C-563

ICAAC/ICC
17-21 September, 2015
San Diego, CA

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

I. Morrissey[1*], J. Sutcliffe[2], M. Hackel[3], S. Hawser[1]
[1]IHMA Europe Sàrl, Epalinges, Switzerland.
[2]Tetraphase Pharmaceuticals, Watertown, USA
[3]International Health Management Associates, Inc., Schaumburg, USA
*Presenting author

Contact:
Dr. I. Morrissey
IHMA Europe Sàrl
imorrissey@ihmainc.com

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_{50}	MIC_{90}	MIN	MAX
E. faecalis	501	0.06	0.06	0.008	0.5
E. faecium	459	0.06	0.06	0.008	1
E. faecium 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
S. epidermidis	277	0.25	0.5	0.015	1
S. haemolyticus	157	0.12	0.5	0.015	1
S. agalactiae	199	0.015	0.03	0.008	0.06
S. anginosus	80	0.008	0.03	<= 0.001	0.06
S. pneumoniae	491	0.008	0.015	<= 0.001	0.03
S. pneumoniae MDR	46	0.008	0.015	0.002	0.015
S. pyogenes	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_{90} 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).

Results

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

Organism	Drug	Breakpoints (S|I|R)	%Susc*	%Int	%Res	MIC_{50}	MIC_{90}
E. faecalis (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
E. faecium (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
S. epidermidis (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
S. haemolyticus (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
S. agalactiae (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
S. anginosus (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
S. pneumoniae (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
S. pyogenes (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_{50}	MIC_{90}
E. faecium (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
S. pneumoniae (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).

- 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

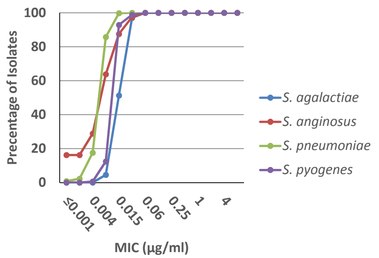


Figure 2. Cumulative percentage MIC distribution for eravacycline against staphylococci

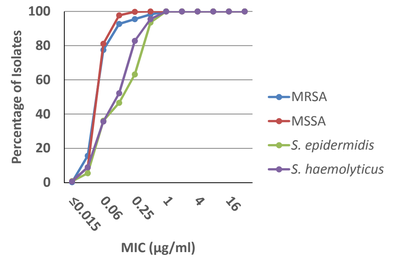


Figure 3. Cumulative percentage MIC distribution for eravacycline against enterococci

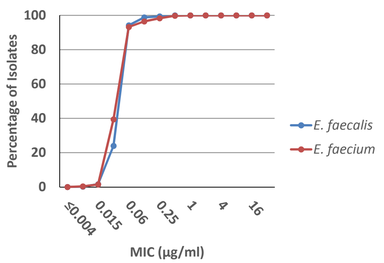
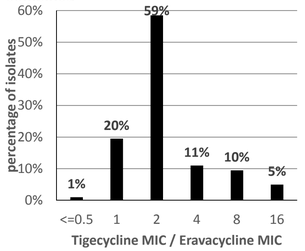


Figure 4. Comparison between tigecycline and eravacycline MIC for all Gram-positive bacteria combined



Conclusions

- Eravacycline was very active against Gram-positive clinical isolates, including MDR strains, with the highest eravacycline MIC at 1 µg/ml. MIC_{90} 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

1. CLSI, 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition M07-A10. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
2. CLSI, 2015. Performance Standards for Antimicrobial Susceptibility Testing; Informational Supplement-Twenty-Second Edition M100-S25. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021821s021lbl.pdf

Acknowledgment

This study was supported by a grant from Tetraphase Pharmaceuticals.