Poster # 629

Microbiological Efficacy of Eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, Including MDR Isolates: A Pooled Analysis from IGNITE1 and IGNITE4, Two Phase 3 Trials of Complicated Intra-Abdominal Infection

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Abstract

Background. IGNITE1 and IGNITE4 were randomized, double-blind, double-dummy, multicenter studies assessing the efficacy and safety of eravacycline (ERV) compared to a carbapenem in subjects with complicated intra-abdominal infections (cIAIs). The primary objective of this analysis was to compare the microbiological and clinical response at the test-of-cure (TOC) visit for subjects in the 2 treatment groups, with an emphasis on the response of multidrug-resistant (MDR) pathogens to ERV.

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- or extra-abdominal specimens in the micro-ITT population. MDR pathogens were defined as resistant to at least one member of 3 or more antibiotic classes.

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 microbiological response among pooled ERV-treated subjects is shown in Table 1.

Baseline Pathogen	Pooled ERV microbiological cure No./Total No. (%)	Pooled ERV clinical cure No./Total No. (%)	Pooled comparator microbiological cure No./Total No. (%)	Pooled comparator clinical cure No./Total No. (%)
Enterobacteriaceae	**277/314 (88.2)**	**271/314 (86.3)**	**296/325 (91.1)**	**289/325 (88.9)**
CEPH-R	41/48 (85.4)[a]	43/48 (89.6)[a]	40/45 (88.9)[a]	40/45 (88.9)[a]
ESBL	32/36 (88.9)	32/36 (88.9)	26/29 (89.7)	25/29 (86.2)
MDR	39/46 (84.7)[a]	40/46 (87)[a]	29/32 (90.6)[a]	29/32 (90.6)[a]
Acinetobacter baumanii	**13/13 (100)**	**13/13 (100)**	**7/7 (100)**	**7/7 (100)**
CEPH-R	13/13 (100)	13/13 (100)	5/5 (100)	5/5 (100)
ESBL	5/5 (100)	5/5 (100)	1/1 (100)	1/1 (100)
MDR	12/12 (100)	12/12 (100)	5/5 (100)	5/5 (100)

[a] = Includes *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae,* and *Morganella morganii*. CEPH-R - 3rd/4th-generation cephalosporin-resistant; ESBL – extended-spectrum beta-lactamases, MDR = Multidrug-resistant. Defined as resistant to at least one member of >=3 antibiotic classes.

Conclusions. In IGNITE1 and IGNITE4 studies, favorable microbiological responses were observed for ERV against Enterobacteriaceae and *Acinetobacter baumannii*, including those demonstrating resistant phenotypes, such as MDR, ESBL and cephalosporin-resistance.

Background

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic that has completed phase 3 clinical development for patients with complicated intra-abdominal infections (cIAI) and is under regulatory review by the Food and Drug Administration and European Medicines Agency. ERV has potent *in-vitro* activity against a broad range of susceptible and multidrug-resistant (MDR) Gram-positive and Gram-negative aerobic and anaerobic strains (including *Staphylococcus aureus, Enterococcus faecium, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii* and *Bacteroides* spp.). It retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)[1-4].

IGNITE1 and IGNITE4 are phase 3 randomized, double-blind, double-dummy, multicenter, prospective studies designed to assess the efficacy and safety of twice-daily intravenous ERV (1 mg/kg every 12 hours) compared to a carbapenem in patients with cIAI. The primary endpoint was the clinical response at the TOC visit based on the micro-ITT population, 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 margin for IGNITE1 and IGNITE4 was 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- or extra-abdominal specimens in the micro-ITT population.

The objective of this analysis was to compare the clinical and microbiological response at the TOC visit in subjects that received ERV versus the comparator agents based on the resistant phenotypes and genotypes present in baseline Gram-negative pathogens.

Methods

Antibacterial agents:

- Eravacycline (Tetraphase Pharmaceuticals), ertapenem (Eurofins Medinet), and meropenem (USP)

Bacterial strain collection

- To determine baseline pathogens, both blood and intra-abdominal samples were acquired. Four 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
- Isolates were initially speciated by the local/regional lab and speciation was confirmed by the central laboratory.
- Isolates showing resistance to carbapenems or 3rd/4th generation cephalosporins were sent to JMI Laboratories, North Liberty, Iowa to determine resistance mechanism

Methods (continued)

β-Lactamase characterization

- Enterobacteriaceae
  - Enterobacteriaceae that met the susceptibility screening criteria for ESBL according to CLSI guidelines[5] were screened for ESBLs, inhibitor-resistant ESBLs and plasmidic AmpC-encoding genes.
  - Enterobacteriaceae isolates exhibiting non-susceptibility to imipenem (MIC ≥ 2 µg/mL) were also screened for carbapenemase-encoding genes.
- Non-fermentative Gram-negative organisms
  - *A. baumannii* with unique PFGE patterns and ceftazidime MIC values ≥ 16 µg/mL were screened for ESBL-encoding genes at the transcription level of chromosomally-encoded AmpC.
  - IGNITE1: Microarray-based (Check-MDR CT101; Wageningen, The Netherlands) and/or PCR reactions targeting common β-lactamase-encoding genes were performed using purified total genomic DNA extracts from all unique isolates. All amplicons generated were sequenced on both strands for confirmation of PCR products and determination of allelic variants. Nucleotide and deduced amino acid sequences were analyzed using the Lasergene software package (DNASTAR, Madison, WI, USA). Amino acid sequences were compared with those available through the internet using BLAST (http://www.ncbi.nlm.nih.gov/blast/).
  - Expression of chromosomally-encoded AmpC for selected Enterobacteriaceae species was quantified using total mRNA from log phase bacterial cultures and was performed by real-time PCR in triplicate reactions that were normalized to an endogenous reference gene. The AmpC expression from clinical isolates was compared to those from reference strains and transcription levels was considered significantly higher if at least a 10-fold difference was observed
- IGNITE4: Whole Genome Sequencing was performed. DNA libraries were prepared using the Nextera XT™ library construction protocol and index kit (Illumina, San Diego, California, USA) and sequenced on a MiSeq Sequencer (Illumina) using a MiSeq Reagent Kit v2 (500 cycle) and v3 (600 cycle). FASTQ format files for each sample set were assembled to analyze resistance determinants.
  - *Escherichia coli* absent of ESBL, transferrable AmpC or carbapenemase, and all *Serratia* spp., *Citrobacter* spp., and *Enterobacter* spp. were evaluated using quantitative real-time PCR to determine the expressions of chromosomal AmpC.

Results

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

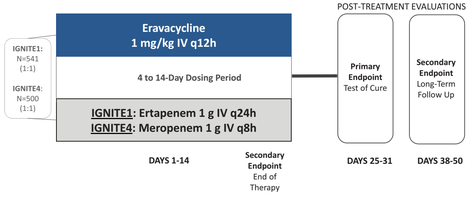

Figure 2. IGNITE1 Baseline Pathogen Distribution[6]

- 47.1% Gram-negative aerobes, 26.1% Gram-positive aerobes and 26.8% anaerobes
- 1298 baseline isolates; 3 isolates/patient

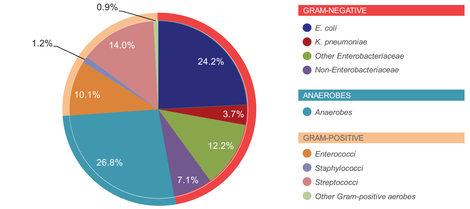

Figure 3. IGNITE4 Baseline Pathogen Distribution[8]

- 39% Gram-negative aerobes, 26% Gram-positive aerobes and 35% anaerobes
- 1445 baseline isolates; 3.6 isolates/patient

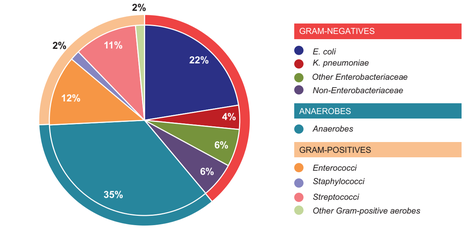

Table 1. Clinical and Microbiological Outcomes at TOC in the micro-ITT Population for Subjects with Gram-Negative Bacilli Pathogens

Baseline Pathogen		Pooled ERV microbiological cure No./Total No. (%)	Pooled ERV clinical cure No./Total No. (%)	Pooled comparator microbiological cure No./Total No. (%)	Pooled comparator clinical cure No./Total No. (%)
Enterobacteriaceae		**277/314 (88.2)**	**271/314 (86.3)**	**296/325 (91.1)**	**289/325 (88.9)**
CEPH-R		41/48 (85.4)[a]	43/48 (89.6)[a]	40/45 (88.9)[a]	40/45 (88.9)[a]
	ESBL	32/36 (88.9)	32/36 (88.9)	26/29 (89.7)	25/29 (86.2)
	Confirmed ESBL				
	Citrobacter freundii CTX-M-15-like SHV-30	3/3 (100) 1/1 (100)	3/3 (100) 1/1 (100)	2/2 (100) --	2/2 (100) --
	Enterobacter cloacae CTX-M-15-like	2/2 (100)	2/2 (100)	5/5 (100)	5/5 (100)
	Escherichia coli CTX-M-1-like CTX-M-3-like CTX-M-14 CTX-M-15-like CTX-M-32 CTX-M-55/79	1/1 (100) 0/1 (0) 1/2 (50) 15/16 (93.8) 1/1 (100) 1/1 (100)	1/1 (100) 0/1 (0) 1 /2 (50) 15/16 (93.8) 1/1 (100) 1/1 (100)	1/1 (100) 1/1 (100) -- 9/10 (90) -- --	1/1 (100) 1/1 (100) -- 10/10 (100) -- --
	Klebsiella pneumoniae CTX-M-15-like	10/11 (90.1)	10/11 (90.1)	5/6 (83.3)	4/6 (66.7)
MDR		39/46 (84.7)[a]	40/46 (87)[a]	29/32 (90.6)[a]	29/32 (90.6)[a]
Acinetobacter baumanii		**13/13 (100)**	**13/13 (100)**	**7/7 (100)**	**7/7 (100)**
CEPH-R		13/13 (100)	13/13 (100)	5/5 (100)	5/5 (100)
	ESBL	5/5 (100)	5/5 (100)	1/1 (100)	1/1 (100)
	Confirmed ESBL				
	GES-1 PER-1	4/4 (100) 1/1 (100)	4/4 (100) 1/1 (100)	1/1 (100) --	1/1 (100) --
MDR		12/12 (100)	12/12 (100)	5/5 (100)	5/5 (100)

[a] = Includes *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae,* and *Morganella morganii*. CEPH-R - 3rd/4th-generation cephalosporin-resistant; ESBL – extended-spectrum beta-lactamases. MDR = Multidrug-resistant. Defined as resistant to at least one member of >=3 antibiotic classes . NOTE: Results are presented as n/N (%), where n=subjects with favorable outcomes, N=total subjects in the category, and % = n/N*100; Clinical response is based on the Surgical Adjudication Committee assessment.

Conclusions

In the IGNITE1 and IGNITE4 studies, eravacycline demonstrated excellent clinical cure rates for commonly observed Gram-negative pathogens. Favorable microbiological and clinical responses were observed for eravacycline against Enterobacteriaceae and *A. baumannii* Gram-negative pathogens that were 3rd/4th generation cephalosporin-resistant, ESBL-producing, or multidrug-resistant suggesting a promising role for eravacycline in treating patients with cIAI who harbor resistant pathogens.

References

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