Poster # 1978

# Efficacy of Eravacycline in Secondary Bacteremia: A Post Hoc Analysis of Two Phase 3 studies of Complicated Intra-Abdominal Infection

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## Abstract (Revised)

**Background:**

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic that was evaluated for the treatment of complicated intra-abdominal infections (cIAI) in two Phase 3 clinical trials[1]. The objective of this analysis was to evaluate microbiological response at the test of cure (TOC) visit in patients with baseline cIAI and bacteremia who received eravacycline versus comparators (ertapenem and meropenem).

**Methods:**

Pooled data from IGNITE1 and IGNITE4 studies were analyzed. All patients enrolled were randomized (1:1) to receive eravacycline (1 mg/kg IV q12h) or ertapenem 1 g IV q24h (IGNITE1), or meropenem 1g IV q8h (IGNITE4), for 4-14 days. Blood (aerobic and anaerobic bottles) and intra-abdominal samples were collected from all patients. Clinical outcome at the TOC visit (28 days after randomization) in the microbiological-intent to treat population (micro-ITT) was the primary efficacy endpoint[2,3].

**Results:**

520 patients treated with eravacycline and 517 with comparators of with 32 (6.2%) and 31 (6%), respectively had concurrent bacteremia. Demographic and baseline characteristics were similar among the groups. In the micro-ITT population, the pooled clinical response at the TOC visit for eravacycline versus comparators was 88.7% and 89.3% (-0.7; 95% CI, -4.9, 3.6), respectively. The baseline pathogens associated with concurrent bacteremia and the microbiological eradication for selected pathogens are presented in Table 1.

**Table 1. Microbiological Eradication at the Test of Cure Visit by Baseline Pathogen from Blood Specimen in Patients with Concurrent Bacteremia**

| | Eravacycline (n=32) n (%) | *Comparators (n=31) n (%) |
|---|---|---|
| **Gram-negative** | **14/15 (93.3)** | **14/15 (93.3)** |
| *E. coli* | 5/6 (83.3) | 6/7 (85.7) |
| **Gram-positive** | **13/13 (100)** | **10/10 (100)** |
| *Streptococcus spp.* | 8/8 (100) | 4/4 (100) |
| *Enterococcus spp* | 2/2 (100) | 5/5 (100) |
| **Anaerobes** | **7/7 (100)** | **10/11 (90.9)** |
| *Bacteroides spp.* | 6/6 (100) | 7/7 (100) |

* Meropenem and Ertapenem

**Conclusion:**

Eravacycline demonstrated a similar microbiological eradication rate as comparator agents in patients with cIAI associated with secondary bacteremia.

## Introduction

Empiric treatment of cIAI represents a clinical challenge because of the polymicrobial infecting flora and the emergence of antibiotic resistance in multiple classes of organisms. The management of bacteremia, occurring in some 10% of cIAI patients, is uncertain[4].

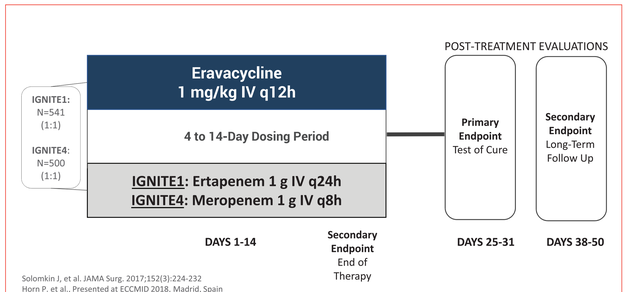
To explore this subject, we examined a subgroup of patients in IGNITE1 and IGNITE4 with complicated intra-abdominal infection (cIAI) and concurrent bacteremia at baseline.

The objective of this analysis was to explore the rates of clinical cure and microbiological eradication at the test-of-cure (TOC) visit in patients with concurent bacteremia treated with eravacycline versus the comparator agents for cIAI.

## Methods

IGNITE1 and IGNITE4 were randomized, double-blind, double-dummy, multicenter, prospective, non-inferiority phase 3 trials designed to assess the efficacy and safety of eravacycline compared to ertapenem or meropenem, respectively, for the treatment of cIAI. The primary endpoint was clinical response at the TOC visit, which occurred 25 to 31 days after the initial dose of study drug. The primary efficacy analysis for the FDA was conducted using a 10% (IGNITE1) and 12.5% (IGNITE4) non-inferiority margin in the microbiological intent-to-treat (micro-ITT) population[2,3].

**Figure 1. IGNITE1 and IGNITE4 Study Design**




Solomkin J, et al. JAMA Surg. 2017;152(3):224-232
Horn P. et al., Presented at ECCMID 2018, Madrid, Spain

**Key Inclusion Criteria**

- Male or female participant hospitalized for cIAI
- At least 18 years of age
- Evidence of a systemic inflammatory response
- Abdominal pain or flank pain (with or without rebound tenderness), or pain caused by cIAI that is referred to another anatomic area
- Able to provide informed consent
- Not pregnant and committed to use of contraception

**Key Exclusion Criteria**

- Creatinine clearance of ≤50 milliliter (mL)/minute
- Presence or possible signs of significant hepatic disease
- Immunocompromised condition, including known human immunodeficiency virus (HIV) positivity, transplant recipients, and hematological malignancy
- History of moderate or severe hypersensitivity reactions to tetracyclines, carbapenems, β-lactam antibiotics, or to any of the excipients contained in the study drug formulations
- Known or suspected current central nervous system (CNS) disorder that may predispose to seizures or lower seizure threshold (for example, severe cerebral arteriosclerosis, epilepsy)
- Antibiotic-related exclusions:
  - Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of >24-hours during the 72-hours preceding randomization
  - Receipt of meropenem or any other carbapenem, or tigecycline for the current infection
  - Need for concomitant systemic antimicrobial agents effective in cIAI other than study drug
  - The anticipated need for systemic antibiotics for a duration of more than 14 days
- Known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs

## Results

**Table 2. Pooled Subject Baseline Characteristics from IGNITE1 and IGNITE4, MITT Population**

| | Eravacycline (n=520) | **Eravacycline CB (n=32)** | Comparators (n=517) | **Comparators CB (n= 31)** |
|---|---|---|---|---|
| Gender, male, n (%) | 295 (56.7) | **18 (56.3)** | 292 (56.5) | **22 (70.9)** |
| Race, White, n (%) | 512 (98.5) | **32 (100)** | 506 (97.9) | **32 (100)** |
| Age, n (%) | | | | |
| <65 | 362 (69.6) | **20 (62.5)** | 367 (71.0) | **20 (64.5)** |
| ≥65 | 158 (30.4) | **12(37.5)** | 150 (29.0) | **11 (35.5)** |
| APACHE II score, n (%) | | | | |
| 0-10 | 455 (87.5) | **28 (87.5)** | 429 (83.0) | **23 (74.2)** |
| 11-15 | 55 (10.6) | **3 (9.4)** | 71 (13.9) | **6 (19.4)** |
| >15 | 8 (1.3) | **1 (3.1)** | 14 (2.7) | **1 (3.3)** |
| Missing data | 2 (0.4) | **0 (0.0)** | 3 (0.6) | **1 (3.3)** |
| Primary Disease Diagnosis, n(%) | | | | |
| Complicated Appendicitis | 173 (33.3) | **9 (28.1)** | 173 (33.5) | **7 (22.6)** |
| Other cIAI | 347 (66.7) | **23 (71.9)** | 344 (66.5) | **24 (77.4)** |

MITT=Modified Intent to Treat; CB = concurrent bacteremia

**Figure 2. Baseline Blood Pathogen Distribution In Patients with Concurrent Bacteremia, micro-ITT Population (n = 71)**

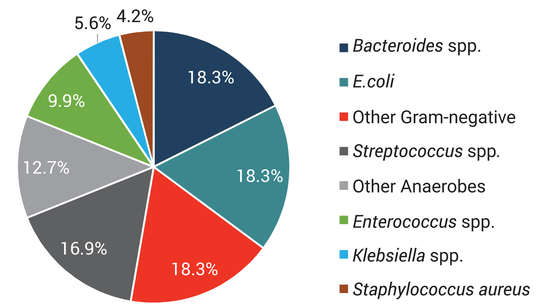



**Figure 3. Pooled Clinical Response in Patients with cIAI from IGNITE1 and IGNITE, micro-ITT Population**

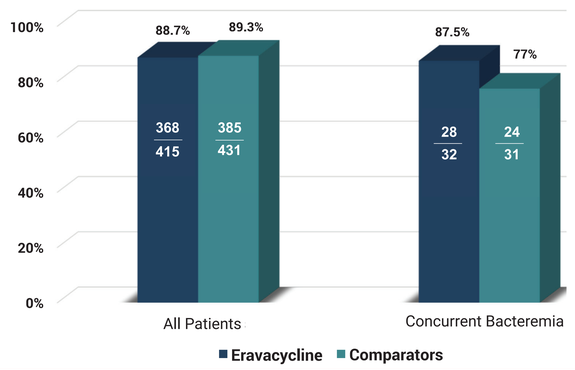



**Table 3. Microbiological Eradication at the Test of Cure Visit by Baseline Pathogen from Blood Specimen in Patients with Concurrent Bacteremia**

| | Eravacycline (n=32) n (%) | *Comparators (n=31) n (%) |
|---|---|---|
| **Gram-negative** | 14/15 (93.3) | 14/15 (93.3) |
| *E. coli* | 5/6 (83.3) | 6/7 (85.7) |
| *Klebsiella oxytoca* | 0 | 2/2 (100) |
| *Klebsiella pneumoniae* | 1/1 (100) | 1/1 (100) |
| *Acinetobacter baumanii* | 1/1 (100) | 0 |
| *Acinetobacter Iwoffii* | 0 | 1/1 (100) |
| *Burkholderia cepacia* | 1/1 (100) | 1/1 (100) |
| *Pseudomonas aeruginosa* | 1/1 (100) | 1/1 (100) |
| *Pseudomonas stutzeri* | 1/1 (100) | 0 |
| *Stenotrophomonas maltophilia* | 2/2 (100) | 0 |
| Other non-Enterobacteraceae | 3/3 (100) | 2/2 (100) |
| **Gram-positive** | 13/13 (100) | 10/10 (100) |
| *Staphylococcus aureus* | 2/2 (100) | 1/1 (100) |
| *Streptococcus* spp. | 8/8 (100) | 4/4 (100) |
| *Enterococcus* spp. | 2/2 (100) | 5/5 (100) |
| **Anaerobes** | 7/7 (100) | 10/11 (90.9) |
| *Bacteroides* spp. | 6/6 (100) | 7/7 (100) |
| Other Anaerobes | 1/1(100) | 3/4 (75) |

*ertapenem and meropenem

## Conclusions

Clinical response at the TOC visit in patients with cIAI was similar regardless of the presence of concurrent bacteremia. Microbiological eradication in the subset of patients with cIAI complicated by concurrent bacteremia occurred at comparable rates for patients randomized to eravacycline or carbapenems. This demonstrates that eravacycline is an effective, empiric treatment option for cIAI comparable to carbapenems.

***References***

1. XERAVA™ (eravacycline) [package insert]. Watertown, MA; Tetraphase Pharmaceuticals; 2018.
2. Solomkin J, Evans D, Slepavicius A, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intraabdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg* 2017;152:224-32.
3. Solomkin J, Gardovskis J, Lawrence K, et al. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs. Meropenem in the Treatment of Complicated Intra-Abdominal Infections. [Manuscript in Review, 2018].
4. Tellor B, Skrupky LP, Symons W, et al. Inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. *Surgical Infections* 2015;16:6.785-93.