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Combined Microbiological Response Rates From Two Phase 3 Trials Demonstrating the Activity of Eravacycline in the Treatment of Complicated Intra-Abdominal Infections: A Pooled Analysis of IGNITE1 and IGNITE4

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Abstract

Background: IGNITE1 and IGNITE4 were randomized, double-blind, double-dummy, multicenter studies which demonstrated the efficacy and safety of eravacycline (ERV) compared to a carbapenem in subjects with complicated intra-abdominal infections (cIAI). The primary objective of this analysis was to compare the microbiological response at the test-of-cure (TOC) visit for subjects in the 2 treatment groups.

Methods: Appropriate aerobic and anaerobic specimens for culture at the time of the initial procedure were collected from the site of infection and directly inoculated into transport media. Blood and intra-abdominal specimens were cultured, and species identified according to local laboratory practice. Pure cultures of isolates were sent to a reference laboratory for susceptibility analysis to ERV and comparators. Favorable microbiological response rates at the TOC visit were determined for each baseline pathogen isolated from blood and/or intra-abdominal specimens in the micro-ITT population.

Results: For subjects with infections caused by Enterobacteriaceae, the overall favorable microbiological response rates for ERV-treated subjects were 86.3% and 91.8% for IGNITE1 and IGNITE4, respectively. The favorable microbiological response rates among pooled ERV-treated subjects are shown in the Table.

Baseline Pathogen	ERV No./Total No. (%)	Baseline Pathogen	ERV No/Total No. (%)
Enterobacteriaceae	277/314 (88.2)	*Streptococcus viridans* group	109/120 (90.8)
E. coli	223/253 (88.1)	*E. faecalis*	45/54 (83.3)
E. cloacae	18/21 (85.7)	*E. faecium*	39/45 (86.7)
K. pneumoniae	38/39 (97.4)	*S. aureus*	24/24 (100)
A. baumannii	13/13 (100)	*B. fragilis*	74/84 (88.1)

Conclusion: In IGNITE1 and IGNITE4 studies, high favorable microbiological responses were observed for ERV. More than 88% of five Enterobacteriaceae spp. and *B. fragilis*, the most common bacteria associated with intraabdominal infections, were eradicated by ERV. Comparable eradication rates were observed following ertapenem and meropenem therapy, further establishing that ERV was at least as effective as carbapenem treatments. These data support in vitro observations that ERV has broad-spectrum activity against common isolates found in intra-abdominal infections.

Introduction

Eravacycline is a fully-synthetic fluorocycline antibacterial of tetracycline class that has recently received Food and Drug Administration (FDA) approval for the treatment of complicated intra abdominal infections[1]. It retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)[2,3]. Eravacycline has shown activity against a broad range of Gram-negative, Gram-positive and anaerobic strains.

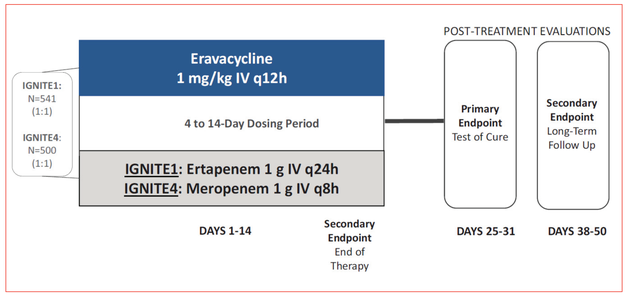
The objective of this analysis was to compare the clinical and microbiological responses at the TOC visit in subjects that received eravacycline versus the comparator agents by baseline pathogen including Gram-negative pathogens with resistant phenotypes and genotypes.

Methods

IGNITE1 and IGNITE4 were phase 3 randomized, double-blind, double-dummy, multicenter, prospective studies designed to assess the efficacy and safety of twice-daily intravenous eravacycline (1 mg/kg every 12 hours) compared to a carbapenem in patients with cIAI. The primary endpoint was clinical response in the micro-ITT population at the TOC visit, which occurred 25 to 31 days after the initial dose of study drug. The difference in clinical cure rates between treatment groups was determined along with the 95% confidence interval. The non-inferiority margins for IGNITE1 and IGNITE4 were 10% and 12.5%, respectively. Favorable microbiological response rates at the TOC visit were determined for each baseline pathogen isolated from blood and/or intra-abdominal specimens in the micro-ITT population.

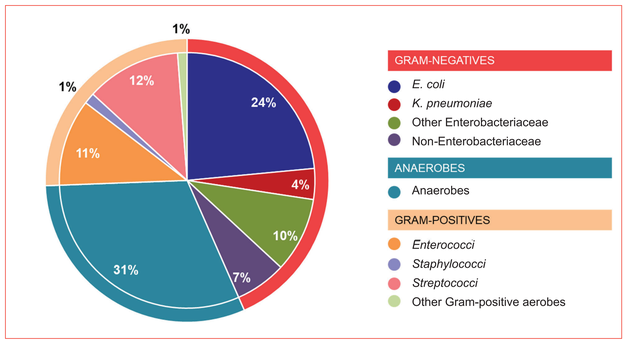
Blood and intra-abdominal samples were acquired from each patient at the time of initial procedure for determination of baseline pathogens. Blood samples taken from at least two separate venipuncture sites were obtained at the time of screening for aerobe and anaerobe cultures. Specimens were collected via aspiration and/or tissue sample from the intra-abdominal cavity at the time of initial surgical intervention and directly inoculated into transport media. Isolates were initially speciated by the local/regional lab and speciation was confirmed by the central laboratory. Susceptibility to eravacycline and comparator agents was determined according to CLSI standards[4,5]. Microbiological response rates at the TOC visit were determined for each baseline pathogen within the micro-ITT population.

Figure 1. IGNITE1 and IGNITE4 Study Design[6,7]



Results

Figure 2. IGNITE1 and IGNITE4 Baseline Pathogen Distribution



- 2717 total baseline isolates; 3.6 isolates/patient

Results (cont'd)

Table 1. Clinical and Microbiological Outcomes at TOC in the micro-ITT Population

	Pooled Microbiological Eradication		Pooled Clinical cure	
	ERV	Comparator	ERV	Comparator
Baseline Pathogen	n/total (%)			
Enterobacteriaceae	277/314 (88.2)	296/325 (91.1)	271/314 (86.3)	289/325 (88.9)
ESBL	32/36 (88.9)	26/29 (89.7)	32/36 (88.9)	25/29 (86.2)
Carbapenemase	1/1 (100)	2/3 (66.7)	1/1 (100)	2/3 (66.7)
AmpC	9/9 (100)	9/10 (90.0)	9/9 (100)	8/10 (80.0)
E. coli	223/253 (88.1)	243/266 (91.4)	220/253 (87)	237/266 (89.1)
ESBL	19/22 (86.4)	13/14 (92.9)	19/22 (86.4)	12/14 (85.7)
bla $_{CTXM-15}$-like	15/16 (93.8)	9/10 (90.0)	15/16 (93.8)	10/10 (100)
bla $_{CMY-2}$-like	3/3 (100)	3/3 (100)	3/3 (100)	2/3 (66.7)
AmpC	4/4 (100)	3/3 (100)	4/4 (100)	2/3 (66.7)
C. freundii	19/22 (86.4)	8/10 (80)	19/22 (86.4)	8/10 (80)
ESBL	4/4 (100)	2/2 (100)	4/4 (100)	2/2 (100)
bla $_{CTXM-15}$-like	3/3 (100)	2/2 (100)	3/3 (100)	2/2 (100)
bla $_{SHV-30}$	1/1 (100)	-	1/1 (100)	-
AmpC	4/4 (100)	2/3 (66.7)	4/4 (100)	2/3 (66.7)
E. cloacae	18/21 (85.7)	23/24 (95.8)	17/21 (81)	23/24 (95.8)
ESBL	2/2 (100)	6/6 (100)	2/2 (100)	6/6 (100)
bla $_{CTXM-15}$-like	2/2 (100)	5/5 (100)	2/2 (100)	5/5 (100)
bla $_{SFO-1}$-like	-	1/1 (100)	-	1/1 (100)
AmpC	1/1 (100)	3/3 (100)	1/1 (100)	2/3 (66.7)
K. pneumoniae	38/39 (97.4)	43/50 (88.9)	37/39 (94.9)	42/50 (84.0)
ESBL	10/11 (90.9)	8/9 (88.9)	10/11 (90.9)	7/9 (77.8)
bla $_{CTXM-15}$-like	10/11 (90.9)	5/6 (83.3)	10/11 (90.9)	4/6 (66.7)
bla $_{KPC-2}$	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
K. oxytoca	14/15 (93.3)	17/19 (89.5)	14/15 (93.3)	16/19 (84.2)
A. baumannii	13/13 (100)	7/7 (100)	13/13 (100)	7/7 (100)
ESBL	5/5 (100)	1/1 (100)	5/5 (100)	1/1 (100)
bla $_{GES-11}$	4/4 (100)	1/1 (100)	4/4 (100)	1/1 (100)
Carbapenemase	2/2 (100)	4/4 (100)	2/2 (100)	4/4 (100)
AmpC	5/5 (100)	2/2 (100)	5/5 (100)	2/2 (100)
S. viridans group	105/120 (87.5)	93/102 (91.2)	106/120 (88.3)	91/103 (88.3)
E. faecalis	46/54 (85.2)	49/54 (90.7)	45/54 (83.3)	47/54 (87)
E. faecium	39/45 (86.7)	48/53 (90.5)	38/45 (84.4)	48/53 (90.5)
S. aureus	24/24 (100)	13/14 (92.6)	24/24 (100)	12/14 (85.7)
B. fragilis	72/81 (88.9)	76/79 (96.2)	74/84 (88.1)	76/80 (95)

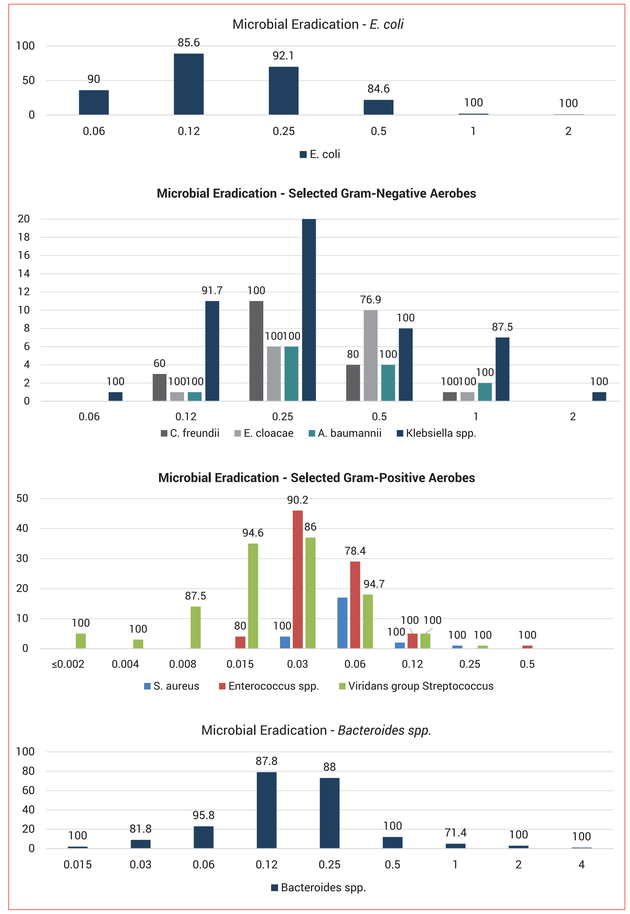
ESBL = isolates which tested positive for extended spectrum beta-lactamase activity; Carbapenemase = isolates which tested positive for carbapenemase activity; AmpC = isolates showing elevated expression of AmpC enzymes. Clinical response is based on the Surgical Adjudication Committee assessment.
Comparators = ertapenem and meropenem

Table 2. Eravacycline MIC Distributions for Selected Gram-Negative Species in the micro-ITT Population

Organism	Pooled Phase 3 cIAI studies - $MIC_{50/90}$ µg/ml (n)	
Acinetobacter baumannii	Total isolates	0.25/0.5 (25)
	Ceph-R	0.25/0.5 (21)
	MDR	0.25/1 (19)
Enterobacteriaceae	Total isolates	0.25/0.5 (991)
Citrobacter braakii	Total isolates	0.12/0.25 (14)
Citrobacter freundii	Total isolates	0.25/0.5 (33)
Enterobacter cloacae	Total isolates	0.5/0.5 (51)
	3rd -GC-I/R	0.5/0.5 (15)
Escherichia coli	Total isolates	0.12/0.25 (630)
	Ceph-R	0.25/5 (52)
Klebsiella oxytoca	Total isolates	0.25/0.25 (34)
Klebsiella pneumoniae	Total isolates	0.25/1 (106)
	Ceph-R	1/1 (28)
Stenotrophomonas maltophilia	Total isolates	0.25/1 (13)

Ceph-R = 3rd/4th generation cephalosporin resistant

Figure 3. Eradications by MIC value



Microbial eradication in eravacycline treated patients at each MIC value (in µg/ml). Bar values represent number of isolates with the percentage of eradications given for each MIC above the bar.

Conclusions

In IGNITE1 and IGNITE4, high favorable clinical and microbiological responses were observed for eravacycline. More than 88% of five Enterobacteriaceae spp. and B. fragilis, the most common bacteria associated with cIAI, were eradicated by eravacycline. Comparable eradication rates were observed following ertapenem and meropenem therapy, further establishing that eravacycline was at least as effective as carbapenem treatments. These data support in vitro observations that eravacycline has broad-spectrum activity against common cIAI pathogens, including ESBL-positive, carbapenemase-positive, and MDR strains.

References

1. XERAVA™ (eravacycline) [package insert]. Watertown, MA; Tetraphase Pharmaceuticals; 2018.
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