Poster # 75 E

# Eravacycline is Effective in High-Risk Complicated Intra-Abdominal Infection Subgroups

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## Abstract

**Background.** Eravacycline is a FDA approved, fully-synthetic fluorocycline antibacterial, for the treatment of complicated intra-abdominal infection (cIAI) in adults. Eravacycline is active against Gram-negative pathogens, including ESBL-producing Enterobacteriaceae and many Gram-positive and anaerobic bacteria found in cIAI. Eravacycline was proven to be non-inferior to carbapenems (CT) in two pivotal clinical cIAI studies when used as monotherapy1. The purpose of this analysis was to compare clinical outcomes in high-risk subgroups from two phase 3 cIAI studies. The effects of age, APACHE II score, site of infection, and presence of baseline bacteremia were examined in this pooled analysis of phase 3 clinical trials in cIAI.

**Methods:** In the IGNITE1 and IGNITE4 trials, adult patients hospitalized with cIAI were randomized to ERV vs ertapenem or meropenem, respectively. Clinical outcome in the microbiological-intent-to treat population (micro-ITT) at the test of cure visit, 25-31 days after randomization, was the primary efficacy endpoint. The effects of age, APACHE II score, site of infection, type of procedure, and presence of baseline bacteremia on the primary end point were examined in a pooled analysis2,3.

**Results:** The micro-ITT population included 415 patients received ERV and 431 received CT. For ERV vs CT groups respectively: the number of patients ≥ 65 years was 118 (28.4%) vs 127 (29.4%); APACHE II scores ≥ 10 occurred in 86 (20.7%) vs 92 (21.3%) patients; non-appendiceal sites of infection were present in 255 (61.4%) vs 274 (63.6%) patients; an open surgical procedure was performed in 251 (60.5%) vs 275 (63.8%) patients; baseline bacteremia was present in 32 (7.7%) vs 31 (7.2%) patients. Clinical cure (CC) rates in 65-75 and >75year subgroups were 81% and 94% for ERV vs 81.6% and 92.2% for CT, respectively, as compared to 90.2% for ERV vs 90.8% for CT in patients < 65 years. For ERV vs CT groups respectively: CC rates seen with APACHE II scores ≥ 10 were 88.4% vs 84.8% and for APACHE II scores < 10 were 88.7% vs 91.1%; non-appendiceal CC rates were 88.6% vs 89.8% and in complicated appendicitis CC rates were 88.8% vs 88.5%; CC rates in open surgical procedures were 87.3% vs 88.4%; CC rates in patients with bacteremia were 87.5% (28/32) vs 77.4% (24/31).

**Conclusions:** ERV was effective in treating cIAI subgroups who may be at higher risk of poor outcomes. The results support the use of ERV as an alternative to carbapenems for empiric treatment of cIAI.

## Introduction

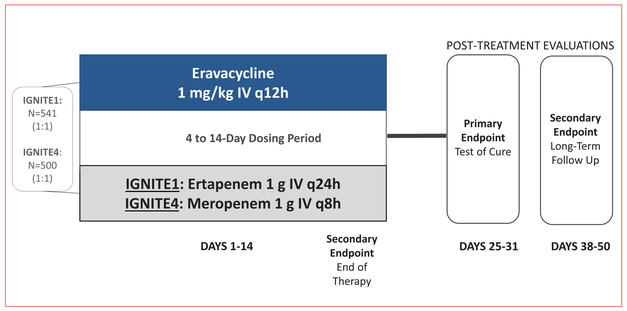
Eravacycline is a fully-synthetic fluorocycline antibacterial of the tetracycline class that has recently received the Food and Drug Administration's (FDA) approval for the treatment of complicated intra-abdominal infections in patients ≥18 years of age.[1] It retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection).[4,5] Eravacycline has shown activity against a broad range of Gram-negative, Gram-positive and anaerobic strains.

The purpose of this analysis was to compare clinical outcomes in high-risk subgroups from two phase 3 cIAI studies in patients treated with eravacycline versus CT[6]. The effects of age, APACHE II score, site of infection, and presence of baseline bacteremia were examined in a pooled analysis from the phase 3 trials.

## 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 the clinical response at the TOC, which occurred 25 to 31 days after the initial dose of the 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**




### Key Inclusion Criteria

- Male or female patient 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

### 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

For the purposes of this evaluation, subjects were classified into 3 categories based on age, < 65 years, 65-75 years, > 75 years and based on APACHE II Score, < 10, ≥ 10, ≥ 15.

Clinical outcomes for all high-risk subgroups were analyzed in the micro-ITT population at TOC.

## Results

**Table 1. Baseline Characteristics: Micro-ITT Population**

| Parameter | Eravacycline N=415 | Comparators N=431 |
|---|---|---|
| Gender, male, n (%) | 235 (56.6) | 237 (55) |
| Race, white, n (%) | 408 (98.3) | 420 (97.4) |
| Age, Mean, yr (SD) | 52.7 (17.5) | 53.9 (17.2) |
| < 65 | 297 (71.6) | 304 (70.5) |
| ≥ 65 to 75 | 84 (20.2) | 76 (17.6) |
| > 75 | 34 (8.2) | 51 (11.8) |
| Open surgical procedure, n (%) | 251 (60.5) | 275 (63.8) |
| Mean APACHE II score (SD) | 6.6 (4) | 6.6 (4) |
| Complicated appendicitis, n (%) | 160 (38.6) | 157 (36.4) |
| All other cIAI, n (%) | 255 (61.4) | 274 (63.6) |

**Table 2. Clinical Cure Rates By Location Of Infection: Micro-ITT Population**

| Diagnosis | Eravacycline N = 415 n/N (%) | Comparators N = 431 n/N (%) |
|---|---|---|
| Complicated Appendicitis | 145/163 (89) | 140/158 (88.6) |
| Intra-abdominal Abscess | 232/264 (87.9) | 216/246 (87.8) |
| Perforation of Intestine | 41/47 (87.2) | 49/57 (86) |
| Gastric/Duodenal Perforation | 28/31 (90.3) | 36/38 (94.7) |
| Peritonitis | 152/167 (91) | 159/176 (90.3) |
| Complicated Cholecystitis | 77/83 (92.8) | 86/90 (95.6) |
| Diverticulitis with Perforation, Peritonitis, or Abscess (IGNITE4 only) | 7/8 (87.5) | 8/8 (100) |
| Other | 11/12 (91.7) | 8/9 (88.9) |

**Figure 2. Clinical Cure Rates by Age: Micro-ITT Population**

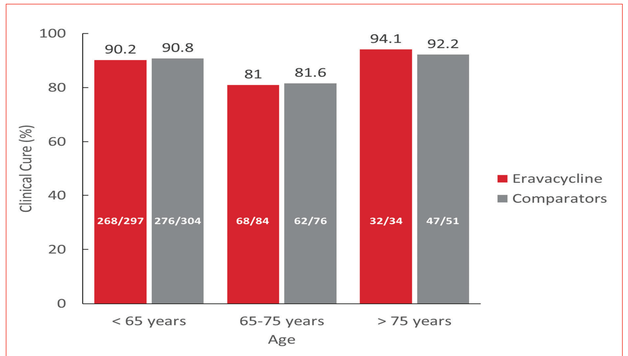



**Figure 3. Clinical Cure Rates by APACHE II score: Micro-ITT Population**

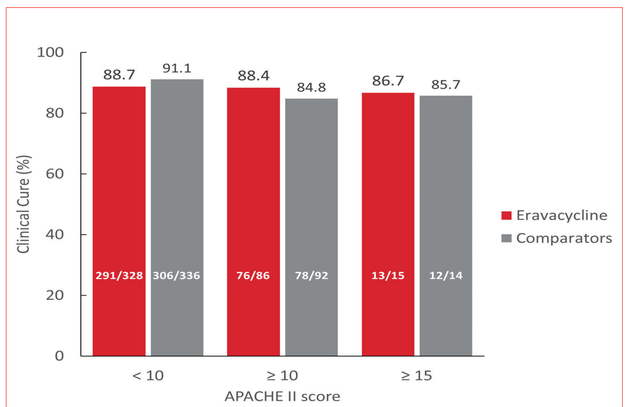
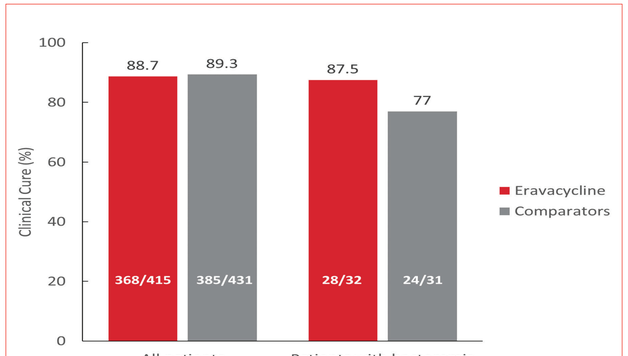



**Figure 4. Clinical Cure Rates in Baseline Bacteremia: Micro-ITT Population**




## Conclusions

Risk factors such as APACHE II score ≥ 10, advance age, and various infection characteristics have been associated with worse outcomes in cIAI6. Eravacycline was effective in treating cIAI subgroups that may be at higher risk of poor outcomes. The results support the use of eravacycline as an alternative to CT for empiric treatment of cIAI in patients at high-risk for clinical failure.

### *References*

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