycline was investigated in Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

The current study assessed the activity of eravacycline against Gram-positive bacteria from the USA and Europe, including MDR isolates.

### Methods

A total of 3,467 Gram-positive clinical isolates comprising nine species and MDR isolates were tested. MDR was defined as resistant to 3 or more drug classes.

Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1). Panels were prepared at IHMA using cation-adjusted Mueller-Hinton broth (CAMHB).

Quality control testing was performed each day of testing as specified by the CLSI using *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619.

Antibiotic susceptibility was determined using CLSI 2014 breakpoints (2), with the exception of tigecycline where FDA breakpoints were used (3).

**Table 1. Summary MIC data for eravacycline, tetracycline and tigecycline against Gram-positive isolates**

Organism	Drug	Breakpoints (S I R)	%Susc*	%Int	%Res	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>E. faecalis</i> (n = 501)	Eravacycline	NB*	-	-	-	0.06	0.06
	Tetracycline	<=4   8   >=16	25.4	0.8	73.9	32	> 32
	Tigecycline	<=0.25   -   -	97.8	-	-	0.12	0.25
<i>E. faecium</i> (n = 459)	Eravacycline	NB	-	-	-	0.06	0.06
	Tetracycline	<=4   8   >=16	32.0	0.2	67.8	32	> 32
	Tigecycline	<=0.25   -   -	95.6	-	-	0.12	0.25
MRSA (n = 493)	Eravacycline	NB	-	-	-	0.06	0.12
	Tetracycline	<=4   8   >=16	86.2	0.2	13.6	0.5	32
	Tigecycline	<=0.5   -   -	98.2	-	-	0.12	0.25
MSSA (487)	Eravacycline	NB	-	-	-	0.06	0.12
	Tetracycline	<=4   8   >=16	92.4	1.2	6.4	0.5	1
	Tigecycline	<=0.5   -   -	100.0	-	-	0.12	0.25
<i>S. epidermidis</i> (n = 277)	Eravacycline	NB	-	-	-	0.25	0.5
	Tetracycline	<=4   8   >=16	82.7	1.8	15.5	2	> 32
	Tigecycline	NB	-	-	-	0.25	0.5
<i>S. haemolyticus</i> (n = 157)	Eravacycline	NB	-	-	-	0.12	0.5
	Tetracycline	<=4   8   >=16	79.0	0.0	21.0	1	> 32
	Tigecycline	NB	-	-	-	0.25	0.5
<i>S. agalactiae</i> (n = 199)	Eravacycline	NB	-	-	-	0.015	0.03
	Tetracycline	<=2   4   >=8	20.6	0.0	79.4	> 8	> 8
	Tigecycline	<=0.25   -   -	100.0	-	-	0.03	0.03
<i>S. anginosus</i> (n = 80)	Eravacycline	NB	-	-	-	0.008	0.03
	Tetracycline	<=2   4   >=8	76.3	7.5	16.3	0.12	> 8
	Tigecycline	<=0.25   -   -	100.0	-	-	<= 0.008	<= 0.008
<i>S. pneumoniae</i> (n = 491)	Eravacycline	NB	-	-	-	0.008	0.015
	Tetracycline	<=1   2   >=4	75.6	0.6	23.8	0.12	> 8
	Tigecycline	<=0.06   -   -	99.8	-	-	<= 0.008	0.015
<i>S. pyogenes</i> (n = 323)	Eravacycline	NB	-	-	-	0.015	0.015
	Tetracycline	<=2   4   >=8	86.4	0.0	13.6	0.12	> 8
	Tigecycline	<=0.25   -   -	100.0	-	-	0.015	0.03

\*NB, no breakpoint available; %Susc, %Int, %Res, percent susceptible, percent intermediate or percent isolates resistant. Breakpoints for tigecycline vs. enterococci are based on FDA breakpoints for *E. faecalis* (vancomycin-susceptible).

**Table 2. Summary MIC data for eravacycline, tetracycline and tigecycline against MDR Gram-positive isolates**

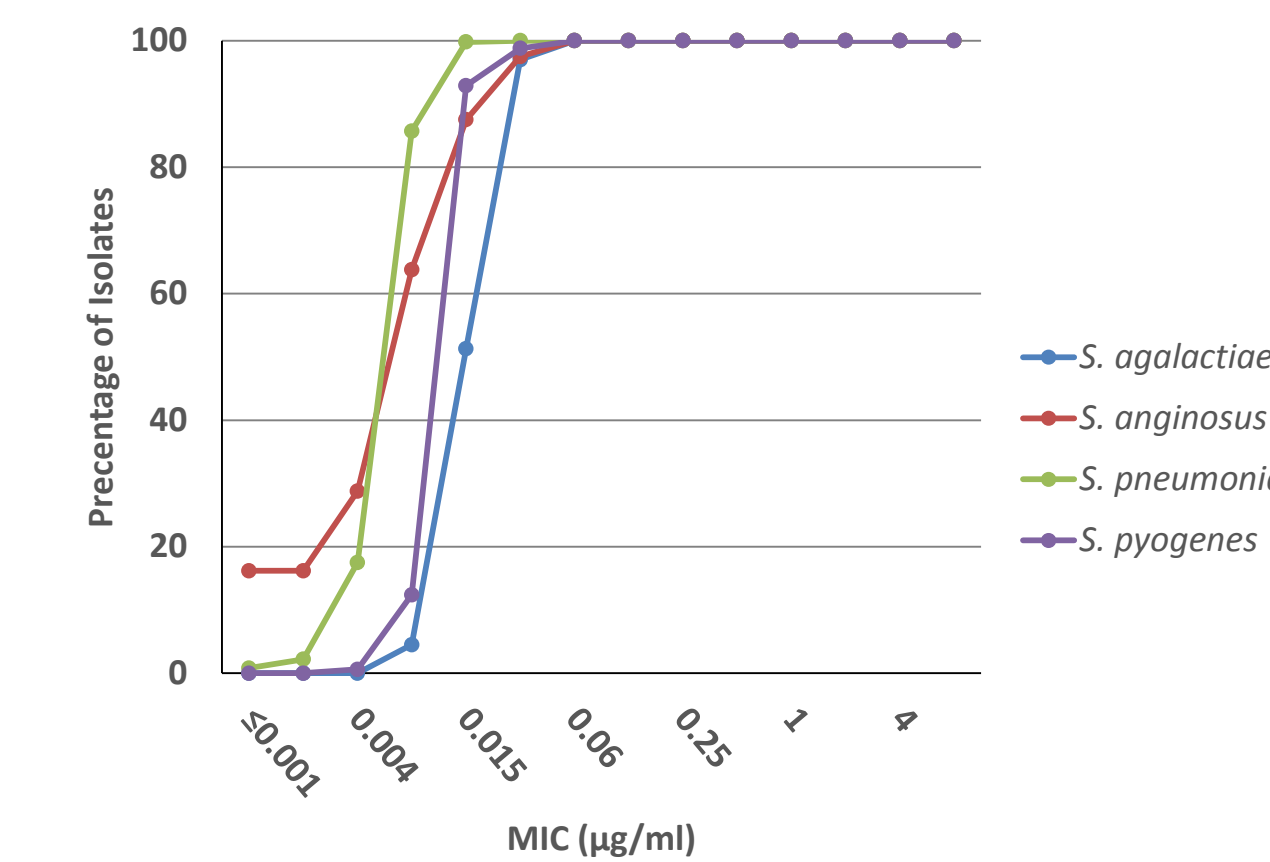
Organism	Drug	Breakpoints (S I R)	%Susc	%Int	%Res	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>E. faecium</i> (n = 305)	Eravacycline	NB	-	-	-	0.06	0.06
	Tetracycline	<=4   8   >=16	4.3	0.0	95.7	> 32	> 32
	Tigecycline	<=0.25   -   -	93.4	-	-	0.12	0.25
MRSA (n = 37)	Eravacycline	NB	-	-	-	0.12	1
	Tetracycline	<=4   8   >=16	0.0	0.0	100.0	> 32	> 32
	Tigecycline	<=0.5   -   -	83.8	-	-	0.25	1
<i>S. pneumoniae</i> (n = 46)	Eravacycline	NB	0.0	0.0	0.0	0.008	0.015
	Tetracycline	<=1   2   >=4	4.4	0.0	95.7	> 8	> 8
	Tigecycline	<=0.06   -   -	0.0	0.0	0.0	<= 0.008	0.015

\*NB, no breakpoint available; %Susc, %Int, %Res, percent susceptible, percent intermediate or percent isolates resistant. Breakpoints for tigecycline vs. MDR *E. faecium* are based on FDA breakpoints for *E. faecalis* (vancomycin-susceptible).

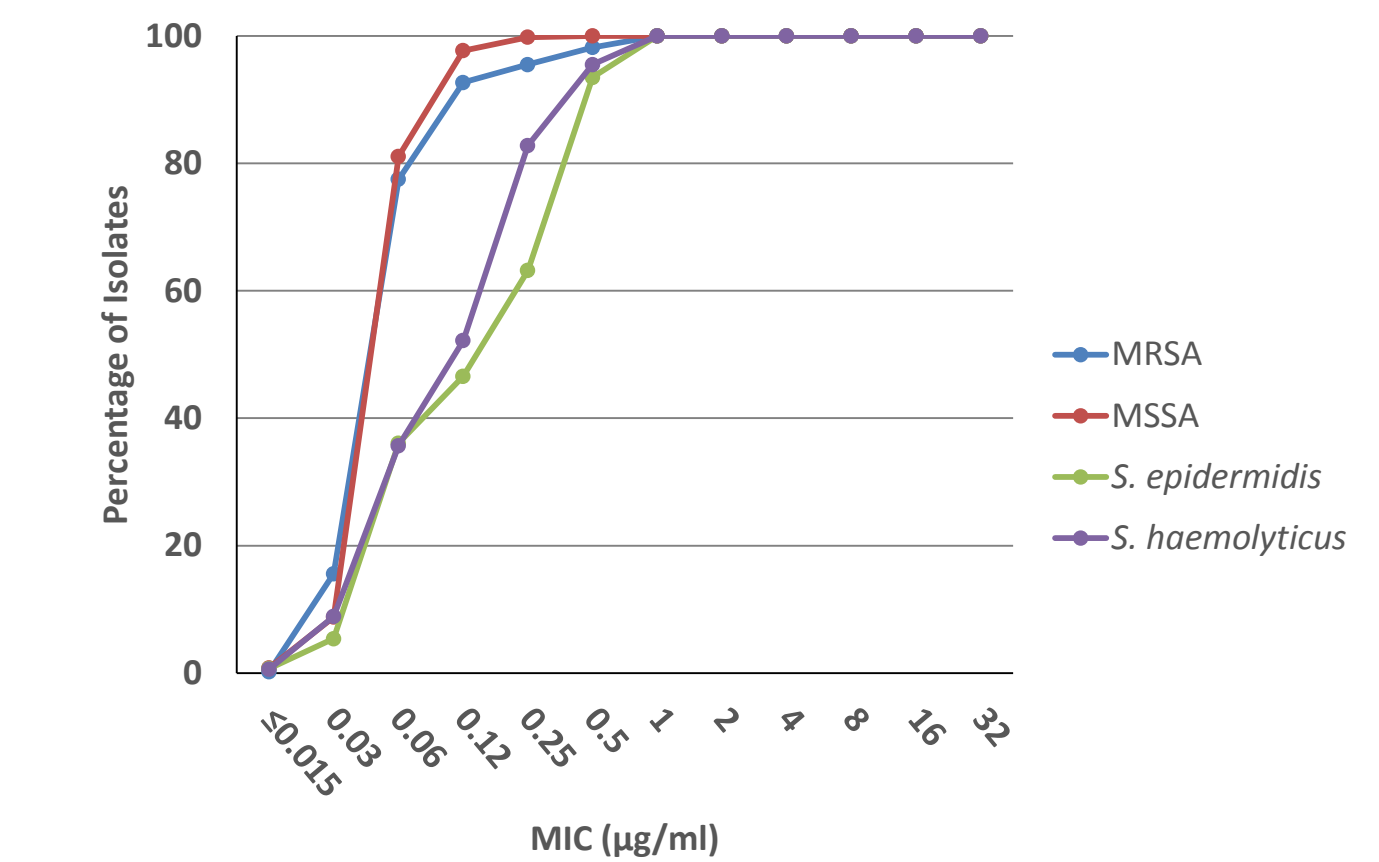
### Results

- Table 1 shows summary MIC and susceptibility data for eravacycline, tigecycline and tetracycline and comparators against Gram-positive bacteria.
- Table 2 shows summary MIC and susceptibility data for eravacycline, tigecycline and tetracycline and comparators against MDR Gram-positive bacteria.
- Cumulative percentage MIC distribution data for eravacycline, tigecycline and tetracycline against streptococci, staphylococci and enterococci are shown in Figures 1 to 3, respectively.
- A direct comparison of tigecycline versus eravacycline MIC for all Gram-positive bacteria combined is shown in Figure 4.

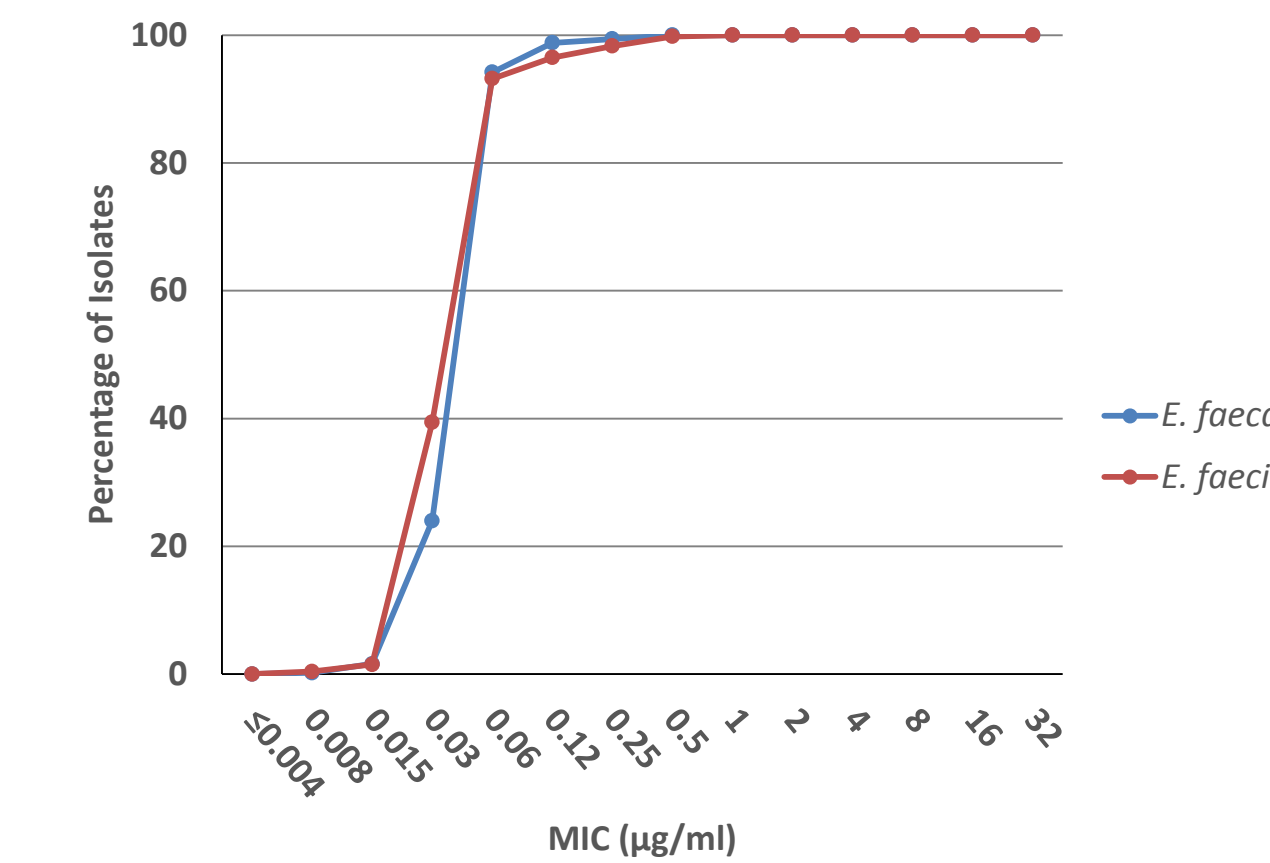
**Figure 1. Cumulative percentage MIC distribution for eravacycline against streptococci**



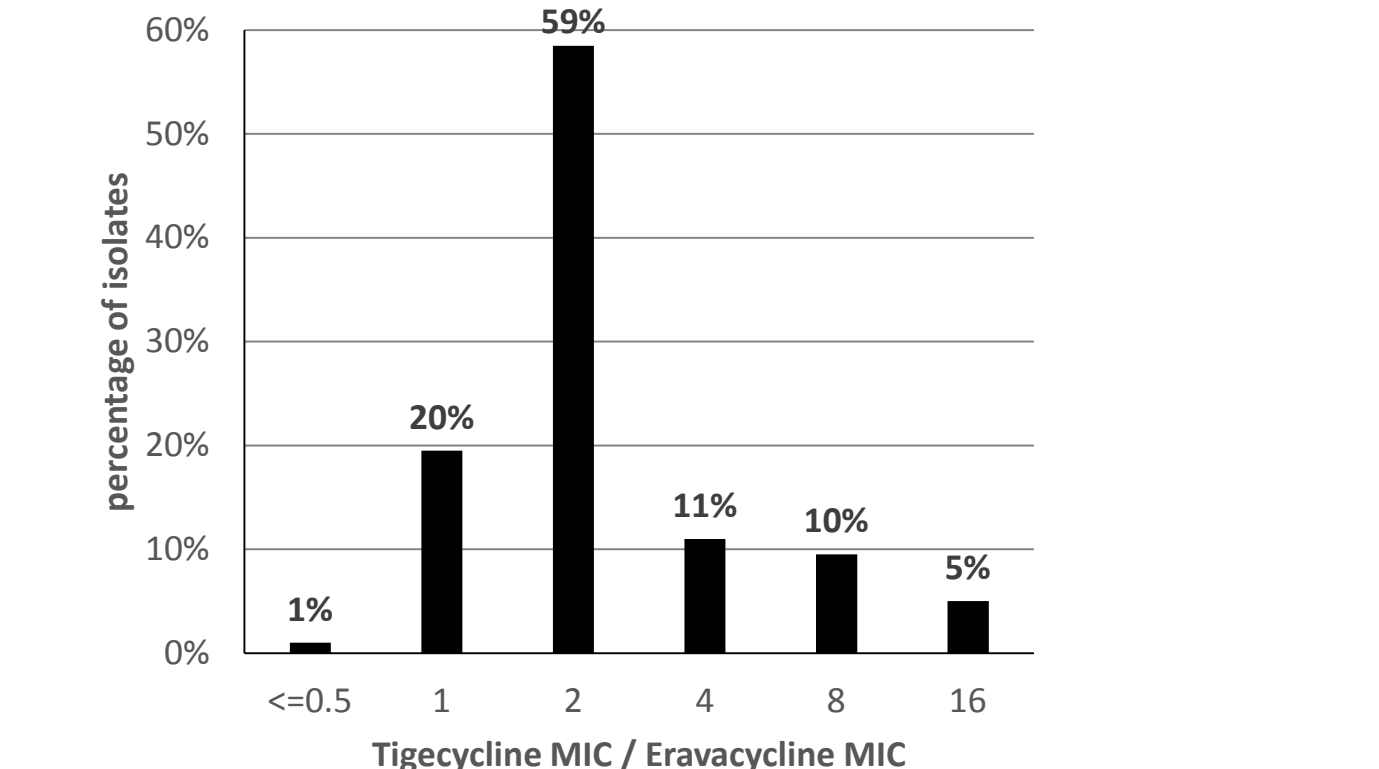
**Figure 2. Cumulative percentage MIC distribution for eravacycline against staphylococci**



**Figure 3. Cumulative percentage MIC distribution for eravacycline against enterococci**



**Figure 4. Comparison between tigecycline and eravacycline MIC for all Gram-positive bacteria combined**



### Conclusions

- Eravacycline was very active against Gram-positive clinical isolates, including MDR strains, with the highest eravacycline MIC at 1 µg/ml. MIC<sub>90</sub> ranged from 0.015 to 1 µg/ml. Overall, eravacycline showed promising activity against all strains tested including MDR isolates.
- All strains taken together, eravacycline had a lower MIC distribution than tetracycline or tigecycline, with 85% of isolates having a 2-fold or lower eravacycline MIC than tigecycline.
- Data from the recently completed Phase 3 trials will be used in determining the clinical breakpoints
- Eravacycline exhibited excellent activity against many isolates and may show promise for the treatment of infections caused by Gram-positive bacteria, including MDR

### References

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