Poster # 48211

# Effect of Renal Function in IGNITE1 and IGNITE4: Two Phase 3 Studies to Evaluate the Efficacy and Safety of Eravacycline

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## Abstract

**Introduction:** Treatment failure risk increases in certain complicated intra-abdominal infection (cIAI) subgroups.[1] Eravacycline , a novel fluorocycline antibiotic, was evaluated in two phase 3 randomized control trials (RCTs) to assess its efficacy and safety vs carbapenems in adults with cIAI. These RCTs met the primary endpoints of non-inferiority for clinical response.[2,3]

**Research Question or Hypothesis:** We sought to explore how baseline creatinine clearance (CrCl) affects the clinical efficacy of eravacycline.

**Study design:** IGNITE1 and IGNITE4 were randomized, double-blind, non-inferiority phase 3 trials in patients >18 years of age with a diagnosis of cIAI.

**Methods:** In IGNITE1 and IGNITE4, adult patients hospitalized with cIAI were randomized to weight-based dose eravacycline (1 mg/kg IV q12h) vs ertapenem (1 g IV Q24H) or meropenem (1 g IV Q8H), respectively. Clinical outcome in the microbiological-intent-to treat (micro-ITT) population at the test-of-cure (TOC) visit, 25-31 days after randomization, was the primary efficacy endpoint.[2,3] Subjects were classified into 3 categories based on renal function (CrCl).

**Results:** The micro-ITT population consisted of 846 patients who grew at least one pathogen consistent with cIAI in baseline intra-abdominal cultures. After exclusions, 415 patients received eravacycline vs 431 received comparator therapy (CT).

Clinical outcomes analyzed by renal function in the micro-ITT population at TOC were:

| Group | Eravacycline % Cure (n/N) | CT % Cure (n/N) | Difference | 95% CI (LL, UL) |
|---|---|---|---|---|
| All subjects | 88.7 (368/415) | 89.3 (385/431) | -0.7 | (-4.9, 3.6) |
| Moderately to Severely Decreased [CLCR 15 to <60 mL/min] | 84.8 (28/33) | 75.9 (22/29) | 9.0 | (-10.8, 30.0) |
| Mildly Decreased to Normal [CLCR ≥60 to <130 mL/min] | 87.0 (194/223) | 91.1 (225/247) | -4.1 | (-10.0, 1.6) |
| Augmented [CLCR ≥130 mL/min] | 91.9 (137/149) | 92.8 (128/138) | -0.8 | (-7.2, 5.8) |

n=number of subjects with clinical cure; N=number of subjects within a specific category; CT=comparator therapy

**Conclusion:** Eravacycline was an effective treatment for patients diagnosed with cIAI regardless of renal function. Eravacycline provides an alternative to carbapenems for the empiric treatment of cIAI.

## Introduction

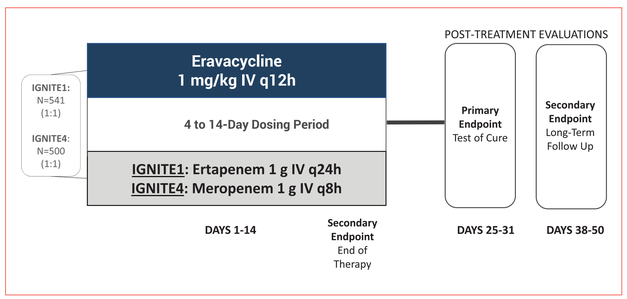
Eravacycline is a fully-synthetic fluorocycline antibacterial of the tetracycline class that has recently received the Food and Drug Administration's (FDA) approval for the treatment of complicated intra-abdominal infections[5]. Eravacycline retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)[6,7]. Eravacycline has shown activity against a broad range of Gram-negative, Gram-positive and anaerobic strains.

Treatment failure risk increases in certain complicated intra-abdominal infection (cIAI) subgroups.[1] The objective of this analysis was to explore clinical outcomes at the test-of-cure (TOC) visit in patients with different levels of renal function 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 1 mg/kg IV Q12H compared to ertapenem 1 g IV Q24H or meropenem 1 g IV Q8H, respectively, for the treatment of cIAI. The primary endpoint was the clinical response at the TOC visit, 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 and committed to use of contraception

## Methods (cont'd)

### 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 renal function (Moderately to Severely Decreased [CrCl 15 to <60 mL/min], Mildly Decreased to Normal [CrCl ≥ 60 to <130 mL/min], Augmented [CrCl ≥ 130 mL/min]). Clinical outcomes were analyzed by renal function in the micro-ITT population at TOC.

## Results

**Table 1. Pooled Micro-ITT Demographics and Baseline Characteristics**

| | Eravacycline (N=415) | Comparators (N=431) |
|---|---|---|
| Gender, male, n (%) | 235 (56.6) | 237 (55.0) |
| Race, White, n (%) | 408 (98.3) | 420 (97.4) |
| Age, n (%) | | |
| <65 | 297 (71.6) | 304 (70.5) |
| ≥65 | 118 (28.4) | 127 (29.5) |
| APACHE II score, n (%) | | |
| 0-10 | 328 (79.0) | 336 (78.0) |
| ≥10 | 86 (20.7) | 92 (21.3) |
| ≥15 | 15 (3.6) | 14 (3.2) |
| Missing Data | 1 (0.3) | 3 (0.7) |
| Site of Infection, n (%) | | |
| Complicated Appendicitis | 163 (39.3) | 158 (36.7) |
| Other cIAI | 252 (61.7) | 273 (63.3) |

## Results (cont'd)

**Figure 2. Distribution of Micro-ITT Population by Renal Function**

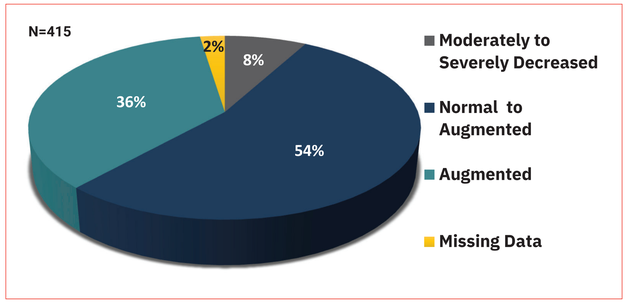
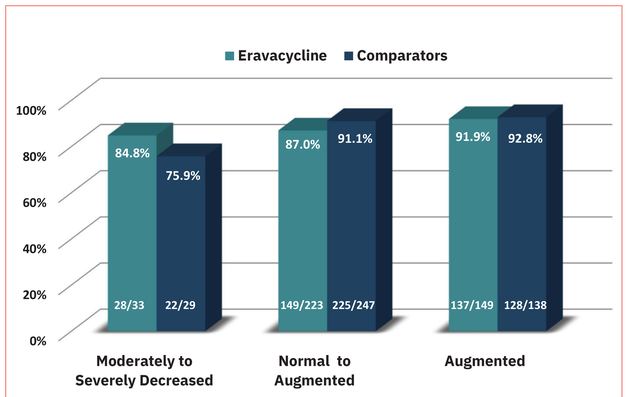



**Figure 3. Micro-ITT Clincal Cure by Renal Function**




## Conclusions

Similar clinical cure rates were observed for eravacycline across all categories of renal function. These data further support that eravacycline is an effective, empiric treatment for cIAI comparable to carbapenem antibiotics. Additionally, eravacycline may provide an alternative to the use of antibiotics that require dosing modification in patients with a diagnosis of cIAI and who also have altered renal function.

### *References*

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