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Revised Abstract

Background: Eravacycline is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity in development for the treatment of multidrug-resistant (MDR) infections. Eravacycline has recently completed two 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 1,079 anaerobic bacteria collected from European hospitals in 2013-2014.

Methods: A total of 1,079 clinical anaerobic isolates from Europe were tested. MICs were determined by agar dilution 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) for all anaerobes combined and major species collected (where N≥30) are shown in the following Table:

Organism/MIC (µg/ml)	N	MIC ₅₀	MIC ₉₀	MIN	MAX
All anaerobes	1,079	0.12	1	0.004	8
<i>Bacteroides fragilis</i>	198	0.25	2	0.06	8
<i>Clostridium difficile</i>	117	0.03	0.06	0.004	0.5
<i>Finnegoldia magna</i>	84	0.06	0.12	0.015	0.25
<i>Clostridium perfringens</i>	76	0.06	0.5	0.015	2
<i>Bacteroides thetaiotaomicron</i>	62	0.5	2	0.03	8
<i>Prevotella bivia</i>	62	0.25	1	0.06	4
<i>Parvimonas micra</i>	56	0.008	0.03	0.008	0.12
<i>Peptostreptococcus anaerobius</i>	51	0.03	0.06	0.015	0.5
<i>Bacteroides ovatus</i>	35	0.25	1	0.03	2
<i>Bacteroides vulgatus</i>	34	0.25	1	0.03	2
<i>Peptoniphilus harei</i>	31	0.03	0.06	0.004	0.12

Conclusions: Eravacycline demonstrated potent in vitro activity against anaerobic bacteria collected from Europe. These data along with the data from the Phase 3 trials will be used in determining the clinical breakpoints.

Introduction

Eravacycline is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity in development 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 a collection of recent anaerobic clinical isolates from Europe.

Methods

A total of 1,079 clinical anaerobic isolates from Europe (collected in 2013 and 2014) were tested. Country of origin is shown in Figure 1.

Minimum inhibitory concentration (MIC) endpoints were determined by agar dilution under anaerobic conditions according to CLSI guidelines (1).

Quality control testing was performed each day of testing as specified by the CLSI using *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741 and *C. difficile* ATCC 700057, as required.

Antibiotic susceptibility was determined using CLSI 2015 breakpoints (2), with the exception of tigecycline where FDA breakpoints were used (3).

Results

- Summary MIC data for eravacycline against anaerobic isolates where N ≥ 20 is shown in Table 1.
- Summary MIC and susceptibility data for eravacycline and comparators against *Bacteroides* spp. (n = 366), *Clostridium* spp. (n = 280) and *Prevotella* spp. (n = 179), including clindamycin-resistant and tetracycline-resistant strains, are shown in Tables 2 to 4.
- MIC₅₀ values ranged from 0.03 - 2 µg/ml.
- A comparison of the ratio of tigecycline versus eravacycline MICs for anaerobic isolates is shown in Figure 2.

Figure 1. Country of origin (n,%) for the 1,079 anaerobic clinical isolates tested

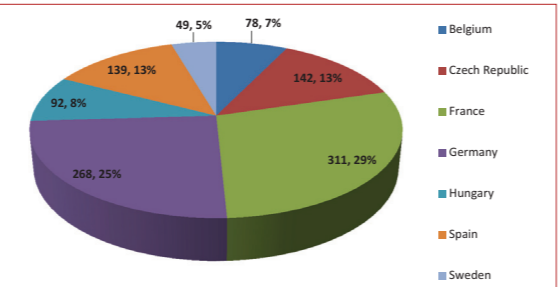


Figure 2. Ratio of Tigecycline MIC and Eravacycline MIC for all anaerobes combined

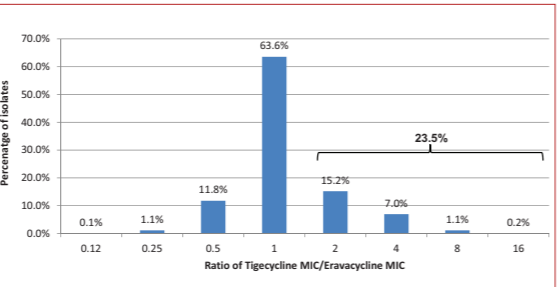


Table 1. Summary MIC data for eravacycline against anaerobes (where N≥20)

Organism	N	MIC (µg/ml):			
		MIC ₅₀	MIC ₉₀	Min	Max
All anaerobes	1079	0.12	1	0.004	8
All Gram-negative anaerobes	561	0.25	1	0.008	8
All Gram-positive anaerobes	518	0.03	0.12	0.004	2
<i>Bacteroides fragilis</i>	198	0.25	2	0.06	8
<i>Clostridium difficile</i>	117	0.03	0.06	0.004	0.5
<i>Finnegoldia magna</i>	84	0.06	0.12	0.015	0.25
<i>Clostridium perfringens</i>	76	0.06	0.5	0.015	2
<i>Bacteroides thetaiotaomicron</i>	62	0.5	2	0.03	8
<i>Prevotella bivia</i>	62	0.25	1	0.06	4
<i>Parvimonas micra</i>	56	0.008	0.03	0.008	0.12
<i>Peptostreptococcus anaerobius</i>	51	0.03	0.06	0.015	0.5
<i>Bacteroides ovatus</i>	35	0.25	1	0.03	2
<i>Bacteroides vulgatus</i>	34	0.25	1	0.03	2
<i>Peptoniphilus harei</i>	31	0.03	0.06	0.004	0.12
<i>Prevotella buccae</i>	23	0.06	0.12	0.008	0.25
<i>Clostridium innocuum</i>	22	0.03	0.06	0.008	0.12
<i>Prevotella melaninogenica</i>	20	0.12	0.12	0.03	0.5

Table 2. Summary MIC and susceptibility data for eravacycline and comparators against *Bacteroides* spp. (n=366), including clindamycin-resistant (n=125) and tetracycline-resistant (n=274) strains

Antibiotic	Breakpoints (S/I/R)	MIC (µg/ml):							
		S	I	R	MIC ₅₀	MIC ₉₀	Min	Max	
Cefoxitin	<=16 32 >=64	ALL	85.0	12.3	2.7	8	32	<=2	>32
		Cl-R	69.6	24	6.4	16	32	<=2	>32
		Tet-R	82.9	14.2	2.9	8	32	<=2	>32
Clindamycin	<=2 4 >=8	ALL	61.5	4.4	34.2	1	>8	<=0.25	>8
		Cl-R	0	0	100	>8	>8	>8	>8
		Tet-R	59.9	3.7	36.5	1	>8	<=0.25	>8
Eravacycline	No Breakpoints Defined	ALL	-	-	-	0.25	2	0.015	8
		Cl-R	-	-	-	0.5	2	0.03	8
		Tet-R	-	-	-	0.5	2	0.03	8
Meropenem	<=4 8 >=16	ALL	99.5	0.6	0.0	0.12	0.5	<=0.06	8
		Cl-R	98.4	1.6	0	0.25	1	<=0.06	8
		Tet-R	99.3	0.7	0.0	0.12	0.5	<=0.06	8
Metronidazole	<=8 16 >=32	ALL	100.0	0.0	0.0	0.5	1	<=0.12	4
		Cl-R	100	0	0	0.5	1	<=0.12	4
		Tet-R	100.0	0.0	0.0	0.5	1	<=0.12	4
Pip/Taz	<=32/4 64/4 >=128/4	ALL	100.0	0.0	0.0	0.25	8	<=0.06	32
		Cl-R	100	0	0	2	16	<=0.06	32
		Tet-R	100.0	0.0	0.0	0.25	8	<=0.06	32
Tetracycline	<=4 8 >=16	ALL	21.3	3.8	74.9	32	64	<=0.06	>64
		Cl-R	16.8	3.2	80	32	64	0.25	>64
		Tet-R	0.0	0.0	100.0	32	64	16	>64
Tigecycline	<=4 8 >=16*	ALL	96.2	3.0	0.8	0.5	4	<=0.06	16
		Cl-R	95.2	4	0.8	0.5	4	<=0.06	16
		Tet-R	94.9	4.0	1.1	0.5	4	<=0.06	16

* FDA breakpoints were used for Tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam; Cl-R, clindamycin-resistant; Tet-R, tetracycline-resistant.

Table 3. Summary MIC and susceptibility data for eravacycline and comparators against *Clostridium* spp. (n=280), including clindamycin-resistant (n=88) and tetracycline-resistant (n=72) strains

Antibiotic	Breakpoints (S/I/R)	MIC (µg/ml):							
		S	I	R	MIC ₅₀	MIC ₉₀	Min	Max	
Clindamycin	<=2 4 >=8	ALL	58.2	10.4	31.4	2	>8	<=0.25	>8
		Cl-R	0.0	0.0	100.0	>8	>8	>8	>8
		Tet-R	72.2	5.6	22.2	0.5	>8	<=0.25	>8
Eravacycline	No Breakpoints Defined	ALL	-	-	-	0.03	0.25	0.004	2
		Cl-R	-	-	-	0.03	0.25	0.008	1
		Tet-R	-	-	-	0.25	0.5	0.008	2
Meropenem	<=4 8 >=16	ALL	100.0	0.0	0.0	0.5	2	<=0.06	4
		Cl-R	100.0	0.0	0.0	1	2	<=0.06	4
		Tet-R	100.0	0.0	0.0	0.12	2	<=0.06	2
Metronidazole	<=8 16 >=32	ALL	100.0	0.0	0.0	0.5	1	<=0.12	4
		Cl-R	100.0	0.0	0.0	0.25	1	<=0.12	4
		Tet-R	100.0	0.0	0.0	0.5	2	<=0.12	4
Penicillin	<=0.5 1 >=2	ALL	56.2	26.1	15.7	0.5	2	<=0.25	32
		Cl-R	20.5	45.5	34.1	1	2	<=0.25	4
		Tet-R	70.8	18.1	11.1	<=0.25	2	<=0.25	32
Pip/Taz	<=32/4 64/4 >=128/4	ALL	100.0	0.0	0.0	1	8	<=0.06	16
		Cl-R	100.0	0.0	0.0	4	8	<=0.06	16
		Tet-R	100.0	0.0	0.0	0.25	8	<=0.06	16
Tetracycline	<=4 8 >=16	ALL	67.1	7.1	26.7	0.25	32	<=0.06	64
		Cl-R	79.6	2.3	18.2	0.12	32	<=0.06	64
		Tet-R	0.0	0.0	100.0	32	64	16	64
Tigecycline	<=4 8 >=16*	ALL	100.0	0.0	0.0	<=0.06	1	<=0.06	2
		Cl-R	100.0	0.0	0.0	<=0.06	1	<=0.06	2
		Tet-R	100.0	0.0	0.0	0.5	1	<=0.06	2

* FDA breakpoints were used for Tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam; Cl-R, clindamycin-resistant; Tet-R, tetracycline-resistant.

Table 4. Summary MIC and susceptibility data for eravacycline and comparators against *Prevotella* spp. (n=179), including clindamycin-resistant (n=55) and tetracycline-resistant (n=81) strains

Antibiotic	Breakpoints (S/I/R)	MIC (µg/ml):							
		S	I	R	MIC ₅₀	MIC ₉₀	Min	Max	
Cefoxitin	<=16 32 >=64	ALL	100.0	0.0	0.0	<=2	4	<=2	16
		Cl-R	100.0	0.0	0.0	<=2	4	<=2	16
		Tet-R	100.0	0.0	0.0	<=2	4	<=2	16
Clindamycin	<=2 4 >=8	ALL	69.3	0.0	30.7	<=0.25	>8	<=0.25	>8
		Cl-R	0.0	0.0	100.0	>8	>8	>8	>8
		Tet-R	64.2	0.0	35.8	<=0.25	>8	<=0.25	>8
Eravacycline	No Breakpoints Defined	ALL	-	-	-	0.12	0.5	0.008	4
		Cl-R	-	-	-	0.12	0.5	0.008	4
		Tet-R	-	-	-	0.25	1	0.03	4
Meropenem	<=4 8 >=16	ALL	100.0	0.0	0.0	<=0.06	0.12	<=0.06	0.5
		Cl-R	100.0	0.0	0.0	<=0.06	0.25	<=0.06	0.5
		Tet-R	100.0	0.0	0.0	<=0.06	0.12	<=0.06	0.5
Metronidazole	<=8 16 >=32	ALL	100.0	0.0	0.0	0.5	2	<=0.12	4
		Cl-R	100.0	0.0	0.0	0.5	2	<=0.12	4
		Tet-R	100.0	0.0	0.0	1	2	<=0.12	4
Pip/Taz	<=32/4 64/4 >=128/4	ALL	100.0	0.0	0.0	<=0.06	<=0.06	<=0.06	1
		Cl-R	100.0	0.0	0.0	<=0.06	<=0.06	<=0.06	1
		Tet-R	100.0	0.0	0.0	<=0.06	<=0.06	<=0.06	1
Tetracycline	<=4 8 >=16	ALL	45.8	8.9	45.3	8	64	<=0.06	>64
		Cl-R	41.8	5.5	52.7	16	64	<=0.06	>64
		Tet-R	0.0	0.0	100.0	32	64	16	>64
Tigecycline	<=4 8 >=16*	ALL	100.0	0.0	0.0	0.12	0.5	<=0.06	2
		Cl-R	100.0	0.0	0.0	0.12	0.5	<=0.06	2
		Tet-R	100.0						